COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Mycotoxins in Food and Feed: Present Status and Future Concerns

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ABSTRACT: Disease outbreaks due to the consumption of contaminated food and feedstuff are a recurring problem worldwide. The major factor contributing to contamination are microorganisms, especially fungi, which produce low-molecular-weight compounds as secondary metabolites, with confirmed toxic properties referred to as mycotoxins. Several mycotoxins reported to date are cosmopolitan in distribution and incur severe health-associated risks (including cancer and neurological disorders). Hence, creating awareness among consumers, as well as developing new methods for detection and inactivation is of great importance for food safety. In this review, the focus is on the occurrence of various types of mycotoxins in food and feed associated with risks to humans and livestock, as well as legislation put forth by various authorities, and on presently practiced detoxification methods. Brief descriptions on recent developments in mycotoxin detection methodology are also inlcuded. This review is meant to be informative not only for health-conscious consumers but also for experts in the field to pave the way for future research to fill the existing gaps in our knowledge with regard to mycotoxins and food safety.

Introduction

Contamination of food and agricultural commodities by various types of toxigenic molds (fungi) is a serious and a widely neglected problem. Regardless of decades of extensive research, mold infection still remains a challenging problem (Munkvold 2003). It has been estimated by FAO that worldwide approximately 25% of the crops get contaminated by molds and are affected by mycotoxins (CAST 1989; Rice and Ross 1994), and the estimated loss extends to billions of dollars (Trail and others 1995). Molds have been designated to rank second only to insect pests as a cause of damage during the storage of grains (CAST 1989). Poor harvesting practices, improper drying, handling, packaging, storage, and transport conditions contribute to fungal growth and increase the risk of mycotoxin production.

Major loss of fresh harvest that renders it to be an impediment for safe consumption can be attributed mainly to 3 factors: biological (storage pests), microbial (bacteria, fungi), and chemical (insecticide, fungicide residues). These 3 factors, singly or in combination, can readily react with the substrate or the raw material leading to the production of off-flavors, discoloration of the product, and reduction in nutritional value. Today, in most of the cases, chemical fumigants or chemical-based protective agents are used for the safe preservation of fresh produce. However, increasing concern and demand by consumers for safe and high-quality foods have made it mandatory to look for better alternatives to chemicals. In this regard, it has been a major challenge for the scientific community around the world, as some of the chemical fumigants (like ethylene dioxide, methyl bromide), which are routinely used for postharvest preservation purposes, have been reported to be highly toxic. Some of these chemicals are either banned in developed countries or are likely to be banned in developing countries (by 2015) (Anonymous 1995; FAO 2005).

Worldwide, it is generally claimed that natural products are safe. However, contamination of human or animal food (or feed) via natural biotoxins produced by microbes might result in outbreaks of several diseases. Among the microbes, fungal toxins assume more importance due to their worldwide distribution. The colonizing fungi are capable of producing toxins, and can cause deleterious health effects in humans or in livestock consuming the contaminated products. Such cases of fungal poisoning may cause death in animals, but are rarely fatal to humans (Pfohl-Leszkowicz 2000). As there is an increasing concern among consumers regarding food safety, as well as demand for high-quality foods with minimal "bio" or "chemical" contaminants, frequent occurrence of these toxins will definitely have a negative impact on the economy of the affected region/country.

Fungal toxins have been detected in various food commodities from many parts of the world and have been recognized to be one of the most dangerous contaminants of food and feed (CAST 1989). The production of toxins by a fungus does not correlate directly with its growth, but is also dependent on the fungistatic and fungicidal compounds that might affect the invasion and

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colonization. Even though research papers, reviews, monographs, and reports are available on the contamination of food and feed by fungal toxins, most of the information available is either restricted to one type of mycotoxin or the data are scattered. Hence, keeping this in mind, in the present review, we have aimed at providing a detailed overview on the mycotoxigenic fungi, diversity of mycotoxins, associated health risks to humans and livestock, and on the formal governmental regulations/legislation put in place. A brief input on the various types of detection methods (see Table 1) has been included to provide baseline information for future research, as well as to create awareness among the general population and health-conscious consumers.

Fungi, Conditions Promoting Their Growth, and Production of Mycotoxins

Fungi are eukaryotic, single-celled, multinucleated organisms that are heterotrophic in nature and characterized by a chitinous cell wall. In a majority of the cases fungi occur as filamentous growth and grow in multicellular colonies (grouped together as a mycelium) as compared with yeasts, which are single cells. Nearly 70000 fungal species have been reported and described, but it is estimated that nearly 1.5 million species might still exist (Hawksworth 1991; Hawksworth and others 1995). Details pertaining to fission fungi (bacteria) are not dealt in this review.

The colonizing molds (fungi that reproduce by releasing tiny spores into the air) might live as parasites, symbionts, or as saprophytes on a substrate. Since time immemorial, most of the molds have played a significant role in human life and welfare (as natural bio-degraders in the environment, in the preparation of certain foods and beverages, as antibiotic preparations, and as sources of industrially important chemicals like alcohols, acetone, and enzymes).

Fungi can invade, colonize, and produce mycotoxins either during preharvest (at the field level) or postharvest stages (storage, transport, and processing). However, filamentous fungi (fungi imperfecti) that are adapted to the terrestrial environment are usually recognized as mycotoxin producers. These fungi colonize and utilize solid substrates by penetrating deep into their matrices by secreting enzymes to break down complex products. In most of the cases, the colonizing fungi produce and secrete low-molecular-weight compounds (with confirmed toxic properties), generally referred to as "secondary metabolites" or "mycotoxins," which are usually not required for normal growth and survival.

The word mycotoxin is derived from 2 words: "mukes" referring to "fungi" (Greek) and "toxicum" referring to "poison" (Latin). Mycotoxins are relatively large molecules that are not significantly volatile (WHO 1978; Schiefer 1990).

Mycotoxins are produced by some of the specific strains of filamentous fungi belonging to species of the genera *Aspergillus, Penicillium,* and *Fusarium* that invade crops at the field level and may grow on foods during storage under favorable conditions (temperature, moisture, water activity, relative humidity). Fungi normally grow between 10 and 40 °C, over a pH range of 4 to 8, and at water activity (aw) levels above 0.70 (sometimes can grow on a very dry surface also) (Lacey 1991). The minimal aw requirements of some of the common toxigenic molds may also vary. For example, for *Aspergillus flavus* it is between 0.78 and 0.80 aw, *A. fumigatus* 0.85 and 0.94 aw, *A. parasiticus* 0.78 and 0.82 aw, *Eurotium* spp. 0.71 and 0.81 aw, *Fusarium spp.* 0.85 and 0.87 aw, and *Penicillium chrysogenum* 0.78 and 0.81 aw.

Mycotoxin-producing molds, under favorable environmental conditions, may thrive in almost all the climatic conditions of the world and on any solid or liquid support. The growth conditions of a specific fungal species might vary in the field compared to postharvest stages. For example, *Aspergillus* and *Penicillium* species can grow at low aw and at higher temperatures than *Fusarium* species, which generally require higher aw and low temperature range. However, this growth condition can vary during storage and transportation, wherein a rapid change in relative humidity can occur. Even though swift growth of a particular mold can occur on a substrate, it is not a prerequisite that the mold should produce a mycotoxin. This fact indicates that the production of mycotoxin from a particular species depends entirely on the availability of optimum conditions. As reported by Joffe (1986), *Fusarium* molds associated with alimentary toxic aleukia can grow prolifically at temperatures of 25 to 30 °C without producing any mycotoxin, but at near-freezing temperatures, large quantities of mycotoxins are produced without much mold growth.

Figure 1 shows a few of the mycotoxin-producing fungi growing on legume seeds. Some of the secondary metabolites produced by a fungus might possess high biological activity and can be toxic to other microorganisms (antibiotics), plants (phytotoxins), or animals. A few of the secondary metabolites like fumagillin, fusaric acid, and mycophenolic acid produced by fungi have been used as therapeutic agents, while other metabolites are considered to be potent toxins (Osweiler 2000; CAST 2003). According to Wicklow and others (1994), mycotoxin production in fungi might have evolved as an effective anti-insect or as an anti-rodent agent. Moss and Frank (1987) have opined that the secondary metabolism of molds might be influenced by the presence of inhibitory compounds such as agricultural biocides.

The nature and quantity of mycotoxins produced is entirely influenced by interactions of several factors: types of substrate, moisture content, available nutrition, temperature, humidity in the surrounding environment, maturity of the fungal colony, co-occurrence with other fungi, competition from other microorganisms, stress factors, physical damage of the substrate due to insect activity, and other associated factors (Anonymous 1983; Coulumbe 1993; Hendry and Cole 1993; Viquez and others 1994; Rao 2001). Once produced, mycotoxins might be present on all parts of the fungal colony, including the hyphae, mycelia, on spores, and on or in the substrate on which the colony grows.

Diversity in the toxic effects and the synergetic properties of mycotoxins has made it mandatory to consider them as "risk factor" to humans and in livestock health (Yiannikouris and Jonany 2002; Díaz-Llano and Smith 2006). Concerns over health effects of mycotoxins are being seriously considered worldwide. For example; after the hurricane Katrina, the Centers for Disease Control and Prevention (CDCP, U.S.A.) issued new revised warnings with regard to severe health effects from exposure to mycotoxins produced due to mold growth (Anonymous 2006). Reports are available wherein consumption of mycotoxin-contaminated food/feed is responsible for toxic syndromes in humans and livestock (Smith and others 1995; Berry 1998; Peraica and others 1999; MAFRI 2006). Apart from being highly toxic, some mycotoxins are also linked to the incidence of certain types of cancer and neurological disorders. This feature has induced global concern over safety aspects on the consumption of contaminated food and feed, especially in the case of milk and milk products (Egmond and Paulsch 1986; D'mello and Macdonald 1997; Castegnaro and Mcgregor 1998). Mycotoxins are normally metabolized in the liver, in the kidneys, and by microorganisms in the digestive tract. As a consequence, it is very difficult to derive the chemical structure and associated toxicity of the toxin residues excreted by animals or found in their tissues as they are different from the parent molecules (Ratcliff 2002).

Mycotoxicosis is the general term given for the disease that is caused by mycotoxins (Nelson and others 1993). The severity of a mycotoxicosis depends on the toxicity of the mycotoxin, dose involved, extent of exposure, and age and nutritional status of the

Table 1—Some of the recent methods developed/adapted for the detection of mycotoxins.

Mycotoxin	Raw material	Detection method	Reference
Aflatoxin (B1, B2)	Groundnut	Adsorptive cathodic stripping voltammetry	Hajian and Ensafi (2009)
Aflatoxin (B1, B2,G1, G2, M1)	Peanut	Class-specific monoclonal antibody-based ELISA	Li and others (2009)
Aflatoxin (B1, B2, G1, G2, M1, M2)	Raw and pasteurized sheep, cow and goat milk, egg, and beef samples	HPLC using UV and fluorescent detectors	Herzallah (2009)
Aflatoxin (B1, B2, G1, G2)	Chilli	Vicam immunoaffinity column for the clean-up procedure and with bromine derivatizaton with an electrochemical cell	O' Riordan and Wilkinson (2009)
Aflatoxin B1	Red chilli powder	Rapid FT-NIR method	Tripathi and Mishra (2009)
Aflatoxin B1	Rice	Signal-amplified electrochemical immunosensor	Tan and others (2009)
Aflatoxin B1	Corn	ELIME-array (based on an indirect competitive ELISA format)	Piermarini and others (2009)
Aflatoxin B1	Maize and barley	Near-infrared spectroscopy (NIR)	Fernández-Ibañez and others (2009)
Aflatoxin (B1, B2, G1, G2)	Nuts, cereals, dried fruits, and spices	In-tube solid-phase micro-extraction (SPME) coupled with LC-MS.	Nonaka and others (2009)
Aflatoxin M1	Milk	Immunoaffinity pre-concentration combined with on-column visual detection	Goryacheva and others (2009)
Fusarium toxins (beauvericin and enniatins [A, A1, B, B1])	Egg	LC–MS/MS	Jestoi and others (2009)
Fumonisin B1	Bovine milk	LC-MS/MS	Gazzotti and others (2009)
DON	—	Molecular imprint polymer technology	Weiss and others (2003)
Ochratoxin A (OTA) and citrinin	Cereals, fruit, and coffee products	High-performance liquid chromatography with fluorescence detection (HPLC-FL) using LC/MS/MS	Tabata and others (2008)
OTA	Tunisian foods	HPLC technique preceded by an immunoaffinity clean-up step	Ghali and others (2009)
OTA	Cheese	Solid-phase micro extraction coupled to liquid chromatography-tandem mass spectrometry.	Zhang and others (2009b)
OTA and aflatoxins	—	Dual-label time-resolved fluoroimmunoassay	Huang and others (2009)
OTA and ZEN	Corn	One-step simultaneous immunochromatographic strip test	Shim and others (2009)
OTA	breakfast and infant cereals	Pressurized liquid extraction coupled to liquid chromatography	Zinedine and others (2009)
Multi mycotoxins-trichothecenes, aflatoxin (B1,B2, G1, G2), Alternaria toxins, fumonisins (B1, B2, B3), ochratoxin A, ZEN, beauvericin, and sterigmatocystin	Sweet pepper	Multi-mycotoxin liquid chromatography/tandem mass spectrometry method	Monbaliu and others (2009)
ZEN	Corn	Fluorescence polarization immunoassay (FPIA)	Chun and others (2009)
ZEN and fumonisins	Cereals	Immunoaffinity clean-up and detection by liquid chromatography	Manova and Mladenova (2009)
Patulin	Apple fruit and apple products including juice, cider, and baby food, and also in quince fruit and quince jam	GC-MS	Cunha and others (2009)
Patulin	Apple juice	Single-laboratory validation of a liquid chromatography liquid chromatograph (with a C18 column and diode array detector)	Iha and others (2009)
Patulin	Fruit juice and dried fruit	In-tube solid-phase microextraction coupled with liquid chromatography–mass spectrometry	Kataoka and others (2009)

