Fusarial Toxins: Secondary Metabolites of *Fusarium* Fungi

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1 Introduction

Different types of fungi, belonging primarily to five genera (viz., *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, and *Fusarium*), produce secondary metabolites that are called mycotoxins. There are also other genera, (viz., *Chaetomium*, *Claviceps*, *Diplodia*, *Myrothecium*, *Phoma*, *Phomopsis*, *Pithomyces*, and *Stachybotrys*) that contain mycotoxin-producing fungi. Under favorable environmental conditions, when temperature and moisture are suitable, fungi proliferate and may produce secondary metabolites. These products have no biochemical significance for their own growth and development. The functions of mycotoxins

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D.M. Whitacre (ed.), *Reviews of Environmental Contamination and Toxicology Volume 228*, Reviews of Environmental Contamination and Toxicology 228,
DOI 10.1007/978-3-319-01619-1_5,

have not been clearly established, but they are believed to play a role in eliminating other competing microorganisms in the same environment. They are also believed to help parasitic fungi invade host tissues. Toxigenic molds are known to produce one or more secondary metabolites, but not all molds are toxigenic and not all secondary metabolites from molds are toxic (Brase et al. 2009).

Fungi commonly enter the food chain through contaminated food and feed crops, mainly cereals, which become infested prior to and during harvest, or during (improper) storage. Although there are over 300 fungal toxins that have been isolated and chemically characterized, worldwide research has been focused on those forms that cause significant injuries to humans and animals. Therefore, there are only a few mycotoxins that are of practical relevance (Jakic-Dimic et al. 2010).

Even though there are geographic and climatic differences in the production and occurrence of mycotoxins, exposure to these substances occurs worldwide (Kuiper-Goodman 2004). The diseases that mycotoxins cause in animals and humans are called mycotoxicoses (Bryden 2012). Consumption of a mycotoxin-contaminated diet may induce acute and long-term chronic effects. Generally, the effects produced are teratogenic, carcinogenic, and/or estrogenic or immunosuppressive ones. However, the major problem associated with mycotoxin contamination of the animal feed supply chain is not acute disease episodes but reduced animal productivity. Direct consequences of consuming mycotoxin-contaminated animal feed include: reduced feed intake, feed refusal, poor feed conversion, diminished body weight gain, increased disease incidence (from immune-suppression), and reduced reproductive capacities, which all lead to economic losses. Although mycotoxins mainly affect grains, meat, milk, and eggs can be adversely affected as well. Consuming such products of animal origin has direct consequences for humans, because they are major human foods.

Our purpose in writing this review is to summarize and integrate the most significant data available about this important group of natural contaminants, because they have a major worldwide impact on feed and food safety and consequences for animal and human health. We also address measures pertinent to preventing and controlling fusarial toxins, and summarize the methods used to analyze for the presence of these toxins.

2 Fusarium Fungi

Fungi are a normal component of the microflora that exists in standing crops and stored feeds. Mycotoxin production varies with the fungal species present, agronomic practices used, the composition of the commodity and harvesting techniques used, and handling and storage conditions (Bryden 2009). Mycotoxins that adversely affect human or animal health are mainly found in postharvest crops such as cereal grains or forages. The preponderance of mycotoxins is produced by saprophytic fungi during cereal or other crop storage or by endophytic fungi during plant growth.

Table 1 Selected mycotoxigenic *Fusarium* species and the mycotoxins they produce

Species	Mycotoxin
F. culmorum	Aurofusarin, butenolide, chlamydosporol, culmorin, cyclonerodiol, cyclonerotriol, fusarins, moniliformin, trichothecenes, zearalenone
F. graminearum	Aurofusarin, butenolide, chlamydosporol, culmorin, cyclonerodiol, fusarins, trichothecenes, zearalenone
F. sporotrichioides	Aurofusarin, beauvericin, butenolide, culmorin, enniatins, fusarins, moniliformin, trichothecenes
F. crookwellense	Aurofusarin, butenolide, culmorin, cyclonerodiol, fusaric acid, fusarins, trichothecenes, zearalenone
F. acuminatum	Acuminatum, aurofusarin, beauvericin, chlamydosporol, enniatins, fusarins, moniliformin, trichothecenes
F. equiseti	Beauvericin, equisetin, fusarochromanone, moniliformin, trichothecenes, zearalenone
F. proliferatum	Beauvericin, enniatins, fumonisins, fusaric acid, fusaproliferin, moniliformin
F. verticillioides	Fumonisins, fusaric acid, fusarins, naphthoquinones
F. armeniacum	Beauvericin, fusarins, trichothecenes
F. pseudograminearum	Trichothecenes, zearalenone