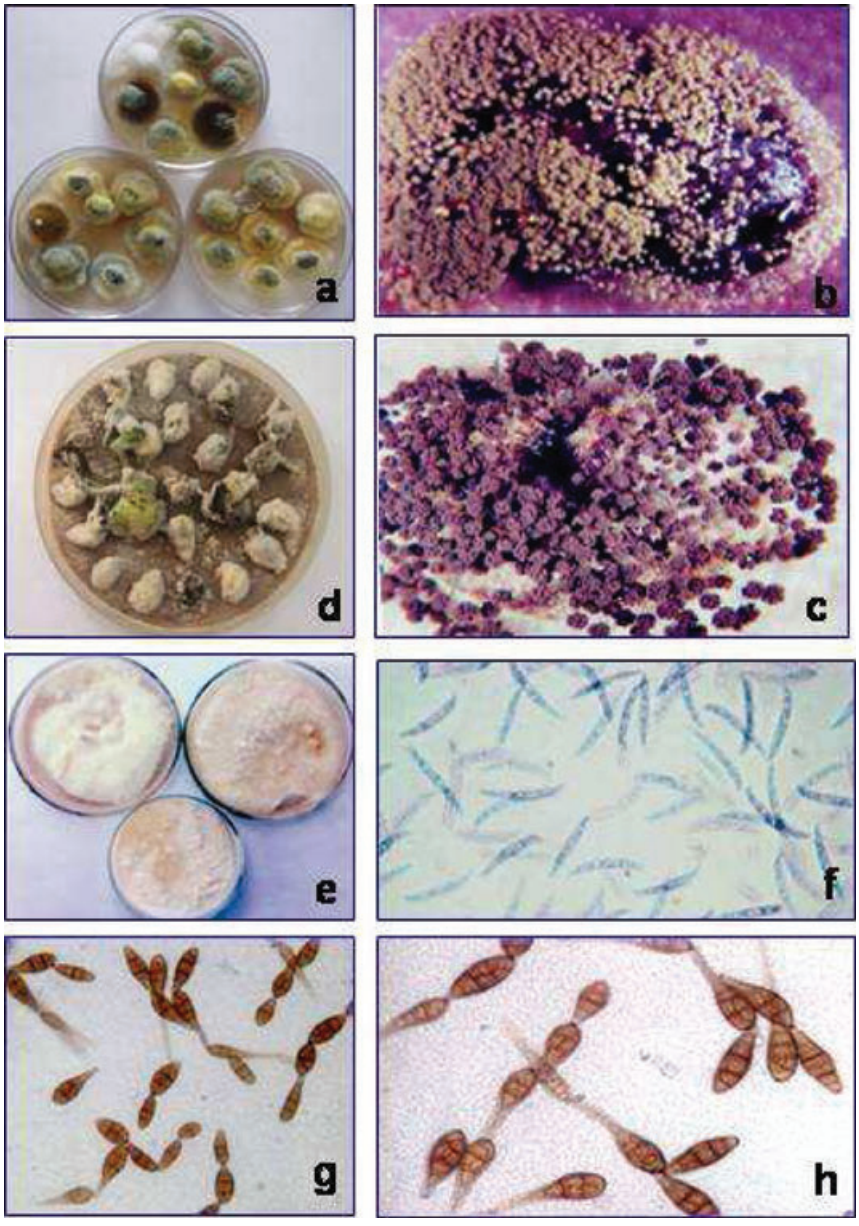

Figure 1—Various toxigenic molds. (a) Different fungi contaminating legume seeds, (b) *Aspergillus flavus*, (c) *Aspergillus niger*, (d) *Fusarium* spp., (e) Pure culture of *Fusarium* sp., (f) micro and macro conidia of a *Fusarium* sp., (g) *Alternaria alternata*, and (h) *Alternaria tenuissima*.

individual. Populations residing in developed countries are generally considered to be less exposed to mycotoxins than those in developing countries. This might be attributed to various factors: execution and practice of modern food handling/preservation technology, as well as successful governmental regulation and commercial control over food quality and safety. The presence of mycotoxin-producing fungi in a substrate (cereals, grains, and other sources) has been well defined and accepted as a natural "bio-contaminant" in many of the EU countries, the U.S., Canada, Russia, and in most of the Asian countries (Smith and Moss 1985). However, even monitoring and exercising of good agricultural and manufacturing practices (GAP and GMP) along with an effective Hazard Analysis and Critical Control Point (HACCP) approach might not completely avoid or eliminate mycotoxins in the food chain. Mycotoxins can enter the food chain directly via plant products such as cereal grains, coffee, oil seeds, spices, fruit juices, and beverages (wine and beer), and indirectly from animal diets (pastures, feeds) contaminated with mycotoxins, which can leave residues in milk, meat, and other products.

Mycotoxins and Associated Health Risks

Nearly 400 types of mycotoxins have been discovered, most of them since the 1960s, and are generally being categorized into groups based on structural similarities (Bennet and Klich 2003) and their major toxic effects. Mycotoxins are classified into cyclopeptides, polycetoacids, terpenes, and nitrogenous metabolites, depending on their biological origin and structure. Devegowda and others (1998) have comprehensively reported on the worldwide distribution of dominant mycotoxins. According to them, in Africa and the Asian subcontinents, aflatoxins are the major toxins; in Australia, it is aflatoxins and fumonisins; in

North America, it is aflatoxins, ochratoxin, zearalenone (ZEN), and vomitoxin; in South America, it is aflatoxins, fumonisins, ochratoxin, vomitoxin (DON), and T-2 toxin; in Eastern European countries, it is ZEN and vomitoxin; and in Western European regions it is ochratoxin, ZEN, and vomitoxin. However, with the increase of international trade and relaxation of quarantine barriers, the time is not too far away when these mycotoxins might also be detected in all areas of the world.

From a health point of view, the important mycotoxins in food and feed include: aflatoxins, ochratoxin, trichothecenes, fumonisins, ZEN, and patulin. Aaflatoxins, fumonisins, and ergot alkaloids are associated with acute mycotoxicoses in both humans and livestock. However, on the positive side, mycotoxin-associated diseases are not contagious.

Human health risks are usually associated with the direct consumption of food products contaminated with mycotoxins like aflatoxins, deoxynivalenol (DON), fumonisins, ochratoxin, and ergot alkaloids. Several of these toxins might be produced before harvest (aflatoxins, DON, ergot toxin), while others are produced mainly during postharvest stages (fumonisin, ochratoxin). The general symptoms of mycotoxicoses in humans are vomiting, diarrhea, and other associated gastro-intestinal problems (discussed in detail later). In general, mycotoxins are known to suppress the immune system. The effects of mycotoxins on immunity have been excellently reviewed earlier by Sharma (1993). Some of the mycotoxins that can suppress the immune system include mainly the trichothecenes (such as DON and T-2 toxin), which can reduce immunity by inhibiting protein synthesis and cell proliferation.

Compared to the individual effects, mycotoxins in combination have been reported to exert even greater negative impact on health and productivity, especially in livestock (Smith and Seddon 1998). In animals, mycotoxins produce a broad range of harmful effects such as reduction in animal productivity, increased incidence of disease due to immuno-suppression, damage to vital organs, and interference with reproductive capacity; and in some extreme cases, death might occur.

Mycotoxins produced in animal feeds generally cause irritation to the digestive tract and are capable of reducing nutrient absorption. When contaminated feeds are ingested by an animal, they usually interfere with the endocrine and exocrine systems. For example, ZEN affects the reproductive performance due to its estrogenic effect. ZEN's estrogenic effect results from the affinity of ZEN and its derivatives to bind with an animal's estrogen receptors (Klang and others 1978). Also, growth and proliferation of molds in animal feeds have been reportedly known to reduce the available nutrients like vitamins and amino acids (lysine) (Kao and Robinson 1972). Animal feeds, especially hay and straw, gets contaminated by fungi during preharvest stages itself, and subsequently from mycelial dust (fungal spores) during the drying stages. Such dust is believed to cause chronic diseases especially related to lungs in cattle and horses. Laan and others (2006) have considered certain dust fractions to be the major cause for chronic and recurrent airway diseases in horses. Pulmonary mycosis, abortion, or mastitis has been reported in animals feeding on contaminated silage and hay (dos Santos and others 2003). Contaminated hay has been shown to result in impaired semen quality in bulls (Alm and others 2002). The details on the health effects related to consumption of contaminated feeds in animals are discussed later in the text.

Historical Perspectives

Earlier reports have clearly indicated the devastating risks associated with the consumption of mold-contaminated products. Death due to ergotism has been described in the Old Testament (Schoental 1984), and the decline of the Etruscan civilization has been ascribed to fusariotoxins (T-2 toxin and ZEN) (Schoental 1991). Also, some of the Egyptian tombs, found to contain ochratoxin A, were held responsible for the mysterious deaths of several archaeologists (Pittet 1998).

However, historically, the longest known mycotoxicosis is "ergotism." This disease is also referred to as "St. Anthony's fire" or "sacred fire/ignis sacer" or "fire sickness." It was considered, during earlier periods, that a pilgrimage by affected people to the shrine of St. Anthony would bring relief in the head from the intense burning sensation experienced, hence the name. Several such epidemics occurred between the 8th and 16th centuries and the possible reason has been attributed to poor dietary conditions, particularly the consumption of flour contaminated by ergots. People affected with ergotism were exposed to lysergic acid diethylamide (LSD), a hallucinogen, produced during the baking of bread made out of ergot-contaminated wheat. In modern times, the 1st recognized acute intoxication was reported from France during 1954, when a large number of persons were victims of ergotism (Van Dongen and De Groot 1995). It was during 1977 to 1978 that Ethiopia saw the last recorded major outbreak of gangrenous ergotism affecting nearly 140 individuals of whom 34% died (King 1979). The cause of this outbreak was attributed to a long wet season which favored the growth of wild oats susceptible to *Claviceps purpurea*.

In 1966, a case of attempted suicide was reported from the U.S. after consumption of pure aflatoxin B1 (Willis and others 1980). During the 1960s, in the U.K., nearly 100000 young turkeys died due to aflatoxicosis and thousands of other animals and humans were affected (Rodricks and Stoloff 1977). During 1972 to'1988, a total of 884 persons were affected when outbreaks of food poisoning occurred described as "moldy sugarcane poisoning" (MSP) caused by an *Arthrinium* species (3-nitropropionic acid) (Liu and others 1988, 1992). Today, some of the mycotoxins have disappeared owing to stringent sanitary and quality measures. For example, citreoviridin-related malignant acute cardiac beriberi, also known as yellow rice disease has not been reported for several decades (the causative mold is *Penicillium citreonigrum*). Another mycotoxicosis not seen for decades is alimentary toxic aleukia, which was common during the 1930s and 40s (1932 to 1947) in the USSR. This disease was caused by trichothecenes produced by *Fusarium* species and was held responsible for the death of nearly 100000 human beings (Gajdusek 1953; Joffe 1978). However, with increasing knowledge and available databases, a relationship is being tried worldwide to correlate the presence and occurrence of recently detected mycotoxins with historical outbreaks, which might assume future importance when exploring and studying newer mycotoxins.

Types of Mycotoxins

Aflatoxins

Aflatoxins are highly toxic, mutagenic, teratogenic, and carcinogenic compounds that are produced as secondary metabolites by fungi belonging to several *Aspergillus* species, mainly *A. flavus* and *A. parasiticus* (Groopman and others 1988; Massey and others 1995; Romagnoli and others 2007; O'Riordan and Wilkinson 2008). Aflatoxins have a high presence in tropical and subtropical regions where humidity and temperature conditions are optimal for toxin production. The name aflatoxin has been derived from the combination of "a" for the *Aspergillus* genus and "fla" for the species *flavus*, and toxin meaning poison (Ellis and others 1991). Discovery of aflatoxins dates back to the 1960s following the severe outbreak of turkey "X" disease (in the

U.K.) that resulted in the death of more than 100000 turkeys and other farm animals. The cause was attributed to feed (Brazilian peanuts) contaminated with *A. flavus*. Aflatoxins are encountered in a wide range of important agricultural commodities, including cereals (maize, sorghum, pearl millet, rice, wheat), spices (chillies, black pepper, coriander, turmeric, ginger), oilseeds (groundnut, soybean, sunflower, cottonseed), tree nuts (almond, pistachio, walnut, coconut), milk (human and animal), and butter.

Until now, nearly 18 different types of aflatoxins have been identified wherein the major ones include aflatoxin B1, B2, G1, G2, and M1. Fungal species belonging to *Aspergillus flavus* typically produce AFB1 and AFB2, whereas *A. parasiticus* produces AFG1 and AFG2 as well as AFB1 and AFB2. The 4 major aflatoxins (aflatoxin B1, B2, G1, and G2) are based on their fluorescence under blue or green light and their relative mobility during separation by thin-layer chromatography (TLC) (Stroka and Anklam 2000; Bennett and Klich 2003). Four other types of aflatoxins, M1, M2, B2A, G2A, that are produced in minor amounts, have been isolated from cultures of *A. flavus* and *A. parasiticus*. A number of closely related compounds, aflatoxin GM1, parasiticol, and aflatoxicol are produced by *A. flavus*.

Aflatoxin-producing fungi show wide variations in their growth requirements. For example, the minimum temperature range for growth of *A. parasiticus* is 6 to 8 °C and maximum is 44 to 66 °C, optimum being 25 to 35 °C (Diener and others 1982), while *A. flavus* can produce toxin between 12 and 42 °C and its optimum is 28 to 30 °C (Brackett 1989). Presently, it is estimated that human consumption of aflatoxins ranges between 0 and 30,000 ng/kg/d with an average intake of 10 to 200 ng/kg/d (Revankar 2003). The maximum acceptable levels of AFB1 in cereals, peanuts, and dried fruits, either for direct human consumption or as an ingredient in foods, has been set by the European Committee Regulations (ECR) as 4 ppb for total aflatoxins (AFB1, AFG1, AFB2, and AFG2) and 2 ppb for AFB1 alone (Moss 2002; Stroka and Anklam 2002). Out of the nearly 18 different types of aflatoxins identified to date, the Intl. Agency for Research on Cancer (IARC) has classified 4 aflatoxins (AFB1, AFG1, AFB2, AFG2) as Group 1 carcinogens (Chiavaro and others 2001).

Aflatoxins in milk. Aflatoxin contamination in milk and its products is of extreme importance and is a serious problem, as most of the human species as well as animals, particularly the young nurturing ones, are dependent on milk as a part of complete basal nutrition. Infants are particularly more sensitive to toxins than adults. The IARC (1993a) categorizes AFM1 as a possible human carcinogen. The European Communities and the Codex Alimentarius have fixed the limit of AFM1 intake to a maximum of 50 ng/kg (Anonymous 2001). Compared to AFB1, AFM1 is rather less carcinogenic and mutagenic; however, it has been reported to exhibit a high level of genotoxic activity in animals (JECFA 2001).

Several reports are available wherein AFM1 has been found in milk. It has been detected in breast milk and in cord blood and maternal blood in African countries (like in Sudan, Ghana, and Kenya), the Guangi Xi region of China (Galvano and others 1996), UAE (Abdulrazzaq and others 2003), Turkey (Keskin and others 2009), Australia, and Thailand (El Nezami and others 1995). Also, reports are available on the high contamination of AFM1 in milk in a few EU countries (between 28 and 1012 ng/kg; Markaki and Melissari 1997; Martin and Martin 2000). Recently, AFM1 has also been detected in powdered milk, pasteurized milk, ultra-high-treated milk, and in other milk-based products (Montagna and others 2008; Ghazani 2009; Shundo and others 2009).

Contamination of milk by AM1 might occur in 2 ways, directly due to intake of contaminated feeds by animals that might pass into the milk, or indirectly following contamination of milk and milk products with fungi (Applebaum and others 1982; Blanco and others 1993; Barrios and others 1997; Sarimehmetoolu and others 2003; Driehuis and others 2008; Sugiyama and others 2008). However, it should be noted that aflatoxin M1 is a metabolite of aflatoxin B1, and therefore the possibilities of any direct carryover of AFM1 from feed to milk could be ruled out. It is generally recognized that contamination of milk and milk products with AFM1 varies according to geographical location (dry or wet) and season (hot or cold). Lafont and others (1980) reported that the carryover of aflatoxins from animal feed to milk is less than 1% in cows and varies between 0.14% and 0.95%, which is dependent not only on the individual animal but also on the lactation stage of the animal.

Aflatoxins in raw drugs. Even though considerable advances have been achieved in modern medicine, there has been a renewed interest in the use of traditional plant-based products for a variety of therapeutic purposes (Rates 2001). Currently, a large share in the health care market has been taken over by products based on the popularity of health foods (nutraceuticals/functional foods) of plant origin (Johnson 1997). Contamination of crude drugs of plant origin (as in Ayurvedic and Chinese medicine, and others) incurs heavy economic losses in the tropics and subtropics. The conventional methods of collection, storage, and marketing usually promote the association with several toxigenic molds (Roy and others 1987). Several reports are available on aflatoxins contaminating raw drugs of plant origin. The potential of producing aflatoxins (AFB1) by some 20 strains of *Aspergillus flavus* contaminating raw drugs has been reported by Chourasia (1990) who reported levels ranging between 0.09 and 0.88 μg/mL of the culture filtrate. Roy and others (1988) analyzed common drug plants to detect aflatoxin contamination. Out of 15 samples analyzed, 14 were positive for aflatoxins ranging between 0.09 μg/g in *Acacia catechu* and 1.20 μg/g in *Piper nigrum*. The researchers also reported that out of 158 isolates of *A. flavus* from the drug-yielding plants 49 were toxigenic in nature and the amount of AFB1 produced by the toxigenic isolates ranged between 0.86 and 5.24 μg/mL. Similar observations on the contamination of medicinal plant samples have been reported by Aziz and others (1998). They examined a total of 84 medicinal plants and spices and reported 17 samples to be contaminated by AFB1 which ranged between 10 and 160 μg/kg. Ali and others (2005) evaluated 23 commercial samples of traditional herbal medicines from Malaysia and Indonesia and found the presence of aflatoxin in most of the samples. The mean levels of AFB1, AFB2, and AFG1 in positive samples were 0.26 (70%), 0.07 (61%), and 0.10 (30%) μg/kg, respectively, and one of the samples was positive for AFG2 at a level of 0.03 (4%) μg/kg.

Though these are just a few of the examples to cite, an alarming increase among consumers relying on food of plant origin, renders it a necessity to undertake safety measures against fungal contamination and mycotoxins that might be present in raw materials possessing nutraceutical value.

Aflatoxins in eggs. Consumption of egg as a rich source of protein is well known. Reports available on aflatoxin contamination in eggs are scarce (Micco and others 1987; Pandey and Chauhan 2007; Aly and Anwer 2009; Herzallah 2009).

Micco and others (1987) reported that AFB1 bio-transformation in the liver of hens could generate a variety of toxic hydroxylated metabolites that can be transferred to eggs. Hens that are fed with contaminated feeds with more than 3300 mg/kg of AFB1 over a period of 28 d were reported to produce contaminated eggs (Wolzak and others 1985). Also, reports are available on the presence of aflatoxin residues transmitted into eggs (Qureshi and others 1998). However, since 1974 the EC has set a limit of 20 μg AFB1/kg of layer feed. A study by Pietri and others (2001a) indicated that if this official limit is respected, then no trace of AFB1 or its metabolites can be detected in eggs.

Health risks associated with aflatoxin consumption

Aflatoxin poisoning (aflatoxicosis). Consumption of foods/feeds contaminated with high levels of aflatoxins may lead to acute aflatoxicosis and regular intake, even at low levels (ppb), is reported to be responsible for stunting and loss of weight among children, and in some cases has led to the development of hepatocellular cancer (Bhat and Vasanthi 2003; Hall and Wild 2003). Aflatoxins have also been linked with kwashiorkor, a protein-energy malnutrition disease (Adhikari and others 1994). Reports are available wherein AFB1 and aflatoxicol (a metabolic product of AFB1) were detected more frequently in the serum, liver, urine, and stools of children suffering from kwashiorkor (Apeagyei and others 1986; Hendrickse and Maxwell 1989; De Vries and others 1990). The role of aflatoxins in the development of Reye's syndrome (encephalopathy with severe lesions in kidney and liver following influenza or varicella) has never been proved, regardless of the frequent detection of aflatoxins in the liver of children who have died of this disease (Dvorackova and others 1977; Hogan and others 1978; Casteels-van Daele and Eggermont 1994). Egal and others (2005) have reported that 90% of children in West Africa (Benin and Togo) are exposed to aflatoxins due to consumption of contaminated maize and groundnuts, which leads to a measurable impairment of child growth.

Severe liver lesions in malnourished adults during the 1970s, with fatal outcome have been reported after severe cases of acute aflatoxicosis in parts of Asia and Africa (Krishnamachari and others 1975; Bhat and Krishnamachari 1977). Aflatoxins are perceived to be co-factors in the higher incidence of liver cancer (hepatocellular carcinoma) along with hepatitis-B virus in tropical Africa (FAO 1997). Hepatitis-B virus (HBV) interferes with the ability of hepatocytes to metabolize aflatoxins, and an aflatoxin M1-DNA conjugate exists for a longer time in the liver, increasing the probability of damage to tumor suppressor genes. This effect is synergistic with the resulting damage far greater than just the sum of aflatoxins or HBV individually (Williams and others 2004).

Among the animals, monogastric farm animals such as poultry and swine are at particular high risk, as a large part of their basal diet consists of cereals. Also, these animals lack the ruminal reservoir of a multitude of microorganisms which can degrade the toxins before they are absorbed by the intestine. The susceptibility of these animals to toxin contamination depends on species, age, and diet. Bonomi and others (1994) have reported that ingestion of aflatoxins-contaminated feeds in farm animals can lead to substantial losses in productivity and meat quality. The major symptoms of acute aflatoxicosis in mammals include lethargy, ataxia, rough hair coat, and enlarged fatty liver. With chronic exposures, early symptoms of aflatoxin poisoning include reduced feed efficiency and milk production and decreased appetite (Nibbelink 1986).

The FDA tolerance level for aflatoxin in human food is 20 μg/kg; for breeding livestock feed 100 μg/kg; breeding cattle feed 20 μg/kg; and poultry feed 300 μg/kg (Park and Liang 1993). According to the FAO/WHO expert committee recommendations (1990) the tolerance limit for AFB1 is 5 μg/kg food products, for AFM1 it is 0.05 μg/kg milk products, and for B1+G1+B2+G2 it is 15 μg/k, as for example in raw peanuts.

Ochratoxin-A (OTA)

Ochratoxin-A (OTA; molecular weight 403.8) is the 2nd most important mycotoxin; it is produced by the fungi *Aspergillus ochraceus* and *Penicillium verrucosum*. It has also been reported that isolates of *Aspergillus niger* as well as *A. carbonarius* are capable of producing OTA (Varga and others 1996; Heenan and others 1998). OTA generally appears during storage of fresh produce (in cereals, coffee, cocoa, dried fruit, spices, and also in pork) and occasionally in the field on grapes. It may also be present in some of the internal organs (particularly blood and kidneys) of animals that have been fed on contaminated feeds. In temperate climates OTA is produced by Penicillium verrucosum, while a number of *Aspergillus* spp. (*A. ochraceous*, *A. niger*, *A. sulphureus*, *A. sclerotiorum*, and *A. melleus*) are known to be responsible for its production in tropical and pan-tropical regions of the world. Moss (1996) isolated Petromyces alliaceus from onion and has shown it to be a good OTA producer under laboratory conditions. OTA has also been shown to be biosynthesized by Aspergillus carbonarius in apple and grape juices (Pitt 2000).

OTA in milk. OTA contaminations in human milk are common in the temperate and cool areas of the world, including Italy (Micco and others 1995; Miraglia and others 1995; Galvano and others 2001), Switzerland (Zimmerli and Dick 1995), Germany (Gareis and others 1988), and France (Boudra and others 2007). OTA levels in milk from cows in Norway were sufficient to cause a higher intake of OTA than the suggested tolerable daily intake of 5 ng/kg body weight/d (Skaug 1999). OTA contamination in milk from tropical/ hot regions have also been reported in India (Rastogi and others 2004), Egypt (El-Sayed Abd Alla and others 2000), and Brazil (Shundo and others 2009). High levels of OTA in human milk have been reported by Jonsyn and others (1995) wherein, in some instances, infants in Sierra Leone were being exposed to OTA levels that exceeded the permissible limits in animal feed in some of the developed countries. In Norway, Skaug and others (1998, 2001) examined the relationship between OTA contamination of human milk and dietary intake and concluded that the risk of OTA was related to dietary intakes (cereals, processed meat products, cheese, cakes, cookies, and juices).

OTA in wine, coffee, tea, cocoa, and herbs. Zimmerli and Dick (1996) in a survey of 133 wines obtained from retail outlets in Switzerland reported, for the 1st time, the occurrence of OTA in wine. OTA was higher in red wines than in white and rose wines. Also, Otteneder and Majerus (2000) have shown OTA to be more common in red wines than in rose and white wines and attributed this to the differences in the winemaking procedure. Impact of geographical effects on the occurrence of OTA in red wines has been reported by Otteneder and Majerus (2000) in Germany; Pietri and others (2001b) in Italy; Stefanaki and others (2003) in Greece; Ratola and others (2004) in Portuguese wines; and in Chilean vineyards (Díaz and other 2009). The occurrence and the concerns pertaining to OTA in grapes and wine have been extensively reviewed (Battilani and others 2006; Leong and others 2006; Hocking and others 2007). Recently, Flajs and others (2009) employed the enzyme-linked immunosorbent assay (ELISA) and high-performance liquid chromatography (HPLC) for OTA analysis in "must" and in "wine" samples collected in Croatia. Their results revealed that OTA concentrations in must (range 19 to 50 ng/L) were higher than in the wines (range 0 to 21 ng/L). The CEC (2002) has fixed an OTA limit of 10 μg/kg in dried wine fruits. Except for Italian red wines, the mean concentration of OTA in wine in the EU countries does not exceed 100 ng/L (Varga and Kozakiewicz 2006).

With regard to coffee and cocoa, the occurrence of OTA is of main concern as the populations dependent on these products are present worldwide. In one of the recent reports, both the wet and dry methods of coffee processing have been reported to represent high levels of OTA (up to 5 μg/kg) (Batista and others 2009).

Contamination of cocoa beans by OTA has been reported (Jørgensen 2005; Vecchio and Finoli 2007; Amézqueta and others 2008a). Cocoa bean powder is also known to contain OTA wherein it was in lower levels in cocoa butter than in the nonfat fraction (powder or cake) (Beckett 1994). A 1998 survey in

the U.K. on exposure of consumers to OTA in cocoa powder and chocolate produced low results which were of little concern (Britannia Foods, http://www.britanniafood.com).

With regard to tea, except for one SCOOP report (Miraglia and Brera 2002) not much information is avaible on OTA contamination. Based on this report on a survey (between 1995 and 1998, for 131 samples) in Germany, 8 tea samples showed OTA contamination (0.28 to 10.3 μg/kg). OTA contamination of medicinal herbs has also been reported to occur under inadequate storage conditions (Petzinger and Ziegler 2000; Rizzo and others 2004).

Associated health risks of OTA. OTA is deemed to be nephrotoxic, immuno-suppressive, carcinogenic, and teratogenic. The IARC has classified ochratoxin A as a compound possibly carcinogenic to humans (Group 2B) (IARC 1987). OTA is also the causal agent for both endemic nephropathy and urothelial tumors (Castegnaro and others 1990). OTA as a causative agent of endemic nephropathy has been reported to occur in rural populations of some regions of Bosnia, Bulgaria, Croatia, Herzegovina, Romania, and Yugoslavia (Krogh 1974). Worldwide, nearly 20,000 people are either suffering from or are suspect of having endemic nephropathy (Pleština 1992), and the main symptoms include bilateral, primarily chronic, lesions of the renal cortex (tubular degeneration, interstitial fibrosis, and hyalinization of the glomeruli) (Vukelić and others 1992). Recently, Zhang and others (2009a) have reported induction of apoptosis in neuronal cells that might be a contributing factor to the pathogenesis of neurodegenerative diseases like Alzheimer's disease and Parkinson's disease.