The genus *Fusarium* was described by Link more than 200 years ago and currently contains over 20 species (De Hoog et al. 2000), some of which are among the most important toxigenic plant pathogenic fungi. *Fusarium* species infect important crops such as soft and durum wheat, barley, oats, rice, maize, potato, asparagus, mango, grasses, and other food and feed grains (Glenn 2007). *Fusarium* species produce long, multicellular, canoe-shaped or banana-shaped macroconidia. These large asexual conidia are the defining morphological characteristic of the genus. Many species also produce small, generally single-celled microconidia that range in shape from fusiform to oval to spherical. Additionally, some species produce thick-walled resistant chlamydospores that are important for long-term survival. Microconidia and macroconidia are important for wind and splash dispersal of the fungi. The conidia are also generally the propagules that result in infection of host plants.

Fusarium species are diverse in their host-associations and mycotoxin profiles, and individual *Fusarium* species are differentiated by using a range of morphological, molecular, and metabolic characteristics. *Fusarium* species cause root, stem, and ear rot, with severe economic crop yield reduction, often estimated at between 10 and 30% (Golinski et al. 2002; Logrieco et al. 2002; Uhlig et al. 2007). *Fusaria* are widespread in all cereal-growing areas of the world, but there are some geographical differences in their natural distribution, as well as of the corresponding mycotoxins they produce, which are influenced primarily by environmental conditions, and crop production and storage methods (Battilani et al. 2009). Selected mycotoxigenic *Fusarium* species and the mycotoxins they produce are presented in Table 1.

3 Fusarium Toxins

Fusarium toxins are produced in cereal grains during high moisture conditions at or near harvest time (Munkvold and Desjardins 1997; Sutton 1982). Wheat, triticale, and maize grains are especially vulnerable to *Fusarium* infection and are also frequently more highly contaminated with their secondary metabolites. In Table 2 we provide examples to illustrate the levels at which *Fusarium* mycotoxins normally appear in natural cereal samples (Döll and Dänicke 2011).

The amount of toxin produced depends upon physical factors (viz., moisture, relative humidity, temperature, and mechanical damage), chemical factors (viz., carbon dioxide, oxygen, composition of substrate, and pesticides used), and biological factors (viz., plant variety, stress, insects, spore load, etc.). Moisture and temperature have a major influence on mold growth and mycotoxin production. Access to water is most critical to microbial growth; hence, the water content of a feed commodity, expressed as a moisture percentage, is an important measure of

Table 2 Levels at which *Fusarium* toxin contaminates European cereals (adapted from Döll and Dänicke 2011)

	No. of samples	Positive (%)	Maximum (mg/kg)
Deoxynivalenol			
Wheat	6,358	61	50.000
Maize	520	89	8.850
Barley	781	47	0.619
Oats	595	33	5.004
Rye	271	41	0.595
Zearalenone			
Wheat	847	30	0.152
Maize	824	79	6.492
Barley	226	5	0.053
Oats	377	20	1.310
Rye	84	5	0.024
T-2 toxin			
Wheat	1,417	21	0.160
Maize	293	28	0.255
Barley	502	3	0.280
Oats	464	16	0.550
Rye	62	21	0.193
Diacetoxyscirpenol			
Wheat	845	14	0.050
Maize	111	51	0.025
Fumonisin B_1			
Wheat	110	79	0.736
Maize	801	66	10.2
Fumonisin B_2			
Maize	544	51	1.268

microbial attraction to such feed. Pathogenic fungi that invade crops prior to harvest usually require higher moisture levels (200–250 g/kg) than other fungi to successfully infect and proliferate in feed during storage (130–180 g/kg). Therefore, most feedstuffs with moisture contents above 130 g/kg are susceptible to mold growth and mycotoxin formation (Bryden 2012; Jakic-Dimic and Nesic 2009, 2011b). In temperate climates, the *Fusarium* toxins are common contaminants of cereal crops. *Fusarium* toxins are stable at high temperatures and during storage, milling, processing, and cooking of food and feed; humans and animals are, therefore, always exposed to them to a certain degree (EFSA 2011a, b; Jakic-Dimic et al. 2009). Below we will describe several of the more important mycotoxins that are produced by *Fusarium*.

3.1 Zearalenone

Zearalenone (ZEA; ZON, F-2 toxin) is a phytoestrogenic compound known chemically as 6-(10-hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcylic acid μ-lactone. It is a metabolite associated with several *Fusarium* species (*F. culmorum*, *F. equiseti*, and *F. verticillioides*), but *F. graminearum* is the species most responsible for producing the estrogenic effects commonly found in farm animals. Maize is the crop most often affected, although these fungi are also found in other crops such as wheat, barley, sorghum, and rye in various countries around the world. Whilst zearalenone is primarily a field contaminant, it may also occur under poor storage conditions. ZEA exhibits estrogenic activity and has been implicated in numerous mycotoxicoses in farm animals, especially pigs. Common clinical signs are vaginal and vulvar swelling, enlargement of mammary glands, and testicular atrophy, as well as other reproductive effects, such as decreased fertility, increased number of resorptions, and reduced litter size (EFSA 2011a; Nesic 2003; Nesic et al. 2008a).