OTA has been detected in blood samples and was found to be more frequent and in higher concentrations in inhabitants from endemic regions (Petkova-Bocharova and Castegnaro 1991; Maaroufi and others 1995). In Italy, significantly higher OTA concentrations were found in patients treated with dialysis than in transplanted ones and in patients with chronic glomerulonephritis, renal calculus, cysts, chronic renal failure, and healthy subjects (Breitholtz-Emanuelsson and others 1994). In endemic regions of Bulgaria, Croatia, and Yugoslavia the incidence of urothelial tumors of the pelvis and urethra was 50, 90, and 100 times greater than in nonendemic regions (Chernozemsky 1991). Studer-Rohr and others (2000) have reported that, in the human body, OTA has a long half-life of 35 d after a single oral dosage attributed mainly to adverse elimination by toxicokinetics. In the human body, OTA is neither stored nor deposited; however, laboratory studies have confirmed that it is distributed via the blood mainly to the kidneys (Hult and Fuchs 1986).

In animals, OTA levels in pigs are of major concern especially in northern European countries. Available reports, as an outcome of several surveys, indicated low levels of OTA. Some of these surveys were performed in Germany (pork sausages) (Frank 1991), in France (pig liver) (Dragacci and others 1999), Denmark (pork meat) (Jorgensen and Petersen 2002), and in Italy (ham) (Chiavaro and others 2002). As OTA is fat-soluble, it is not readily excreted and accumulates in the tissues of animals, particularly pigs.

Lower concentrations of OTA are considered to be nephrotoxic in most mammals. Even though several epidemiological studies have been conducted, a relationship between OTA exposures with human nephropathies has never been established (WHO 2001). Recently, the toxicity and carcinogenicity of OTA in animals and humans have been reviewed by Annie and Manderville (2007). They detailed that OTA is nephrotoxic and is suspected of being the main etiological agent responsible for human Balkan endemic nephropathy (BEN) and associated urinary tract tumors. Fungi belonging to *Penicillium viridicatum* and *P. verrucosum* play a major role in porcine nephropathy and are an important etiological agent in Balkan endemic nephropathy (Krogh 1987).

Fusariotoxins (*Fusarium* toxins)

Fungi belonging to the genus *Fusarium* are associated with the production of fusariotoxins. There are 2 types of toxins produced by these fungi, namely, metabolites that have properties similar to the hormone estrogen such as ZEN (F-2 toxin) and other ones that are the nonestrogenic trichothecenes. There are several synonyms related to fusariotoxin poisoning: fusario-mycotoxicosis, trichothecene mycotoxicosis, T-2 toxicosis, vomitoxicosis, and ZEN toxicosis.

Fumonisins

Fumonisins (synonym: Macrofusine, molecular weight 721.8) are the most recently isolated mycotoxins (first discovered in 1988) that are known to possess high cancer-inducing properties (Gelderblom and others 1988; Bennett and Klich 2003). This toxin was originally isolated from *Fusarium moniliforme* (present name: *F. verticillioides* Sheldon.) and from *Fusarium proliferatum*, a common fungal contaminant of corn (maize) throughout the world (Gelderblom and others 1988; Castelo and others 1998). Of late, 6 different types of fumonisins (FA1, FA2, FB1, FB2, FB3, and FB4) have been reported, wherein the "A" series is the amides and the "B" series possesses a free amine (Gelderblom and others 1992). Even FC1 has also been reported in the "C" series. Fumonisins are also known to be produced by *F. proliferatum* and other related species, especially on maize that has been previously infected during its preharvest stages. Reports are available on the presence of fumonisins in several agricultural products like corn, cornflour, dried milled maize fractions, dried figs, herbal tea, medicinal plants, bovine milk, and others (Omurtag and Yazicioğlu 2004; Gazzotti and others 2009; Karbancioglu-Güler and Heperkan 2009; Pietri and others 2009; Seo and others 2009), indicating high risks to public health. It has been estimated that consumption of fumonisin B1 (FB1) by humans in the U.S. is about 80 ng/kg/d (WHO 2002). Occurrence of fusarial toxins in ensiled grass or hay, originating mainly from preharvest contamination, has been reported by Baath and others (1990).

Associated health risks of fumonisins. Consumption of fumonisin-contaminated foods by humans has been correlated with increased incidence of esophageal cancer in various parts of South Africa, Central America, Asia (Chelule and others 2001; Marasas and others 2004), and among the black population in Charleston, South Carolina (Sydenham and others 1991). Similar observations have been reported from China (Abnet and others 2001), Italy (Franceschi and others 1990), and Brazil (Van der Westhuizen and others 2003). This toxin has also been reported to be immunosuppressive (WHO 2002). The IARC (International Agency for Research on Cancer 1993c) has classified fumonisins under group 2B (possibly carcinogenic to humans). Among the various types, FB1 is known as a cancer promoter and plays an important role in carcinogenesis in humans (Chu and Li 1994). Fumonisin consumption has also been related to neural tube defects in human babies as they (especially FB1) reduce the uptake of folate in different cell lines (Marasas and others 2004).

In the concluding report of the recent task force of the U.S. Council for Agricultural Sciences and Technology (CAST 2003), additional research into the relationship between fumonisin, sphingolipid metabolism disruption, and apoptosis has been asked for to understand the potential carcinogenicity of fumonisins in human health. In a preliminary evaluation report, experts from Nordic countries (Denmark, Norway, Sweden, Finland, and Iceland) have concluded that human daily intake of fumonisins should be less than 1 μg/kg body weight/d (Petersen and Thorup 2001). According to Miller and others (1996), the recommended levels of fumonisin concentration in animal feed is: 5 μg/g for horses and other equine species, 10 μg/g for porcine species, 50 μg/g for cattle, and 50 μg/g for poultry.

Among the animals, in almost all the species tested, FB1 has been shown to be hepatotoxic and nephrotoxic. In most of the animal species, fumonisins are poorly absorbed from the digestive tract and are rapidly distributed and eliminated (WHO 2002). Primary symptoms observed are changes in histology, either in the liver or kidney of fumonisin-treated animals, wherein increased apoptosis followed by regenerative cell proliferation occur. Even though the toxicity of fumonisin is low, it has been linked with several diseases in domestic animals: equine leukoencephalomalacia (ELEM) in horses, toxic feed syndrome in poultry, and porcine pulmonary edema syndrome (PPE) in swine (Ross and others 1992, 1993; Norred and Voss 1994). These diseases involve disturbed sphingolipid metabolism and cardiovascular malfunction. In animals, fumonisin is also known to impair the basic immune function, to cause liver and kidney damage, to be a heart risk, and to reduce weight gains, and thereby augmenting the mortality rates (Casteel and others 1994; Norred and others 1998).

Jones and others (1994) have shown that consumption of FB1 causes respiratory difficulties in swine. *Fusarium moniliforme* that produces mutagenic fusarins and fumonisins has been reported to be responsible for disease symptoms in horses and donkeys (Wilson and others 1991). In dairy cattle, reduction in milk production has been reported, even at low levels of 100 ppm (Diaz and others 2000). However, a detailed survey on the health effects on long-term consumption of Fumonisin-contaminated feedstuffs might give a broader insight on the same.

Some of the *Fusarium* species (*F. avenaceum*, *F. poae*, and *F. tricinctum*) are also known to produce the mycotoxins beauvericin (BEA) and enniatins (ENNs) (Logrieco and others 2002; Thrane and others 2004), which are the cyclic hexadepsipeptides consisting of alternating hydroxyl-acid and N-methylamino acid residues. These 2 types of toxins have been isolated from grains obtained from Scandinavia (Uhlig and others 2007). Jestoi (2008) has reported the occurrence of BEA contamination in cereals obtained from other locations.

Zearalenone and associated health risks

ZEN (molecular weight: 318.4) and zearalenol are estrogenic resorcylic acid lactone compounds produced by *Fusarium* species (Diekman and Green 1992). Among the human population, children are the most affected due to consumption of ZEN-contaminated foods (mainly cereals and cereal-based food products). This toxin has worldwide distribution and can contaminate most of the cereals like barley, maize, oats, sorghum, and others. ZEN has also been detected in wheat and in bread (Tanaka and others 1988; Aziz and others 1997).

Associated health risks. This toxin has been implicated in several incidents of precocious pubertal changes (Kuiper-Goodman and others 1987). In domestic animals, ZEN poisoning has been associated with hyperestrogenic or feminizing syndromes. Pigs are generally the most affected and it causes genital/urinary problems (Zöllner and others 2002; Dänicke and others 2005). The major symptoms of ZEN poisoning include hyperemia and edematous swelling of the vulva in prepubertal gilts and in severe cases prolapse of the vagina and rectum. In some cases, atrophy of the testes in male pigs occurred with decreased libido and hypertrophy of the mammary glands (Marasas and others 1984). In general, poultry are the least affected after ingestion of ZEN. However, swine showed acute symptoms in prepubertal gilts that included enlarged mammae, swelling of uterus and vulva, and atrophy of the ovaries. In severe cases, prolapse of the vulva and rectum have occurred. Effects of ZEN and/or tamoxifen (TAM) on swine and mink reproduction have been studied by Yang and others (1995). Results of their study indicated that TAM was not effective in ameliorating the hyperestrogenic effects of ZEN in swine and mink, but rather acted as an estrogen agonist. Enlarged mammae and atrophied testes were exhibited due to ZEN intake in boars (Flannigan 1991). Consumption of contaminated feed by dairy cows did not result in any of the health hazards to humans (Wood 1992). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established a provisional maximum tolerable daily intake for ZEN to be 0.5 μg/kg of body weight (JECFA 2000).

Vomitoxin (DON) and associated risks

DON (12, 13-epoxy-3,4,15-trihydroxytrichothec-9-en-8-one; molecular weight: 240.26) is commonly known as alpha-methyl phenethylamine, amphetamine deoxynivalenol, 4-deoxynivalenol (DON), or as RD-toxin. Vomitoxin is commonly encountered in food products and feeds prepared from contaminated corn and wheat (Rotter and others 1996). This toxin is the most frequently detected *Fusarium* toxin produced by *Fusarium graminearum*. DON has been reported in most parts of the world (Canady and others 2001) and in the U.S. alone computer simulations have shown annual costs for DON to be 637 million dollars in crop losses of wheat and corn and 18 million in feed losses (CAST 2003). Vomitoxin is considered to be highly stable and can survive various food processing methods (such as milling, powdering). DON and its metabolite de-epoxy-DON have also been reported to be present in low amounts in eggs (Sypecka and others 2004; Valenta and Danicke 2005) and in beer at low levels (Scott 1996). Recently, low levels of deoxynivalenol (2.6 to 17.9 ng/g) and its metabolite de-epoxy-DON (2.4 to 23.7 ng/g) have been reported in 20 home-produced egg samples collected in Belgium (Tangnia and others 2008).

Consumption of vomitoxin-contaminated products has been correlated with reduced milk production in dairy cattle, vomiting in swine, inhibition of reproductive performance and immune function in several animal species, along with induction of apoptosis in mice (Jones and others 1994; Zhou and others 2000). Maximum limit of 1 ppm of DON for bran, flour, and germ meant to be used for human consumption has been set by the U.S. Food and Drug Administration (FDA) (Proctor and others 1995). Maximum tolerated levels in the range of 500 to 1000 μg/kg (0.05 to 0.1 ppm) for DON in most other food products have also been set (van Egmond and Jonker 2004). The maximum level of DON in raw cereals allowed by the European Union is 1250 μg/kg (Food Safety Authority of Ireland, http://www.fsai.ie). In humans, the effects of DON on health are not completely understood. However, some toxicity information after consumption of DON-contaminated cereals, grains, and other products has been reported (Yoshizawa 1983; Luo 1994; Meky and others 2001; Sun and others 2002).

Trichothecenes and associated health risks

Similar to ZEN and vomitoxin, trichothecenes are also produced by *Fusarium* species. Trichothecenes are also known to be produced by other fungal genera like *Trichoderma*, *Trichotecium*, *Myrothecium*, and *Stachybotrys* (IPCS 1990). Trichothecenes are sesquiterpenoid mycotoxins that accumulate in kernels of infected spikelets rendering the grain unsuitable for human or animal consumption (Harris and others 1999; Langevin and others 2004). Trichothecenes are usually found to be contaminants of cereals and their derivatives (Foroud and Eudes 2009).

Nearly 160 trichothecenes have been identified and are classified into 4 groups depending on their chemical structure. The major ones are T-2 and HT-2 toxins (group A) and nivalenol (NIV) (group B).

Associated health risks of trichothecenes. Trichothecene mycotoxicosis (scabby grain toxicosis) has been reported to occur within hours after ingestion of contaminated foods (wheat, corn, rice). Reports available indicate that poisonings have occurred in Japan (Ueno 1971), China (Wang and others 1993), and India (Ramakrishna and others 1989). *Fusarium* head blight, one of the serious epidemics in North America during the 1990s, caused an estimated economic loss of 3 billion dollars in the U.S. alone (McMullen and others 1997). The main symptoms of trichothecene mycotoxicosis are abdominal pain, nausea, vomiting, diarrhea, dizziness, and headache.

Trichothecenes have strong impacts on the health of animals and humans due to their immunosuppressive effects. Group-A trichothecenes are of major concern as they are more toxic than the type B trichothecenes. In animals, these mycotoxins are held responsible for reduced feed uptake, vomiting, and immuno-suppression. In instances of chronic poisoning, Group-A trichothecenes produce significant changes in the blood cell count and in immune function. Among the group A, T-2 toxin is the most important one. It is readily metabolized by the gut microflora of mammals into a number of other metabolites. HT-2 toxin is a primary metabolite in the gut and is absorbed into the blood after ingestion of T-2 toxin. Metabolism continues in the liver along with biliary excretion, resulting in a substantial combined first-pass effect in the gut and liver (WHO 2002). The principal effects of perturbed protein synthesis from T-2 toxin are usually observed in the immune system and include changes in leukocyte counts, delayed hypersensitivity, depletion of selective blood cell progenitors, and depressed antibody formation (WHO 2002). Compounds of the other group of trichothecenes (Group B) generally cause a reduction in dietary consumption, especially in pigs.

The joint FAO/WHO expert committee on food and additives (JECFA 2001) has established a permissible limit of 1 μg/kg body weight and 0.061 μg/kg body weight for T-2 toxin and HT-2 toxin, respectively.

Patulin and associated health risks

Generally, fruits and vegetables are easily contaminated by toxigenic molds leading to quality deterioration (Drusch and Ragab 2003; Moss 2008). Agronomic practices employed during fruit cultivation and juice making have been reported to significantly influence the occurrence and production of patulin and citrinin (Martins and others 2002).

Patulin (molecular weight: 145.1) is a mycotoxin that forms the smallest group of toxic metabolites referred to as polyketides, and is reported to be produced by fungi belonging to *Aspergillus* spp., *Penicillium expansum*, and *Paecilomyces* and *Byssochlamys* spp. (*Byssochlamys nivea*, *B. fulva*) (Dutton and others 1984; Fuchs and others 2008; Moss 2008; Cunha and others 2009). Patulin is being considered as a "possible toxin" in Europe and New Zealand (Lacey 1991) and is regarded as the most dangerous mycotoxin in fruits, particularly apples, pears, and their products (Frisvad and Thrane 1996; Kabak and others 2006; Murillo-Arbizu and others 2009). Patulin is mainly associated with surface-injured fruits, which renders them vulnerable to fungal infection, mainly by *Penicillium* spp. (Sewram and others 2000).

Patulin is also reported to be present in silage/feeds intended for ruminants; and it has been reported to be responsible for the deaths of cattle in France (Moreau 1979). Schneweis and others (2000) reported that lower concentrations of patulin found in silage will rarely cause the typical neurotoxic signs in animals, but might exert detrimental effects on the rumen microflora, mainly because of its antimicrobial activity. The occurrence of patulin in a raw material has been directly related to some of such extrinsic environmental factors as variations in temperature and water activity (Northolt and others 1996).

Associated health risks of Patulin. Patulin toxin is reported to affect the functions of gastrointestinal tissue, kidney, liver, and the overall immune system (Escoula and others 1988; Speijers and others 1988; Wichmann and others 2002). This toxin is regarded to be genotoxic, carcinogenic, can induce oxidative stress response in mammalian cells, generate reactive oxygen species (ROS), and induce apoptosis in human leukemia cells (HL-60) (Barhoumi and Burghardt 1996; Schumacher and others 2006; Liu and others 2007; Wu and others 2008). Contradictorily, Wouters and Speijers (1996) have reported patulin to be noncarcinogenic. However, the IARC has classified patulin as category 3; not classifiable as to its carcinogenicity in humans (IARC 1993b).

The permissible limit for patulin in apples and their products in the U.S. and EU has been set at 50 ppb (FDA, http://www.fda.gov/ora/compliance ref/cpg; EUROPA, http://europa.eu.int/eur-lex/en/archive/2004). A permissible limit of patulin content in apple juice, and as juice ingredients in other beverages, has been set at 50 μg/kg, in solid apple products at 25 μg/kg, and in baby food of 10 μg/kg (Mycotoxin Certification Standard 2008, www.mycotoxin-certification.eu).

Citrinin

Citrinin (molecular weight: 250.25) is the secondary metabolite produced by *Penicillium expansum* and some of the *Aspergillus* and *Monascus* spp. (Kurata 1990; Vinas and others 1993; Li and others 2003; Kim and others 2007; Abramson and others 2009). Citrinin often occurs as a common contaminant of food and feed (fruits, barley, maize, cheese, dietary supplements) (Manabe 2001; Schneweis and others 2001; Bailly and others 2002; Bennett and Klich 2003; Meister 2004). Barley, as well as other cereals employed for producing beer, has been reported to be a good substrate for the growth of many toxigenic fungi capable of producing citrinin (Galvano and others 2005).

Associated health risks of citrinin. In humans, reported health risks due to citrinin are scarce. Some reports do indicate citrinin's association with mycotoxic nephropathy in swine and Balkan endemic nephropathy in humans (IARC 1986; Chernozemsky 1991; Hald 1991). However, details available on the toxic effects of citrinin in animals show its nephrotoxic nature as well as teratogenic effects in rabbits, poultry, dogs, and rats and mice along with induction of apoptosis (Kogika and others 1993; Bennett and Klich 2003; Yu and others 2006; Chan 2007; Kumar and others 2007; Singh and others 2007).

Alternaria toxins

Mycotoxins produced by fungi belonging to *Alternaria* species are referred to as *Alternaria* toxins. *Alternaria* species commonly occur during the pre- and postharvest stages of fruits and vegetables. These fungi are capable of producing a range of mycotoxins and other less toxic metabolites. The most important toxin-producing species is *Alternaria alternate*, which usually contaminates cereals, sunflower seeds, rapeseed, olives, and fruits.

Among the various *Alternaria* toxins, alternariol (AOH) and alternariol monomethyl ether (AME) are reported to be the most toxic (Combe and others 1970; Pero and others 1973). The toxins AOH and AME have been detected in sorghum (Ansari and Shrivastava 1990), sunflower seeds (Chulze and others 1995), barley, wheat, oats (Gruber-Schley and Thalmann 1988; Azcarate and others 2008), olives, tomatoes, mandarin oranges, peppers, and melons (Logrieco and others 1988).

Also, apart from AOH and AME, other naturally occurring *Alternaria* toxins include tenuazonic acid, altenuene, and altertoxin. The significance of tenuazonic acid in fresh tomatoes used for the production of tomato sauce has been detailed by

Mislivic and others (1987). The other fungal species producing these toxins include *A. alternata*, *A. dauci*, *A. cucumerina*, *A. solani*, and *A. tenuissima* (Montemurro and Visconti 1992).

Associated health risks of Alternaria toxins. *Alternaria* toxins have been implicated in humans and animal health disorders. AME is reported to be cytotoxic and along with AOH has been shown to possess synergistic effects. AOH is lethal to unborn mice at levels of 100 mg/kg body weight (Pero and others 1973). Presently, no limits are set for *Alternaria* mycotoxins as various surveys conducted have shown their natural occurrence in foods to be very low and the prospects for direct human exposure are limited.

Claviceps purpurea /ergot toxins and associated health risks

Sclerotia of fungi belonging to the genus *Claviceps* produce ergot alkaloids. A sclerotium is a dark-colored, hard mycelial mass that establishes itself on the seed or kernel of the plant. Usually, wild grass species are considered to favor the cross-contamination of *C. purpurea* onto the cultivated grass (Poo and Araya 1989). Apart from *Claviceps*, ergot alkaloids are also produced as secondary metabolites by fungal species belonging to *Penicillium*, *Aspergillus*, and *Rhizopus* (Flieger and others 1997). The human disease ergotism is entirely influenced by the type of alkaloids present (Burfening 1973) (The term ergotism has occassionally also been used to denote the plant disease).

Associated health risks of ergot toxins. The *Claviceps purpurea* toxin is of not much significance today and human ergotism is extremely rare, which might be attributed to 2 reasons: primarily, due to the recent improvements in the cleaning and milling processes that are able to remove most of the ergots leaving very low levels of the alkaloids in the flour, and, second, these alkaloids might be relatively unstable and can be destroyed easily by conventional processing (baking, cooking, milling). However, it is necessary to cover a few aspects on *C. purpurea* toxins.

Earlier reports are available on ergot poisoning of domestic animals by ingestion of feeds containing *Claviceps purpurea* sclerotia (Groger 1972; van Rensburg and Altenkirk 1974). Ergot alkaloids have been reported in sleepy grass (*Stipa robusta*) which is common in the South-Western parts of the U.S. (Cheeke 1995). The most common intoxications associated with ergot alkaloids is "*fescue toxicosis*" wherein the "*tall fescue*" (*Festuca arundinacea*) pasture grass common to the U.S. was infected by *Claviceps* spp. that produced ergovaline (an alkaloid), which proved to be toxic to animals (Botha and others 2004). These ergot alkaloids have also been reported in pasture grasses of Northern Europe (Fink-Gremmels 2005).

Toxicity symptoms of *Claviceps* toxins include delirium, prostration, violent head pain, abscesses, and gangrene of the extremities. The toxin most likely acts as a vasoconstrictor. Some of the secondary metabolites of fungi that were used as antibiotics in earlier years are now considered toxins (Peraica and others 1999). However, with regard to ergot alkaloids, they are still being used in the treatment of Parkinson's disease, as prolactin inhibitors, in cerebrovascular insufficiency, and in migraine treatments. Ergotamine, a major alkaloid involved, possesses greater biological activity than the other components of ergot and is used in human medicine (mainly as a vasoconstrictor and an oxytoxic) (van Rensburg and Altenkirk 1974).

Cyclopiazonic acid and associated health risks

Cyclopiazonic acid (CPA) (molecular weight: 336.4) is a toxic secondary metabolite that was originally isolated from *Penicillium cyclopium* and later on from other fungal species like: *P. griseofulvum*, *Aspergillus flavus*, *A. versicolor*, and *A. tamarii*. Chemically, it is an indole tetramic acid. The significance of CPA is obscure; however, it is reported to naturally occur in peanuts (Urano and others 1992), corn (Lee and Hagler 1991), and in cheese (LeBars 1979).

The health risks associated with CPA is very minimal, but in high concentrations it may be acutely toxic, especially to animals. This toxin is usually encountered on consumption of contaminated cereals. It is generally claimed to be a co-contaminant with AFB1 in North America. However, due to its co-occurrence, it is believed to reduce the danger of aflatoxins by contributing towards their metabolic inhibition.

Morrissey and others (1984) have assessed the potential effects of CPA on pregnancy and fetal development in Fischer-344 rats, which were given daily doses of CPA (0, 1, 5, or 10 mg CPA/kg body weight). The researchers reported a significant decrease in feed consumption (at high dose) and the animals that died had histologic lesions in the liver, spleen, kidney, and other organs. Significant differences in skeletal development were also observed that showed retardation of ossification of cervical centra and caudal vertebrae.

Toxic effects of CPA in broiler chicks have been reported earlier (Cullen and others 1988; Kubena and others 1994; Balachandran and Parthasarathy 1996). CPA is also being assumed to induce mycotoxicoses in quail in Indonesia (Stoltz and others 1988). Only a few significant findings are discussed in the subsequent text.

Smith and others (1992) evaluated the individual and combined effects of aflatoxins and CPA in day-old Petersen x Hubbard broiler chickens to 3 wk of age. The treatments included supplementation with levels of 0 and 3.5 mg aflatoxins/kg of feed, and 0 and 50 mg CPA/kg of feed. They recorded a significant reduction in the body weight by aflatoxins, CPA, and the aflatoxins-CPA combination at the end of 3 wk. Toxicity of CPA indicated increase in weights of the liver, kidney, and proventriculus with enhancement in the levels of uric acid and cholesterol. A significant decrease in serum phosphorus was also recorded. Activities of aflatoxins and CPA combination showed an increase in weight of the liver, kidney, pancreas, and proventriculus with a decrease in concentrations of serum albumin and phosphorus. An increase in concentrations of serum glutamic oxalacetic transaminase and blood urea nitrogen, and decreases in the relative weight of the bursa of Fabricius were also observed. The postmortem results showed that chickens fed with CPA and the aflatoxin-CPA combination had thickened mucosa and dilated proventricular lumens, hard fibrotic spleen, and atrophy of the gizzard.

Kubena and others (1994) studied the effects of feeding 6 mg T-2 toxin and 34 mg CPA/kg of diet singly and in combination in male broiler chicks from 1 d to 3 wk of age. They found that the body weights were depressed by T-2 or CPA singly or after the combination of T-2 and CPA. A significant synergistic interaction between T-2 and CPA with regard to liver and kidney weights and serum cholesterol and triglyceride concentrations was recorded. However, the efficiency of feed utilization or mortality was not affected by dietary treatments. Oral lesions were observed in chicks fed diets containing CPA.

Gentles and others (1999) evaluated the individual and combined effects of OTA and CPA in Petersen x Hubbard broiler chickens from 1 d to 3 wk of age, wherein treatments of 0 and 2.5 mg OTA/kg feed and 0 and 34 mg CPA/kg feed were administered. Results showed a decrease in the body weight gain by OTA, CPA, and OA-CPA in combination at the end of 3 wk. Increased relative weights of the proventriculus and activity of creatine kinase were the main toxic symptoms of CPA. The researchers reported that exposure to OA-CPA was characterized by increased relative weights of the liver, kidney, pancreas, and proventriculus, decreased concentrations of serum albumin, total protein, and cholesterol, and with increased activity of creatine kinase and

in concentrations of triglycerides and uric acid. Postmortem examination showed thickened mucosa and dilated proventricular lumen in chickens fed CPA or OA-CPA. It was concluded that OA, CPA, and the OA-CPA combination can limit broiler performance and adversely affect broiler health.

Mycotoxins encountered in animal feeds

Sporidesmins, slaframine, stachybotryotoxins, lolitrem, and phomopsins

Sporidesmins. These are hepatotoxins (to which sheep are very sensitive) produced by *Pithomyces chartarum*, a saprophytic fungus that grows on dead grass. Sporidesmins include epidithiopiperazine-2,5-dione (ETP), a fungal toxin that can disrupt the cellular functions via oxidative alteration of cysteine residues on key proteins (Srinivasan and others 2006). In France, pastures have been shown to harbor fungi like *Pithomyces* producing sporidesmin, which causes facial eczema (a hepatogenous photosensitization) (Le Bars and Le Bars 1996). Outbreaks of pithomycotoxicosis (facial eczema) have also been reported for ruminants in the Azores Islands of Portugal after warm, humid periods during late summer and autumn (Pinto and others 2005). Death of a captive "Eastern Grey kangaroo" due to consumption of feed contaminated with *Pithomyces chartarum* is believed to have been induced by sporidesmins (Hum 2005).