The strong estrogenic effect of zearalenone results from its competition with 17 β-estradiol to bind cytosolic estrogen receptors present in the uterus, and in hypothalamus and mammary and pituitary glands (Abbes et al. 2006). It is acknowledged that ZEA is of a relatively low acute toxicity (Zinedine et al. 2007).

Although significant differences were found in the metabolic profile of ZEA among animal species, only limited data on this topic are available for man. In pigs and probably in humans, ZEA is rapidly adsorbed after oral administration and can be metabolized in intestinal cells. In these cells, ZEA is degraded into α-zearalenol (α-ZEA), β-zearalenol (β-ZEA), α-zearalanol (α-ZAL), β-zearalanol (β-ZAL), which are subsequently conjugated with glucuronic acid (JECFA 2000). The ZEA derivatives (α-ZEA, β-ZEA, α-ZAL, and β-ZAL and zearalanone (ZAN)) can be detected in corn stems infected with *Fusarium* in the field and in rice culture (Zinedine et al. 2007). Recently, Schollenberger et al. (2006) reported the occurrence of α-ZEA and β-ZEA in corn by-products, corn silage, and soya meal at low levels.

ZEA is rapidly biotransformed and excreted in animals; therefore, its dietary intake from meat and meat products is probably of little significance (Creppy 2002). ZEA can be excreted into milk of lactating cows, when it is fed at high doses. Prelusky et al. (1990) reported that the maximum concentrations in the milk of one cow given an oral dose of 6,000 mg ZEA (equivalent to 12 mg/kg bwt) was 6.1 μg/L (ZEA), 4 μg/L (α-ZEA), and 6.6 μg/L (β-ZEA). However, neither ZEA nor its metabolites were found in the milk (<0.5 μg/L) of three lactating cows fed 50 or 165 mg ZEA (equivalent to 0.1 and 0.33 mg/kg bwt) for 21 days. Nor has ZEA been reported in eggs from commercial production. The main sources of dietary ZEA in humans and animals are wheat, rye, and oats in European countries, and corn, corn products, and wheat products in Canada and the USA. Considering the mean levels of ZEA in the principal foods and their consumption levels, the average daily intake in human adults of ZEA ranged from 0.8 to 29 ng/kg bwt, whereas small children have higher average daily intakes ranging from 6 to 55 ng/kg bwt/day (Minervini et al. 2005).

ZEA causes alterations in the reproductive tract of laboratory animals (mice, rat, guinea pigs, hamsters, and rabbits) and domestic animals. Various estrogenic effects like decreased fertility, increased embryolethal resorptions, reduced litter size, changed weights of adrenal, thyroid, and pituitary glands, and changes in serum levels of progesterone and estradiol have been observed; however, no teratogenic effects were found in mice, rats, guinea pigs, or rabbits (Bacha et al. 1993; JECFA 2000). Recent studies have demonstrated the potential for ZEA to stimulate growth of human breast cancer cells (Ahamed et al. 2001; Yu et al. 2005).

3.2 Fumonisins

Fumonisins are cancer-promoting metabolites of *F. proliferatum* and *F. verticillioides* that have a long-chain hydrocarbon unit (similar to that of sphingosine and sphinganine), which plays a role in their toxicity (Wang et al. 1992). Six fumonisins have been identified: fumonisins A1, A2, B1, B2, B3, and B4. The A series are amides, while B series have a free amine group. Fumonisin B1 (FB1) is the most significant of the fumonisins, in terms of toxicity and occurrence. FB1 is chemically described as 1,2,3-propanetricarboxylic acid, 1,1′-[1-(12-amino-4,9,11-trihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl]ester.

A range of toxic syndromes have been associated with exposure to fumonisins, including Equine Leukoencephalomalacia (ELEM), Porcine Pulmonary Edema (PPE), and hepatic and renal injury in most species tested. Fumonisin exposure also results in hemodynamic alterations that are considered to be involved in the pathogenesis of both ELEM and PPE (EFSA 2005). Poultry are relatively resistant to the toxic effects of FB1 (Bermudez et al. 1995). Fumonisins are both cytotoxic and carcinogenic to animals. The modes of such actions, however, are not completely understood. Wang et al. (1991) demonstrated that FB1 disrupts sphingolipid

metabolism by inhibiting sphingosine *N*-acyltransferase (ceramide synthase) in rat liver microsomes. It also has been shown that FB1 inhibits other intracellular enzymes, including protein phosphatases and arginosuccinate synthetase (Jenkins et al. 2000). Therefore, FB1 exerts its cytotoxicity by inhibiting sphingolipid metabolism, protein metabolism, and the urea cycle. The carcinogenic role of FB1 has been linked to the accumulation of sphingoid bases that cause unscheduled DNA synthesis (Schroeder et al. 1994), alteration of signaling by cAMP (Huang et al. 1995) and protein kinase C (Yeung et al. 1996), and disruption of normal cell cycling (Ramljak et al. 2000).

Esophageal cancer in humans has been linked to consumption of fumonisin-contaminated corn in South Africa (Gelderblom et al. 1992; Rheeder et al. 1992; Thiel et al. 1992) and China (Chu and Li 1994; Yoshizawa et al. 1994). Fumonisins have not been conclusively demonstrated to be carcinogens in humans, but there is epidemiological evidence of their involvement.

3.3 Moniliformin

Moniliformin (MON) is the potassium or sodium salt of 1-hydroxycyclobut-1-ene-3,4-dione, which is produced by at least 30 *Fusarium* species that have been isolated from different substrates and geographical areas (Abramson et al. 2001; De Nus et al. 1996; Fotso et al. 2002; Schütt et al. 1998), but mainly come from *F. proliferatum*. MON is usually found on corn kernels and can be transferred to next generation crops and can survive for years in the soil (Guzman and Casteel 1994). Although fumonisins and moniliformin are produced by the same fungal species, no structural resemblance is found between these toxins, although they frequently occur together in feeds.

Moniliformin is highly toxic and results in rapid death in chicks and rats (Battilani et al. 2009). Cardiac injury, with alterations in the cardiac electrical conductance, was shown to be a primary cause of mortality in birds after prolonged feeding with MON. Bird consumption of MON caused poor growth performance, increased serum pyruvate levels, and cardiopathy (Reams et al. 1997). Acute mortality and gross lesions, including ascites, hydropericardium, and myocardial pallor have been observed in broilers, turkeys, and ducklings (Engelhardt et al. 1989).

The cytotoxic action of moniliformin was attributed to the inhibition of pyruvate dehydrogenase (Gathercole et al. 1986). Moniliformin also has been shown to increase cardiac permeability in young rats and ducklings, suggesting a mechanism for inducing Keshan disease in humans (Zhang and Li 1989). Using rat cardiac tissues (Chen et al. 1990), moniliformin was shown to inhibit other enzymes, including glutathione peroxidase and glutathione reductase. It was suggested, therefore, that free radical metabolism in the heart was compromised from inhibition of these crucial enzymes.

3.4 Trichothecenes

Trichothecenes are compounds containing sesquiterpene rings that are characterized by a 12,13-epoxy-trichothec-9-ene nucleus. They are produced by various *Fusarium* species, including *F. sporotrichioides*, *F. poae*, *F equiseti*, *F. acumninatum*, as well as species from the genera *Myrothecium*, *Cephalosporium*, *Verticimonosporum*, *Trichoderma*, *Trichothecium*, and *Stachybotrys* (EFSA 2011b). *Fusaria* produce type A and B trichothecenes. Types A and B are distinguished by the presence of an oxygen or carbonyl functional group at the C-8 position, respectively. The lack of the carbonyl group tends to make type A trichothecenes more toxic (Smith and Solomons 1994). The type A trichothecenes include T-2 toxin (T-2), HT-2 toxin (HT-2), neosolaniol (NEO), diacetoxyscirpenol (DAS), and monoacetoxyscirpenol (MAS), while type B trichothecenes include deoxynivalenol (DON, also known as vomitoxin) and its 3-acetyl and 15-acetyl derivatives (3AcDON and 15AcDON, respectively), nivalenol (NIV), and fusarenon X (FusX) (Krska et al. 2007). Although more than 150 trichothecenes have been identified, data about their natural occurrence in feed and food mainly concern T-2 toxin and HT-2 toxin, diacetoxyscirpenol (DAS), deoxynivalenol (DON or vomitoxin), and nivalenol (NIV). Both T-2 toxin and DAS are the most toxic and are soluble in nonpolar solvents (e.g., ethyl acetate and diethyl ether), whereas DON and its parent compound nivalenol are soluble in polar solvents such as alcohols (Trenholm et al. 1986). Trichothecenes are classified as gastrointestinal toxins, dermatotoxins, immunotoxins, hematotoxins, and gene toxins. Cytotoxicity of trichothecenes has been attributed to their potent inhibition of protein, RNA, and DNA synthesis. Other toxic effects of trichothecenes involve disruption of membrane transport and function, suppression of the immune response, and abnormal blood function effects (Hussein and Brasel 2001).