Slaframine (1-acetoxy-8-aminooctahydroindolizidine). Slaframine (or slobber factor) is a mycotoxin produced by fungi belonging to the genus *Rhizoctonia* that usually attack cattle and produce drooling. Slaframine poisoning is common during cool and wet seasons, which provide ideal environmental conditions for the proliferation and growth of *Rhizoctonia leguminicola*, commonly called "black patch" indicating "bronze to black spots" or "rings" observed on leaves and stems (Burrows and Tyril 2001). This fungus infects red clover (*Trifolium pratense*), white clover (*Trifolium repens*), alsike clover (*Trifolium hybridum*), alfalfa, and can also be present on pastures and in stored dry hay. Slaframine is generally claimed to be active in stored hay throughout the year. Slaframine is not an active compound but is considered to be converted to an active metabolite by liver microsomal enzymes. Slaframine concentrations above the 10 ppm level in feed are usually associated with clinical signs (Osweiler 1996).

Common clinical symptoms observed in horses due to slaframine poisoning include excessive salivation, lacrimation, colic, and diarrhea. The 1st symptom of slaframine poisoning develops after about 1 to 3 h of consumption of contaminated forage. Even a case of abortion in a mare has been reported (Smith and Henderson 1991). Osweiler (1996) suggested that atropine may provide symptomatic relief of salivation and diarrhea as a preliminary treatment.

Lolitrem toxin. Lolitrem toxin is produced by *Acremonium lolii* on perennial ryegrass, which produces staggers in sheep (Moss 1995). The toxic syndrome involves muscle tremors, muscle weakness and spasms, and takes nearly 14 d for the 1st symptoms to develop in livestock after consuming infected perennial ryegrass. Neurological disease in horses due to lolitrem intoxications has been reported (Goehring and others 2005). Intoxications have also been reported in bulls fed on rye-grass straw that had high levels of lolitrem B (between 2.9 and 4.8 ppm) (Benkhelil and others 2004).

Generally, a mutual association occurs between perennial ryegrass (*Lolium perenne* L.) and the endophytic fungus *Neotyphodium lolii*. These endophytic fungal species produce indole terpenoids among which the lolitrem B toxin is present in ample amounts. These toxins are able to act as antagonists of the GAB-aergic neurotransmission, leading to the cause of "staggers disease." Jensen (2005) has reported *N. lolii* to be capable of providing the host plant with resistance to several pests along with enhancing the growth of the plant. However, the fungus was also observed to trigger the production of toxic metabolites with severe effects on livestock.

No reports are available on the associated health risks to humans and hence further research is a necessity to provide sufficient information on the possible transfer of these toxins from animal products to the human food chain.

Phomopsins. Phomopsins A and B are the 2 secondary metabolites isolated from extracts of lupin seed cultures of *Phomopsis leptostromiformis* (a parasite of field lupin *Lupinus luteus*), known to cause lupinosis (Culvenor and others 1977). Phomopsins are linear hexapeptide compounds having an ether-linked macrocycle between amino acids 1 and 3 in the linear chain (Edgar 1991). The fungus *Phomopsis leptostromiformis* can also grow saprophytically on other species such as *Lupinus albus* and *L. angustifolius*. Poisoning, known as lupinosis, occurs after ingestion of contaminated lupins. This toxin commonly affects sheep, cattle, horses, pigs, and rats. Common symptoms include high hepatotoxicity. Typical characteristic features in affected animals would be: in cattle, excessive salivation and watering eyes (with atrophic arthrosis in chronic cases); in horses, sluggishness or ataxia with production of reddish-brown colored urine; and in sheep and cattle transudation.

Among the 2 groups, phomopsin A is of high clinical significance. Phomopsin A, a macrocyclic heptapeptide isolated from the fungus *Phomopsis leptostromiformis* is a potent inhibitor of microtubule assembly and of vinblastine binding to tubulin. In 1 of the studies by George and others (1979) it was shown that a crystalline mixture of phomopsins A and B (about 4:1) produced clinical, biochemical, and histological changes characteristic of lupinosis when administered to sheep by intraperitoneal route. When separately administered by the same route to nursing rats, the 2 compounds caused typical mitosis-arresting effects in the parenchymal cells of the liver. Phomopsin A was the more important of these 2 agents.

Effects of different doses of pure phomopsins administered to sheep have been reported by Peterson and others (1987). From their study, a dose of 1000 μ/kg administered at daily rates of 50 or 200 μ/kg killed all sheep, while a single dose of 500 μ/kg caused significant liver damage, without being fatal. Single doses of 125 and 250 μ/kg and repeated daily doses of 12.5 μ/kg over 16 wk caused no detectable tissue damage.

However, no risks have been reported to humans due to phomopsins. A maximum contamination limit of 5 ng/g of phomopsins in lupin-based food has been recommended in Australia and Great Britain (Anonymous 1996).

3-Nitropropionic Acid. *Arthrinium* spp. produce a secondary metabolite known as 3-nitropropionic acid (3-NPA), reportedly known to cause acute food poisoning referred to as "moldy sugarcane poisoning" (Liu and others 1988; Ming 1995). The common symptoms of poisoning include vomiting, dystonia, convulsions, carpopedal spasm, and in certain cases coma. The incubation period for the symptoms to develop is 2 to 3 h after ingestion of contaminated sugarcane. In adults, the main symptom is associated with gastrointestinal problems, whereas signs of severe encephalopathy are not common (Ludolph and others 1991). As a result of bilateral symmetric necrosis of the basal ganglia, in certain cases delayed dystonia develops (10% to 50% of patients) and the development of delayed symptoms has been predicted by abnormal basal ganglia that are visible on cranial computerized tomography scans (Ming 1995).

Production of hypothermia and inhibition of histochemical labeling of succinate dehydrogenase in rat brain by 3-NPA have

Table 2—Some of the recent postharvest methods adapted for removal of mycotoxins in human food.

Mycotoxin	Treatments	Reference
Aflatoxin	Chemical agents like ammonia, caustic soda, hydrogen peroxide, bisulfites, chlorinated agents, formaldehyde	Scott (1998)
AFB1	Radiation processing (gamma rays)	Bhat and others (2007), Ogbadu (1980), Temcharoen and Thilly (1982)
AFB1 and G1	Ozone	McKenzie and others (1997)
AFB1	Roasting	Staron and others (1980)
AFB1	Natural botanicals/herbs	Alderman and Marth (1976), Kensler and others (2004), Peterson and others (2006), Reddy and others (2009)
Aflatoxin M1	Organic mycotoxin binders (glucomannans), bentonite clay, hydrogen peroxide, pasteurization	Doyle and others (1982), Devegowda (2000), Kiermeier and Mashaley (1977), Yousef and Marth (1985);
Citrinin	phosphate–ethanol extraction	Lee and others (2007)
DON, ZEN, and FB1 and FB2	Fermentative bacteria, thermal treatments	Niderkorn and others (2007), Young and others (1987)
Fumonisin (FB1)	Alkaline treatments, thermal treatments, genetic modification of plant	Duvick (2001), Hendrich and others (1993), Jackson and others (1996)
OTA	Radiation processing	Paster and others (1985)
OTA	Thermal treatments	Boudra and others (1995), Scudamore (2005), La Pera and others (2008)
OTA	Polishing and milling	Osborne and others (1996)
OTA	By use of bentonite, modified bentonites, and chitosan	Kurtbay and others (2008)
OTA	Lactic acid bacteria	Del Prete and others (2007)
Patulin	Fermentation, heat treatments	Kadakal and Nas (2003), Ough and Corison (1980)
Trichothecene mycotoxins	Chicken intestinal microbes	Young and others (2007)

also been reported (Nony and others 1999). A delayed dystonia syndrome in children subsequent to initial gastrointestinal symptoms and acute noninflammatory encephalopathy on ingestion of mildewed sugarcane containing 3-nitropropionic acid (3-NPA) has been reported by He and others (1995).

Onyalai disease. Onyalai, an endemic disease of Africa (southern Sahara region) is caused by the mycotoxin produced by isolates of *Phoma sorghina*, which often contaminates millet. Onyalai has also been reported in a few black populations of central southern Africa (Kavango, Namibia) with a recorded incidence of 1 in 660 inhabitants/year (Hesseling 1992). The disease is known to be produced in rats fed with intentionally contaminated maize and wheat. This disease is characterized by hemorrhaging lesions in the mouth (Rabie and others 1975). Information on the possible pathways of the toxin is scarce.

Pre- and postharvest methods adapted to control mycotoxins

Increasing knowledge and awareness on the consumption of food and feeds contaminated with mycotoxins has turned the focus towards development of inactivation procedures. Reports are available wherein inactivation or removal of some of the common mycotoxins (like aflatoxins, OTA, fumonisins) have been explored, and in certain cases have been successful. However, a wide gap still persists with regard to exploring the possibilities of removal or inactivation of other commonly occurring mycotoxins (both in food and feed), which have been described previously. Even though good agricultural practice and good manufacturing practice (GAP and GMP, respectively) are the best available option to minimize mycotoxins at the field level, certain reports are available wherein various processing methodologies have been adapted to eliminate these toxins. Table 2 highlights some of the recent postharvest methods adapted for removal of mycotoxins in human food, while Table 3 details on the maximum tolerable limits set for certain mycotoxins in food and feed. In the following text, a few are being discussed with regard to aflatoxins, OTA, and *Fusarium* toxins.

Removal or inactivation of aflatoxins. Cotty and Bhatnagar (1994) proposed a new method that involves isolation of *A. flavus* and *A. parasiticus* (nonvirulent strains that do not produce aflatoxins), to compete with the natural toxin-producing strains. These strains occupied the same ecological niche as toxin-producing strains and they decreased the level of contamination with toxin-producing molds.

Fungal co-occurrence in any product indicates the possible competition and succession or antagonism among the colonizing fungi. Co-occurrence of fungal species has been shown to inhibit or reduce the toxin concentration in a substrate (Mann and Rehm 1976). Co-inoculation of *A. niger* and *Trichoderma viride* onto maize or peanuts contaminated with *A. flavus* has been shown to reduce aflatoxin production (Wicklow and others 1980; Aziz and Shahin 1997).

Reports are available (El-Nemazi and others 1998; Yoon and Baeck 1999) wherein specific strains of lactic acid bacteria (such as propionibacteria and bifidobacteria) possessing typical cell wall structures can bind aflatoxins and limit their bioavailability. These toxins could then be eliminated in the feces/excreta without any negative impact on the animals or any risk for toxic residues to be found in edible animal products. Also, some of the microbes (for example, *Corynebacterium rubrum*) have been shown to metabolize mycotoxins (aflatoxins) in contaminated feed or to bio-transform them (Nakazato and others 1990).

Table 3—Maximum tolerable limits set for certain mycotoxins in food and feed.

Mycotoxin	Products	Limits set	Reference
Aflatoxins	in cereals, peanuts, and dried fruits	2ppb for AFB1 and 4 ppb for AF B1+B2+G1+G2	Moss (2002), Stroka and Anklam (2002) EC (European Commission) (2006)
AFM1	in milk	50 ng/kg	Anonymous (2001)
OTA	in milk	5 ng/kg body weight/d	Skaug (1999)
OTA	in dried wine fruits	10 μg/kg	CEC (2002)
OTA	cereals, cereal products, raisins, roasted coffee, wine, grape juice, and food for children	120 ng/kg body weight	EU Commission Regulation (2006a)
Fumonisins	from all food source	2 μg/kg body weight (bw)/d for fumonisins	WHO (2002)
Fumonisins	maize-based formulae	200 μg/kg (infants and young children)	EU Commission Regulation (2006a)
Fumonisin B1	maize and other cereals	80 ng/kg/d	WHO (2002)
Fumonisins	animal feed for horses and other equine species, and for cattle	5 to 50 μg/g for horses	Miller and others (1996)
ZEN	in food and feed	0.5 μg/kg of body weight	Creppy (2002), JECFA (2000)
DON	in raw cereals	1250 μg/kg	
Trichothecenes (T-2 toxin)	in food & feed	1 μg/kg body weight	JECFA (2001)
Trichothecenes (HT-2 toxin)	in food and feed	0.061 μg/kg body weight	JECFA (2001)
Patulin	in adult foods	0.4 g/kg body weight.	EU Commission Regulation (2006b)
Patulin	in baby food	10 μg/kg body weight	www.mycotoxin-certification.eu (accessed on 24 July 2009)
Patulin	apple juice and in solid apple products	50 μg/kg and 25 μg/kg, respectively	
Phomopsins	lupin-based food	5 ng/g	Anonymous (1996)

Presently, natural organic mycotoxin binders (such as glucomannans extracted from the external part of the cell wall of the yeast *Saccharomyces cerevisiae*) are also being used to bind certain mycotoxins. Devegowda (2000) has shown that 500 g of glucomannans from yeast cell-wall have the same adsorption capacity as 8 kg of clay. These types of binders have been shown to reduce the AFM1 content of milk by 58% in cows supplemented with diets contaminated with aflatoxin B1 at a concentration of 0.05% of dry matter (Withlow and Hagler 1999).

Degradation of mycotoxins, particularly aflatoxins in contaminated feeds through the application of various chemical agents such as acids, bases (ammonia, caustic soda), oxidants (hydrogen peroxide, ozone), reducing agents (bisulfites), chlorinated agents, and formaldehyde have been reported by Scott (1998). However, no detailed reports are available on the side effects of using these agents.

Previously, Masimango and others (1978) reported that adsorbents like bentonite clay can bind and remove aflatoxin B1 from solutions. Also, bentonite was able to remove AFM1 from milk up to 79% (Doyle and others 1982). Addition of hydrogen peroxide (1%) to UV-irradiated milk (10 min) completely (100%) eliminated the AFM1 (Yousef and Marth 1985).