3.4.1 T-2 and HT-2 Toxins

T-2 and HT-2 toxins are mainly products of *Fusarium langsethiae*, but it may not be the only one producing these toxins, because other species, such as *Fusarium poae* or *Fusarium sporotrichioides* were also identified to possibly produce them. T-2 and HT-2 are toxic to all animal species, including humans. Symptoms of human intoxications are described as being Alimentary Toxic Aleukia (ATA), characterized by sepsis and hemorrhages and a general pancytopenia. One toxic effect exerted by the T-2 and HT-2 toxins is the inhibition of protein synthesis, which also affects immunoglobulin synthesis and, therefore, humoral immunity. Cell membrane functions and lipid peroxidation are also altered and account for many of the acute effects of T-2 and HT-2 toxins, including the necrotic lesions observed at contact sites. The systemic toxic effects that follow T-2 and HT-2 dietary exposure cause apoptosis of proliferating cells, such as bone marrow cells (inhibition of hematopoiesis) and cells of the immune system (lymphoid depletion) (EFSA 2011b). Comparable

symptoms have been described in farm animal species, often accompanied by local necroses in the upper gastrointestinal tract (Nesic et al. 2012). There are significant differences in the sensitivity of monogastric species and ruminants to the T-2 and HT-2 toxin, which is attributed to the effective presystemic elimination (de-epoxidation) of the toxins by the rumen of ruminant microflora (Jakic-Dimic and Nesic 2011a).

3.4.2 Deoxynivalenol

Deoxynivalenol (DON, vomitoxin) is produced by *F. graminearum*, *F. culmorum*, *F. crookwellense*, *F. sporotrichioides*, *F. poae*, *F. tricinctum*, and *F. acuminatum* (Pittet 1998). Intoxication with vomitoxin is manifested by a decrease in food intake or its refusal, vomiting, and digestive disorders with subsequent losses of weight gain. From a practical viewpoint DON is of outstanding importance among the B type trichothecenes because of its frequent occurrence at levels high enough to cause adverse effects, especially in pigs, which are the most susceptible. Ruminants and poultry are regarded to be less sensitive (Dänicke 2002; Dänicke et al. 2008; EFSA 2004a, b; Seeling and Dänicke 2005). Partial species differences were also found in DON metabolism. Susceptibility to DON is influenced by gender as well, i.e., males are more susceptible than females. A dose of 2 ppm DON in pig feed caused a reduction in feed conversion and body weight. Poultry tolerated 5 mg DON per ton of feed (5 ppb). A slight decrease in feed conversion was observed in dairy cows fed a diet containing 1% DON (Trenholm et al. 1984). The gastrointestinal system is the target organ of this toxin. In practice, the co-occurrence of DON and ZEA, or even additional mycotoxins in contaminated cereals exacerbates the management of affected animals (Döll and Dänicke 2011).

3.4.3 Diacetoxyscirpenol (DAS, Anguidine)

Diacetoxyscirpenol is one of the most toxic of the trichothecene mycotoxins. It is produced by certain species of *Fusarium* (e.g., *F. poae*, *F. semitectum*, *F. moniliforme*, *F. sporotrichioides*, *F. acuminatum*, *F. culmorum*, *F. crookwellense*, *F. venenatum*, *F. sambucinum*, *F. graminearum*, *F. equiseti*, *F. solani*, *F. roseum*, *F. tricinctum*, *F. avenaceum*, *F. langsethiae*, *F. compactum*, and *F. clamydosporum*; Omurtag et al. 2007; Schollenberger et al. 2007). A sublethal dose of the toxin resulted in cellular depletion and necrosis in the lymphopoietic organs, multifocal necrosis in the intestinal epithelium, and diffuse necrosis of germinal epithelium, with consequent progressive tubular degeneration of the testicles. After 3 exposure days, lymphopenia, neutropenia, and anemia were observed (Conner et al. 1986). The toxic effects of DAS in humans and animals are similar and include vomiting, diarrhea, hypotension, and myelosuppression (Battilani et al. 2009).

3.4.4 Nivalenol (NIV)

Nivalenol is primarily produced by *Fusarium cerealis* (*F. crookwellence*), *F. poae*, and *F. nivale* and to a lesser extent by *F. culmorum* and *F. graminearum* (Eriksen 2003). NIV belongs to type B trichothecenes, which are characterized by the presence of a carbonyl group at C-8 position. Nivalenol has often been reported in maize red ear rot throughout the European maize growing areas (Logrieco et al. 2002). It is a typical metabolite after dry and hot summers when harvest is performed earlier than usual (Pettersson 1996). Different NIV effects have been reported in acute toxicity studies. Such effects included bone marrow toxicity, erythropenia and slight leucopenia, hemorrhage and congestion in the intestine, and toxicity to lymphoid organs (Ryu et al. 1988), diarrhea, damage to epithelial mucous membranes of the intestine, the thymus, and testis (Ueno 1984). Major toxic effects produced in subacute, subchronic, and chronic toxicity experiments with NIV in mice were immunotoxicity, hematotoxicity, and reduced body weight gain, reduced feed intake, and organ weight changes (without histopathology findings). In subacute feeding studies with swine, NIV caused mild pathological changes in the gastrointestinal tract, spleen, and kidney, body weight gain, and food consumption (Pronk et al. 2002).

4 Prevention and Control of Fusarial Toxins

There are a number of approaches that can be taken to minimize mycotoxin contamination of the feed chain. They include prevention of fungal growth, and therefore mycotoxin formation, strategies to reduce or eliminate mycotoxins from contaminated feedstuffs or to divert contaminated products to low-risk uses.

Agricultural practices such as crop rotation and soil tillage are recommended to control plant contamination with *Fusarium* spp., even if these techniques are not always recognized as being efficient. In addition, removal, burning, or burial of crop residues is likely to reduce *Fusarium* inoculum for the following crop (Jouany 2007).

Because the contamination by *Fusaria* is most likely when the crop flowering stage occurs at the time of spore release, planting maize at earlier dates in temperate areas will often result in a lower contamination levels; this is true even if annual weather changes challenge the potential advantage of planting earlier (Blandino et al. 2009; Munkvold 2003). In wheat and barley, winter varieties develop and mature earlier than spring varieties and consequently have a reduced risk of *Fusarium* infection (Jouany 2007).

The harvest and postharvest control of pathogens is linked to the timing of harvest because, generally, earlier harvest results in lower concentrations of mycotoxins (Jones et al. 1981). Grain cutting height is another important factor in preventing postharvest contamination. Post harvest, damaged grains should be eliminated and the humidity level of the kernels lowered to reduce the possibilities of fungal infection and toxin production. Plant hydration and humidity are also important. A plant water activity <0.65 and a humidity level <14% in cereals usually limit

fungal growth; effectively, *Fusarium* spp. need 17–19% humidity to grow. The storage temperature after harvest has an effect on fungal growth too and, especially in silo storage temperature control is important. In particular, good ventilation that incorporates cooling and drying operations are necessary to avoid enhanced contamination during storage (Jouany 2007).

One strategy for controlling toxin production is to plant cereal varieties that are more resistant to injury by *Fusarium* spp. and insects. Fungal geneticists have unraveled the pathways and the genes responsible for synthesizing and regulating mycotoxin production, especially aflatoxin and the trichothecenes (Bhatnagar et al. 2008; Yu and Keller 2005). Information from this work may assist in developing plants that are resistant to toxin accumulation. What is sought is to achieve the success already achieved by incorporating Bt genes in maize hybrids, i.e., protection against insect attack (Wu et al. 2004). The transgenic Bt maize contains a gene from the soil bacterium *Bacillus thuringiensis*, which encodes for a protein delta-endotoxin that is toxic to common lepidopteran maize pests. These hybrids assist in managing mycotoxins because insect damage is often a major etiological factor in facilitating toxigenic fungal infection of crops (Dowd 1998). Bt maize is effective in reducing the incidence of fumonisin contamination, but is less effective in reducing deoxynivalenol contamination (Munkvold 2003). This response difference reflects different disease patterns and pathogens as deoxynivalenol is associated with Gibberella ear rot, whereas fumonisin production is associated with Fusarium ear rot, and the occurrence of Gibberella ear rot is not as strongly influenced by insect damage as is fumonisin accumulation (Munkvold and Desjardins 1997). Lower levels of *Fusarium* mycotoxins, fumonisin, and deoxynivalenol in Bt corn could have significant market and health impacts, both in the USA and around the world. It is estimated that at current planting levels, Bt corn saves farmers in the USA about $17 million annually through reduced fumonisin and deoxynivalenol damage alone (Wu et al. 2004).

Chemical control of the pathogen is difficult because, to be efficient, any fungicides applied must be totally lethal to *Fusarium* spp.; if not, they stimulate mycotoxin production in vitro (D'Mello et al. 1998).

Another control alternative is to utilize biological control with microbial antagonists or competitors to *Fusarium* spp. These can be integrated into contamination control strategies by spraying selected microbial competitors on plants at the flowering stage to eradicate or limit the growth of toxin producers (Jouany 2007). Some biological agents, such as some strains of *Bacillus subtilis*, *Bacillus thuringiensis*, *Candida*, *Pseudomonas,* or *Trichoderma* spp., are already approved in the European Union.