The impact of radiation processing (a physical, nonthermal method of preservation) on the sensitivity of fungi and mycotoxins has been well established for various foodstuffs (Mitchell 1988; Refai and others 1996). Inhibition of AFB1 production in *A. flavus*-contaminated soybeans and groundnuts (peanuts) by radiation has been reported by Ogbadu (1980). Radiation processing by gamma rays reduced AFB1 by 75% and 100% in peanut meal at doses of 1 and 10 kGy (Temcharoen and Thilly 1982). Significant reduction of AFB1 at 10 kGy irradiation dose in *Mucuna pruriens* seeds, an underutilized nutraceutically valued legume, has been reported recently (Bhat and others 2007). The reduction/destruction was attributed mainly to the radiolysis of water that leads to formation of highly reactive free radicals, which readily attack the AFB1 at the terminal furan ring, producing products of low biological activities.

The decomposition temperature of aflatoxin is very high (237 to 306 °C). Betina (1989) reported that AFB1 can be degraded at high temperature of 267 °C. Roasting of artificially contaminated peanut meal (in a microwave oven) for 4 min has been shown to destroy aflatoxin by about 95% (Staron and others 1980). Treatments with ozone have also been reported to eliminate AFB1 and G1 in aqueous model systems (McKenzie and others 1997).

According to Purchase and others (1972), pasteurization of milk at 62 °C for 30 min was found to reduce AFM1 by 32%. Also, storage of milk at 5 °C for 1 and 3 d reduced AFM1 in milk by 18.8% and 24.2%, respectively (Kiermeier and Mashaley 1977). The ability of *Lactobacillus* and *Bifidobacterium* species to remove AFM1 in reconstituted milk has recently been reported by Kabak and Var (2008). However, contradictory to their results, reports are also available wherein AFM1 could not be destroyed during pasteurization or during yogurt and cheese preparation (Galvano and others 1996; Creppy 2002).

Certain plant-derived natural products like spices, herbs, and essential oils are known to contain compounds that can inhibit fungal growth and mycotoxin production (Bullerman and others 1984). Decreases in the medicinal potency of herbal drugs due to fungal contamination that affect the chemical composition of the raw materials have been reported (Roy 2003). Inhibition of mold growth by mustard, green garlic, and cinnamon bark along with the reduction of toxin production by peppers, cloves, thyme, and green tea has been reported (Hitokoto and others 1978). Bullerman and others (1977) reported strong antimycotic properties and inhibition of aflatoxin production by cinnamon, clove, and their oils. Antimycotic properties (like cinnamon, cloves, and mustard) and antiaflatoxigenic properties (as with thyme and oregano spices) have been reported by Llewellyn and others (1981). Alderman and Marth (1976) showed the efficacy of employing essential oils extracted from citrus fruits (lemon and orange) in inhibiting the growth of *A. flavus* and *A. niger*, thus suppressing aflatoxin formation. Singh and others (2008) in 1 of their studies explored the fungal infection and AFB1 contamination of 6 medicinal plant samples. They were able to recover a total of 858 fungal isolates from the raw materials. High levels of AFB1 (394.95 ppb) were produced by the isolates of *A. flavus* in *Glycyrrhiza glabra* Linn. Further, they were able to show the efficacy of employing the essential oil (obtained from leaves) of *Cinnamomum camphora* (L.) Presl. The oil completely inhibited AFB1 production at low levels (750 ppm), and thus the oil of *C. camphora* has been recommended as an herbal fungistat/fungicide against mold contamination of raw materials.

Natural honey has been shown to possess a rich antifungal, antiaflatoxigenic effect (against *A. flavus* and *A. parasiticus*) (Wellford and others 1978). Kensler and others (2004) reported the possible protective role of chlorophyllin (a water-soluble, semisynthetic sodium or copper derivative of chlorophyll, which is commonly used as a food additive as well as in alternative medicine) against AFB1 toxicity in humans.

Peterson and others (2006) have shown that a regular diet which includes apiaceous vegetables (carrots, celery, and parsley), reduces the carcinogenic effects of aflatoxin. Recently, Reddy and others (2009) reported a reduction in AFB1 by a few plant extracts and bio-control agents in stored rice. From their results, an extract of *Syzigium aromaticum* (5 g/kg) showed complete inhibition on the growth of *A. flavus* and AFB1 production, while *Curcuma longa*, *Allium sativum*, and *Ocimum sanctum* effectively inhibited *A. flavus* growth (65% to 78%) and AFB1 production (72.2% to 85.7%, 5 g/kg concentration). With regard to the biocontrol agents used, culture filtrate of *Rhodococcus erythropolis* completely inhibited AFB1 production at 25 mL/kg concentration, while *Pseudomonas fluorescens*, *Trichoderma virens*, and *Bacillus subtilis* showed 93%, 80%, and 68% reduction of *A. flavus* growth and 83.7%, 72.2%, and 58% reduction of AFB1 at 200 mL/kg, respectively. The inhibitory activity has been attributed to the antifungal components in plant extracts and extracellular metabolites produced by these biocontrol agents in the growth medium.

Diaz and others (2004) used 6 sequestering agents that can bind dietary AFB1 in animal models. Usually, the sequestering agents bind dietary AFB1 and reduce absorption from an animal's gastrointestinal tract. As a result, they protect an animal from the toxic effects of AFB1 and reduce transfer of the metabolite, aflatoxin M1, into milk. A total of 6 agents used by Diaz and others (2004) (SA-20®, an activated carbon [AC-A]; Astra-Ben-20®, a sodium bentonite [AB-20]; MTB-100®, an esterified glucomannan [MTB-100]; Red Crown®, a calcium bentonite [RC]; Flow Guard®, a sodium bentonite [FG]; and Mycrosorb®, a sodium bentonite [MS]) were previously tested for AFB1 binding *in vitro*. The results revealed that 5 of the 6 sequestering agents significantly reduced AFM1 contamination of milk (AB-20, 61%; FG, 65%; MS, 50%; MTB-100, 59%; and RC, 31%); whereas AC-A and activated carbon had no effect on AFM1 transmission at 0.25% of feed.

Removal/inactivation of OTA. Apart from good agricultural and manufacturing practices, designing proper storage conditions is the only available alternative for minimizing OTA contaminants. Paster and others (1985) have indicated the application of radiation-processing for the removal of OTA. However, concerns are being raised on the application of ionizing radiation at doses that can damage spores but do not kill them, which might possibly enhance OTA production when these spores germinate

on the return of favorable conditions. Also, once OTA has been formed in food it would be very difficult to remove it by the usual food processing. Boudra and others (1995) have reported that temperature as high as 250 °C cannot completely destroy OTA. Wheat flour production that involves polishing and milling has been reported to reduce ochratoxin levels (Osborne and others 1996). Similarly, a decrease in OTA has been reported after wet milling of corn wherein reduction in its germ and grits fractions was 96% and 49%, respectively (Wood 1982). Appropriate and safe thermal, chemical, and physical treatments can effectively reduce OTA levels in food products. For example, methods like decaffeination, roasting, brewing, and other similar thermal processing methods have been shown to reduce the level of OTA in coffee (Heilmann and others 1999; Van der Stegen and others 2001; Scudamore 2005; La Pera and others 2008).

Reduction in OTA levels in cocoa beans by use of essential oil of *Aframomum danielli* (at concentrations of 500, 1000, 1500, and 2000 ppm) has been reported by Aroyeun and others (2009). The presence of active components of *A. danielli* such as monoterpenes, alkaloids, and phenolic acids are opined to be responsible for the reduction of OTA. Reduction of OTA in cocoa shells by chemical methods (using aqueous solutions of 2% sodium bicarbonate and potassium carbonate) has also been successful (Amézqueta and others 2008b).

Removal/detoxification of fusario-toxins. Reduction in fumonisin (FB1) levels and activity has been shown by alkaline treatments, wherein ester bonds of fumonisin are hydrolyzed to release its tricarballylic groups to yield aminopentol (Hendrich and others 1993). The ability to remove *Fusarium* toxins by fermentative bacteria was evaluated *in vitro* by Niderkorn and others (2006). Nearly 29 strains of lactic (LAB) and propionic acid bacteria (PAB) were tested for their capacity to remove DON and FB1 and FB2 from an acidic medium (pH 4). LAB proved to be useful and more efficient than PAB for the toxin removal. However, differences among strains of LAB were observed. Elimination was up to 55% for DON, 82% for FB1, and 100% for FB2. Selected strains were also capable of removing up to 88% ZEN. From their observations the researchers concluded that selected fermentative bacteria were able to bind major *Fusarium* mycotoxins and the binding ability by selected strains could be used to decrease the bioavailability of toxins in contaminated silages. Niderkorn and others (2007) studied the potentiality of employing various fermentative bacteria to detoxify corn silage contaminated by *Fusarium* toxins (DON, ZEN, and FB1 and FB2). They reported that nearly 8 lactobacilli and 3 leuconostoc bacteria biotransformed ZEN into alpha-zearalenol, without any apparent biotransformation of DON and fumonisins. Bacteria capable of binding the toxins belonged to *Streptococcus* and *Enterococcus* species that could bind up to 33%, 49%, 24%, and 62% of DON, ZEN, FB1, and FB2, respectively. Accordingly, the researchers concluded that fermentative bacteria have the capacity to bind *Fusarium* toxins and thereby could decrease their toxicity in animals.

Sydenham and others (1994) reported on the effects of physical treatments for the partial decontamination of fumonisin-contaminated maize in bulk shipments. They randomly selected 10 maize samples from a bulk shipment imported into South Africa and further characterized them by dividing them based on particle size. Fractionation by sieving through a 3-mm screen was done, wherein the "kernels" (fractions > or = 3 mm), between 80% and 95.3% of the samples by mass, revealed contamination by fumonisin levels that ranged between 530 and 1890 ng/g. The fractions that were termed as "fines" (< 3 mm) had significantly higher total fumonisin concentrations of between 12340 and 27460 ng/g and accounted for 4.7% and 20% of the samples by mass. They concluded that removal of the "fines" can result in overall reductions in total fumonisin levels (between 26.2% and 69.4%) and recommended that initial removal of "fines" from bulk shipments of maize, prior to further processing, can serve as an initial step for fumonisin decontamination.

Significant reduction in fumonisin concentrations on heating aqueous solutions (150 °C and above) have been reported by Jackson and others (1996). Heating moist maize kernels were also successful in reducing this toxin (Murphy and others 1996). Other thermal treatments usually employed during conventional food processing like baking and frying has been shown to reduce fumonisin levels in corn. Muffins prepared by baking corn batter at around 175 to 200 °C (for 20 min) reduced fumonisin levels up to 30%. Further decrease was observed with an increase in temperature. Reductions in fumonisin levels were higher on the surface of muffins, which has been attributed to better heat penetration corresponding to enhanced baking temperatures (Jackson and others 1997). Heating results in the hydrolysis of the primary amine of the fumonisins. Also, autoclaving at 121 °C (1 h) in the presence of 8.33% aqueous sodium bisulfite has been shown to reduce DON levels in corn by 95% (Young and others 1987). Transformation of DON to a lesser toxic metabolite (de-epoxy-DON) by microbes in the large intestine of chickens has been reported by He and others (1992).

Hendrich and others (1993) have reported reduction in fumonisin levels by alkaline processing, wherein the ester bonds of the toxin were hydrolyzed to release its tricarballylic groups and yield aminopentol (Hendrich and others 1993). The application of chemical methods has been unsuccessful for the elimination of fumonisins. Wang and others (1991) used the commercially available enzymes and tested their ability for detoxifying fumonisins; however, the reduction in the fumonisins was not significant. However, to date no reliable and effective methods have been developed for the removal of fusario-toxins in food, a gap that needs to be filled at the earliest to reduce further economic losses, as well as for safety purpose.

Inactivation/removal of Patulin. Even though removal of the rotten and injured portion of the fruits has been recommended for minimizing patulin concentrations, this does not completely ensure the elimination of the toxin (Beretta and others 2000). Ough and Corison (1980) have reported that fermentation can destroy patulin during cider production. Filtration employed to clarify apple juice and concentrates has been reported to decrease patulin levels up to 40% (Bissessur and others 2001). Also, a pasteurization or evaporation condition, wherein the temperature is between 70 and 100 °C, has been shown to reduce patulin (by 25%) in naturally contaminated apple juice (Kadakal and Nas 2003). The adoption of various control methods for patulin in food products has been well reviewed by Moake and others 2005.

Mycotoxins—mode of action

Generally, understanding the chemical structure and basic mechanism of action of an individual mycotoxin can provide sufficient base to develop protocols or methods to efficiently manage the mycotoxins associated problems, as well as to understand their biological effects. Even though several mycotoxins have been identified to date, the basic mechanism of action has been workedout for only a few of them (aflatoxins, OTA, fumonisins) indicating a wide gap to persist. Of late, several excellent studies are available wherein the basic mechanisms of action of certain mycotoxins have been discussed in detail (like aflatoxins, DON, fumonisin, OTA) (Kiessling 1986; Ueno 1991; Riley and Norred 1996; Riley 1998; Tashiro 2000).

Methods of mycotoxin detection

For qualitative, quantitative, and accurate determinations of mycotoxins in foods and feeds, several analytical methods have

been developed and refined since the 1960s. Accurate detection of mycotoxins depends on various factors, as their distribution is not uniform in a substrate.

According to Whittaker and others (1991), a statistically valid sample must be drawn from a single lot; if not, a sampling error of up to 90% may occur. Also, mycotoxin analysis should always be performed in replicates ($n = 3$ to 5) for conformation of the actual concentration in the samples. However, if the method is validated in a proper way, and the validation results are satisfactory, there is no need to run every sample for 3 to 5 times. Care should be taken to finely grind a sample and further divide it into subsamples for analysis.

Traditionally employed analytical methods to detect mycotoxins involve lengthy extraction procedures, expensive chemical clean-up, and use of hazardous materials (Donnelly and others 2003). Such concerns and the necessity for the rapid analysis of mycotoxins have led to the development of many test kits that can qualitatively or quantitatively provide results within a few minutes. Also, improved protocols to minimize sampling errors have been established (Campbell and others 1986; Park and Pohland 1989). According to Magan (2004), availability of rapid diagnostics instruments is an area that has been developed in the recent past, principally as a response to fulfill governmental legislative regulatory requirements put forth and recommendations such as by the FAO (1995). Limits and regulations for mycotoxins and their validation have been reported by many researchers (van Egmond 1989; Stoloff and others 1991; Boutrif and Canet 1998; Rosner 1998; van Egmond and others 2007).