Biological methods or application of physical or chemical methods are different possibilities for the postharvest decontamination strategies. Many of these strategies are still at the study level. Farm feed storage and on-farm feeding systems can also contribute to mycotoxin exposure of the animals being fed. Simple measures can be used to significantly reduce the risk of mycotoxin exposure on the farm. Storage of grain at an appropriate moisture content (<130 g/kg), measuring grain temperature regularly, and inspecting for insects and wet spots regularly will limit the possibility

of fungal infection of feeds and feedstuffs. The risk of feed contamination will be reduced in animal units with rapid turnover of feed because there will be less time for fungal growth and toxin production. Recently, Australian researchers performed a survey (Moore et al. 2008), in which they investigated the on-farm occurrence of aflatoxin, deoxynivalenol, and zearalenone in cereal grains, forage, and straw. All three mycotoxins were found in all commodities, with zearalenone having the highest occurrence rate. Interestingly, grains had the lowest frequency of contamination but are often the only source of mycotoxins considered when examining a field toxicosis. These results highlight the potential risk of contamination of feedstuffs and forages, other than grain used in animal production. Moreover, the contamination of straw, which may be used as a roughage source in horse and ruminant diets, or as bedding for pigs, poultry, and horses, may also be a source of mycotoxin exposure on farms, as can grain dust (Degen 2011).

An important method for mycotoxin control is to alleviate and/or prevent harmful effects of mycotoxins already present in feed. To minimize the impact of mycotoxins one approach is to dilute feed with uncontaminated feedstuffs. Dilution of mycotoxin-contaminated grain with uncontaminated grain is one of the simplest and most widely utilized methods for improving feed intake and weight gain of animals. However the success of this approach depends on the degree of contamination, the dilution achieved, and the availability of a source of uncontaminated grain. In some countries, this practice is prohibited.

There is also the possibility of using various feed additives, which either adsorb mycotoxins on their surface or foment enzyme degradation of mycotoxins. The efficacy of alleviating harmful effects depends mostly on chemical structure of the adsorbent, as well as on the type of mycotoxin present. These are substances that are not resorbable from the gut. These substances act by physically binding some chemicals and blocking their resorption. Mineral adsorbents (e.g., hydrated sodium calcium aluminosilicate, sodium bentonit, dietary clay, and zeolites) and active charcol are among those commonly used for this purpose. The feasibility of utilizing organic adsorbents has also been examined, particularly esterified glucomanane which is isolated from the inner layer of yeast cell wall and which possesses significant adsorption capacity (Devegowda et al. 2004; Nesic 2003; Nesic et al. 2008a, b). Recently a new type of additive was developed which contains microorganisms that have the ability to enzymatically modify the mycotoxin structure (Fuchs et al. 2002; Nesic et al. 2011, 2012).

A program to control mycotoxin contamination from field to table is needed, and should involve applying the criteria of the HACCP (Hazard Analysis Critical Control Points) approach. This approach requires an understanding of the important aspects of interactions that occur at different levels of the food chain:

- Toxigenic fungi and crop plants interaction
- The on-farm plant production and crop harvest methods
- The production of livestock using grains and processed feeds
- Development of processed foods for human consumption
- Understanding the marketing and trade channels, including storage and delivery of foods to the consumer's table.

A good testing protocol for mycotoxins is necessary to manage all of the control points for finally being able to ensure a food supply free of toxic levels of mycotoxins for the consumer (Richard 2007).

5 Mycotoxin Detection

Mycotoxins present a major analytical challenge because of the range of chemical compounds they represent, and the array of feed matrices in which they are found. Analysis is essential for determining the extent of mycotoxin contamination, for risk analysis, for confirming the diagnosis of a mycotoxicosis and for monitoring mycotoxin mitigation strategies. Quantifying these compounds requires sophisticated laboratory equipment that includes high performance liquid chromatography, gas chromatography, gas chromatography/mass spectrometry, or liquid chromatography/mass spectrometry (Krska et al. 2008; Rahmani et al. 2009).

There are still several areas of mycotoxin analysis that require further study and refinement. These include improvements in commodity sampling techniques, performing analysis of conjugated toxins, and developing field or feed-mill screening techniques for feedstuffs.

Sampling is the single greatest source of error when quantifying mycotoxin contamination. The reason is that it is difficult to obtain feed samples representative of what may have caused a mycotoxicosis incident. Similarly, it is difficult to obtain representative samples to analyze for regulatory purposes from large grain consignments. These difficulties arise because of the uneven distribution of toxin within a commodity, in which mycotoxins occur (CAST 2003; Jakic-Dimic and Nesic 2011a; Whitaker 2003, 2006).