Table 1 details some of the recently employed methods for the detection of several mycotoxins. In the subsequent section, a few of the most important techniques available today have been discussed to provide some basic information.

Several analytical methods have been developed and standardized to detect mycotoxins: thin-layer chromatography (TLC), liquid chromatography, high-performance liquid chromatography (HPLC) with fluorescence or diode array detector, gas chromatography coupled to mass spectrometry (GC–MS) or electron capture detection (GC–ECD), enzyme-linked immunosorbent assays (ELISAs), and a combination of immuno-affinity column techniques (WHO 2002). In recent years, liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique has also been often applied for multiple-mycotoxin detection, and this approach looks to be the most promising one at the moment. These analytical methods are exclusively employed for the detection of various types of mycotoxins and have been proven successful, especially with aflatoxins, ochratoxin A, fumonisin, and deoxynivalenol (DON) in different commodities, like cereals and legumes (Scudamore and others 2003; Yumbe-Guevara and others 2003), coffee (Pittet and Royer 2002; Santos and Vargas 2002; Sibanda and others 2002; Vatinno and others 2008), black pepper (Gatt and others 2003), paprika seed (Hernandez-Hierro and others 2008), wine and beer (Leitner and others 2002; Stefanaki and others 2003), and cheese (Zambonin and others 2002; Manetta and others 2009).

Some of the analytical methods developed are considerably more suitable for certain types of mycotoxins than others. For example, mini-columns and scanning of crushed-sample for blue–green–yellow fluorescence (BGYF) with a black light (UV lamp) have been used extensively as an initial screening test for aflatoxins (Chu 1991). Use of mini-column methods is limited to those emitting fluorescence, including aflatoxins, OTA, ZEN (Shotwell 1983), and sterigmatocystin (Ramakrishna and Bhat 1990). The use of different types of analytical techniques in combination with others or singly to detect a single mycotoxin has often been successful. For example, according to the WHO (2002), both thin-layer chromatography and liquid chromatography with fluorescent detection along with ELISA can be used to identify ochratoxin A.

Thin-layer chromatography (TLC) is one of the most popular and easy methods to detect mycotoxins in a sample; and more than one toxin can be detected simultaneously. This technique is based on the separation of compounds by how far they migrate on a specific matrix (TLC coated plates) in the presence of specific solvents. The distance traveled by a compound is specific for that compound, and based on the retention factor (Rf) a mycotoxin's identity can be determined. As with any other detection method, a control containing purified mycotoxins must be run in parallel to ensure accuracy. However, today, with the availability of many other options and modern instruments, in the majority of labs this technique is being used for preliminary screening only.

Immunological assays. Mycotoxins are not immunogenic and are recognized as haptens or small molecules that do not stimulate antibody production by themselves. However, in some instances, antibodies can be produced for a specific mycotoxin by conjugating it to a protein carrier, which might cause the mycotoxin to become immunogenic. Animals that recognize various regions of foreign particles produce several types of antibodies, including antigens (a substance capable of stimulating an immune response) and haptens, when present on a carrier macromolecule.

The various forms of antibodies include polyclonal and monoclonal types. Polyclonal antibodies react with multiple antigens or haptens on a foreign compound, whereas monoclonal antibodies react only with specific antigens or haptens (Fremy and Usleber 2003). An immunoaffinity method is highly advantageous, as it is rapid and inexpensive. The extracted sample is placed on a mini-column filled with antibodies specific to the toxin and is eluted off the column using methanol. Then a bromine reagent is added and the sample is placed in a direct-reading fluorometer. The mycotoxin is extracted, cleaned up on a silica column, developed on a high-performance plate, and is measured using a scanning fluorometer. This method is used as a visual confirmatory test. Fumonisins are usually detected by purification with immunoaffinity columns followed by TLC or liquid chromatography, however, more rapid screening tests based on TLC and ELISA have been developed (WHO 2002).

New immunochemical methods have recently been developed. For example, a "hit and run" assay for T-2 toxin has been mentioned by Warden and others (1987, 1990). The T-2 toxin column is equilibrated with fluoresceinisothiocyanate (FITCI-labeled Fab fragment of IgG -anti-T-2 toxins) and the sample containing T-2 toxin is injected into the column. The FITC-Fab that is eluted together with the sample containing T-2 toxin is then determined in a standard flow-through fluorometer. Similarly, Warden and others (1990) have reported a method wherein ribonuclease-labeled-Fab is used as the indicator.

A homogeneous immunoassay for T-2 toxin that involves the use of liposomes, which can virtually lead to the development of a biosensor, has been reported by Ligler and others (1987) and Williamson and others (1989). Determination of multiple mycotoxins (about 4 types) in a sample at nanogram per gram detection limits by immunochemical biosensor has been described by van der Gaag and others (2003). Nearly 4 mycotoxins (DON, FB1, ZEN, AFB1) could be detected within 25 min, which includes extraction and clean-up of the sample (approximately 15 min) and measurement (10 min, including regeneration of the sensor chip surface). This assay was designed as an inhibition assay, in which the principle of detection is based on surface plasmon resonance (SPR).

For the determination of aflatoxins (Sarwar and Jolley 2002) and DON (Maragos and Plattner 2002) in grains, PFS-fluorescence polarization immunoassays (FP) have been developed. The assays are based on the competition between free aflatoxin and an aflatoxin–fluorescein tracer for an aflatoxin-specific monoclonal antibody in solution. Degan and others (1989) have developed a time-resolved fluoro-immunoassay aflatoxin analysis, wherein the method involves the use of europium ion (Ed-labeled) antibodies. Takino and others (2004) reported on a highly reliable and sensitive method for the detection of aflatoxins by employing an atmospheric pressure photo-ionization technique (APPI) wherein the level of detection was in the range of 0.11 to 0.5 ng/g.

Nawaz and others (1992) have developed a rapid, simple, and reproducible method for the simultaneous determination of aflatoxins (AFB1, AFB2, AFG1, and AFG2) in palm kernel samples by optimizing sample preparation, solvent extraction, clean-up, and quantification procedures. Aflatoxins in the samples are extracted from palm kernel slurries with a mixture of acetone–water (80 + 20, v/v) and the crude extract is cleaned by solid-phase extraction using a phenyl-bonded phase cartridge. The extract is then passed through the cartridge with a water–methanol (93 + 7) mixture, and subsequent elution of aflatoxins retained on the cartridge is achieved with a 3-mL aliquot of chloroform. The aflatoxin content of eluates was further quantified by employing a bi-directional high-performance thin-layer chromatography (HPTLC) procedure. From this method, a consistent recovery of over 90% could be achieved from spiked palm kernel extracts and detection limits were 3.7, 2.5, 3, and 1.3 μg/kg for AFB1, AFB2, AFG1, and AFG2, respectively.

A novel method for the simultaneous determination of trichothecene mycotoxins (deoxynivalenol, nivalenol, 3-acetyl-deoxynivalenol, and 15-acetyl-deoxynivalenol) has been developed by Shaban and others (2007) (for barley and malt extracts) using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS). The matrices used were diamond and sodium azide and were suitable for the determination of mycotoxins. This technique was found to be highly sensitive, rapid, and detection can be performed using very minute sample quantities.

Pestka (1991) has reported on a new method called HPTLC-ELISA-gram. In that method, separation of mycotoxins is performed by HPTLC, followed by blotting the chromatogram to a nitrocellulose membrane coated with antibody, incubation with mycotoxin-enzyme conjugate, and finally incubation with substrate to develop the color. However, application of this method is limited as use of a large amount of antibody is required.

Currently, the polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) test are emerging as the most reliable tools to detect molds rather than mycotoxins (Chung and others 1989; Zur and others 2002; Niessen 2008; Hooper and others 2009). These techniques are useful for detecting the responsible coding genes of mycotoxin-producing molds. However, the techniques are very expensive, require trained analysts, and cannot be employed routinely in field assessments of contamination. Detection of mycotoxins using commercially available ELISA's is mainly dependent on the competition between the toxins from the sample and a labeled toxin (such as a toxin–enzyme conjugate) for a limited number of antibody-binding sites. The higher the concentration of the toxin, the lower is the binding of the labeled toxin and the lower the signal generated by the assay (Anklam and others 2002; Seefelder and others 2002).

Based on random amplified polymorphic DNA (RAPD) and amplified fragment length polymorphism (AFLP) markers, specific primers for PCR- detection of *A. ochraceus* and *A. carbonarius* in coffee beans have been developed recently (Schmidt and others 2003, 2004; Fungaro and others 2004).

Of late, use of electronic nose and soft X-ray imaging for the detection of fungi in food commodities have received positive attention (Perkowski and others 2008; Concina and others 2009; Narvankar and others 2009). However, these techniques might be useful for the rapid detection of the fungal pathogens only rather than a mycotoxin itself.

It is highly imperative to develop newer detection methods for the rapid analysis of mycotoxins in food, particularly considering the new open global market under the new World Trade Organization (WTO) regime. The new analytical tools developed would be more useful if several mycotoxins could be screened simultaneously within a fraction of minutes in a large number of samples. For example, Gachok and others (2008) have reported the development of a fluorescence polarization immunoassay, which could detect mycotoxins like OTA, AFB1, and ZEN in the samples present in low amounts up to 1 ng/mL, much lower than maximum residue limits (MRL) set for mycotoxins in food (from 10 to 100 ppb for different mycotoxins and in different foods).

Prevention and future outlook

Prevention of fungal contamination and thereby toxin production can be achieved either during preharvest stages by good crop husbandry and appropriate cultural practices and the use of a HACCP plan, as well as during postharvest stages by the application of proper drying, storage, and transport procedures (FAO 2006a, 2006b). Application of fungicides at field levels might reduce mold growth resulting in the reduction of production of mycotoxins. However, it has been opined that the stress generated by the fungicides on the molds can also result in increased mycotoxin production (Gareis and Ceynowa 1994). Hence, further studies have to be initiated to look for a better and environmentally friendly alternative at the field level rather than relying on chemicals.

Development of resistant plant varieties with the application of modern biotechnological methods would prove to be beneficial up to certain extent. Some studies in this regard are already being reported. For example, biotechnologically developed corn (Bt corn) has been reported to possess lower levels of contamination with fumonisin and aflatoxin. A total profit of 23 million dollars annually due to Bt corn's reduction of fumonisin and aflatoxin in the U.S. has been estimated (Wu 2006).

Even though organic farming is well established and has been forecast to reduce mycotoxin contamination in the food chain, it has not yet been possible to establish major differences in this regard when comparing it to conventional farming. However implementation of GAP in organic fields might definitely have a good impact on the contamination and production levels of mycotoxins. Removal of crop residues and undertaking crop rotation is a better option considering the fact that some viable pathogenic fungal spores might be present in the old crops after harvest.

As the detoxification of human food and animal feeds (during postharvest stages) is performed mostly by employing chemical methods, safety, and efficacy along with handling, costs should be taken into consideration. Care should be taken to see that the preservatives or the chemicals employed do not degrade the overall nutritional, sensory, and functional properties of the food product. Hence, development of newer physical methods of preservation is a necessity in the near future. Of late, non-ionizing radiation, like ultraviolet rays (UV), has been shown to be successful in reducing the microbial load and thereby toxin production. However, the penetration of UV rays is not deep at all. Application of UV in combination with heat treatment has been reported to be successful in the inactivation of conidia of *Botrytis cinerea* and *Monilinia fructigena*, which are the 2 major postharvest spoilage fungi of strawberries and cherries (Marquenie and others 2002). Successful prevention of the germination

of contaminating fungi during storage or further dehydration by UV irradiation of harvested grapes has been reported by Valero and others (2007). Also, effective inactivation of food spoilage fungi like *A. flavus*, *P. corylophilum*, *E. rubrum*, and *A. niger* by UV irradiation has been reported by Begum and others (2009).

Further public legislation and regulations with regard to mycotoxins should be instituted to protect health and to facilitate trade among various importing countries. Strict enforcement of the already existing regulations for mycotoxins, especially for aflatoxins, ochratoxins, ZEN, fumonisins, and patulin in the food chain might prove to be successful in minimizing mycotoxin contaminants overall. Nearly 60 countries have now enacted or proposed regulations for the control of mycotoxins in food and animal feeds (van Egmond 1995).

Dietary manipulation has been reported to reduce the adverse effects of mycotoxins. According to Ratcliff (2002), increasing the levels of selenium, methionine, carotenoids, and vitamin supplementation in food can be beneficial in reducing adverse effects of mycotoxins. Jones and others (1994) have reported that increasing protein, energy (fats and carbohydrates), and vitamins in the diet may be advisable towards this end. The addition of antioxidants to animal diets might assist in dealing with the toxic effects of mycotoxins. However, the available data pertaining to dietary habits and mycotoxin reduction are very scarce and, hence, future studies ought to be initiated.

Conclusions

The occurrence of mycotoxins in the food chain is an unavoidable and serious problem the world is facing. Apart from practicing good sanitary measures, awareness has to be created to indicate the toxic effects associated with mycotoxin poisonings in humans and livestock. Wide gaps still exist on the toxicological effects of feeding animals mycotoxin-contaminated feeds. Research in this field is a necessity as there is every possibility that the toxins will enter the human food chain. Further research also needs to be focused on the generation of data dealing with epidemiological and toxicity effects, especially in humans. Implementation of strict quarantine rules with regard to mycotoxin contamination has to be made mandatory worldwide. Emphasis should be laid towards development of newer low-cost mycotoxin detection instruments, which are portable, reliable, and easy to handle at field levels. Development of new genetically modified plants by the application of genetic engineering that might be resistant to fungal invasion might also prove to be a good option. Developing new protocols and strategies to compare the costs and benefits of various controlling agents against fungal pathogens and mycotoxin production might be beneficial for economic stability of a commodity or an agricultural area.

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