It has recently become apparent that there is a connection between "masked," "hidden," "bound," and/or conjugated mycotoxins in feedstuffs and the potential for animals to perform poorly. Mycotoxin conjugates may be formed as a result of plant metabolism (Berthiller et al. 2007; Gareis et al. 1990), but are not detected by using conventional analytical procedures. For example, zearalenone-4-glucoside, a conjugate of zearalenone and deoxynivalenol-3-glucoside, a conjugate of deoxynivalenol, can constitute up to 20% of the total content of the precursor mycotoxin in a feedstuff (Berthiller et al. 2005, 2006). It is likely that these conjugates will be hydrolyzed following ingestion, thereby increasing exposure to the precursor toxin. There is also evidence that ochratoxin A and fumonisins are conjugated by plants (Berthiller et al. 2007) and fumonisins may also be conjugated with sugars and proteins during food processing (Humpf and Voss 2004). Berthiller et al. (2009) reviewed the formation and determination of conjugated mycotoxins.

The development of immunological methods for mycotoxin detection (Pestka 1994), especially enzyme-linked immunosorbent assays (ELISA), although only semiquantitative, was a major step toward developing rapid, repeatable, and sensitive assays. These assays are suitable for field use and for screening feed commodities in feed mills. There are other approaches, most still experimental, that show

promise for rapid mycotoxin analysis without the need of sophisticated equipment. Such tests are flow-through ELISA, where the assay is conducted on a membrane or on gel-based columns, or lateral flow devices (LFD) and biosensors, and those based upon surface plasmon resonance (SPR) (Maragos and Busman 2010).

6 Summary

Exposure to mycotoxins occurs worldwide, even though there are geographic and climatic differences in the amounts produced and occurrence of these substances. Mycotoxins are secondary chemical metabolites of different fungi. They are natural contaminants of cereals, so their presence is often inevitable. Among many genera that produce mycotoxins, *Fusarium* fungi are the most widespread in cereal-growing areas of the planet. *Fusarium* fungi produce a diversity of mycotoxin types, whose distributions are also diverse. What is produced and where it is produced is influenced primarily by environmental conditions, and crop production and storage methods. The amount of toxin produced depends on physical (viz., moisture, relative humidity, temperature, and mechanical damage), chemical (viz., carbon dioxide, oxygen, composition of substrate, insecticides and fungicides), and biological factors (viz., plant variety, stress, insects, spore load, etc.). Moisture and temperature have a major influence on mold growth rate and mycotoxin production.

Among the most toxic and prevalent fusarial toxins are the following: zearalenone, fumonisins, moniliformin and trichothecenes (T-2/HT-2 toxin, deoxynivalenol, diacetoxyscirpenol, nivalenol). Zearalenone (ZEA; ZON, F-2 toxin) is a phytoestrogenic compound, primarily a field contaminant, which exhibits estrogenic activity and has been implicated in numerous mycotoxicoses of farm animals, especially pigs. Recently, evidence suggests that ZEA has potential to stimulate the growth of human breast cancer cells. Fumonisins are also cancer-promoting metabolites, of which Fumonisin B1 (FB1) is the most important. Moniliformin (MON) is also highly toxic to both animals and humans. Trichothecenes are classified as gastrointestinal toxins, dermatotoxins, immunotoxins, hematotoxins, and gene toxins. T-2 and HT-2 toxin, and diacetoxyscirpenol (DAS, anguidine) are the most toxic mycotoxins among the trichothecene group. Deoxynivalenol (DON, vomitoxin) and nivalenol although less toxic are important because they frequently occur at levels high enough to cause adverse effects.

The presence of mycotoxins in the animal diet can produce significant production losses. Any considerable presence of mycotoxins, in major dietary components, confirms the need to adopt a continuous prevention and control program. Such programs are usually based on several common approaches to minimize mycotoxin contamination in the food chain. Major strategies include preventing fungal growth and therefore mycotoxin formation, reducing or eliminating mycotoxins from contaminated feedstuffs, or diverting contaminated products to low risk uses. Because of the complexity of their chemical structures, mycotoxins also present a major analytical challenge. They are also found in a vast array of feed matrices.

Analysis is essential for determining the extent of mycotoxin contamination, for risk analysis, confirming the diagnosis of a mycotoxicosis and for monitoring mycotoxin mitigation strategies.

For the future, adequately controlling the mycotoxin problem in the livestock economy will depend on implementing appropriate agricultural management policies, as well as augmenting production and storage systems and analysis methods. Only such policies offer the opportunity to bring solid and long-lasting economical results to the livestock industry that is afflicted with the mycotoxin problem.

Acknowledgements Publication of this review was supported by the project of Serbian Ministry of science and education No. III 46009.

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