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Mycotoxigenic *Fusarium* species in animal feed☆

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Abstract

Fusarium species are among the most studied plant-pathogenic fungi, with several species causing diseases on maize, wheat, barley, and other food and feed grains. Decreased yield, as well as diminished quality and value of the grain, results in significant worldwide economic losses. Additionally, *Fusarium* species produce a chemically diverse array of mycotoxins such as diacetoxyscirpenol, deoxynivalenol, nivalenol, T-2 toxin, zearalenone, fumonisins, fusarin C, beauvericin, moniliformin, and fusaproliferin. The dominant *Fusarium* species associated with feed grain that produce these mycotoxins are reviewed with emphasis on their current taxonomy, phylogenetic relationships, and general biology. Ecological and environmental factors associated with plant–fungal interactions and potential mycotoxin contamination of feed also are discussed with primary emphasis on two main diseases: head blight of small grains and ear rot of maize. The past quarter-century has provided much detail on the morphology, physiology, genetics and genomics of *Fusarium* species. Such data are critical for understanding these fungi and for managing their impact on the safety, value, and yield of quality grain.
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Keywords: Mycotoxins; *Fusarium*; Head blight; Ear rot; Maize; Wheat; Barley; Oats

Abbreviations: DIMBOA, 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3-one; DIBOA, 2,4-dihydroxy-2H-1,4-benzoxazin-3-one; MBOA, 6-methoxy-2-benzoxazolinone; BOA, 2-benzoxazolinone; HMPMA, *N*-(2-hydroxy-4-methoxyphenyl) malonamic acid; HPMA, *N*-(2-hydroxyphenyl) malonamic acid; BEA, beauvericin; DAS, diacetoxyscirpenol; DON, deoxynivalenol or its acetylated derivatives; FB, fumonisin B_1, B_2, and B_3; FP, fusaproliferin; FUS, fusarin C; GB, gibberellins; HT2, HT-2 toxin; MON, moniliformin; NIV, nivalenol or its acetylated derivatives; T2, T-2 toxin; ZEA, zearalenone

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1. Introduction

The genus *Fusarium* was established by Link (1809) nearly 200 years ago and encompasses a diverse array of species of significance for being devastating plant pathogens that often produce a wide range of secondary metabolites. The association of some of these metabolites with cellular toxicity, effects on growth and development of animals, and cancer in humans and domesticated animals is of particular interest to agriculture and food safety. Fungal secondary metabolites negatively impacting animals are referred to as mycotoxins. The main mycotoxin classes of concern produced by *Fusarium* species include the trichothecenes, fumonisins and zearalenone. Several trichothecenes are of concern, including diacetoxyscirpenol, T-2 toxin, deoxynivalenol, and nivalenol. Information on the chemistry and animal toxicology of these mycotoxins can be found in other reviews in this issue (Fink-Gremmels and Malekinejad, 2007; Krska et al., 2007; Morgavi and Riley, 2007; Pestka, 2007).

Since *Fusarium* species are diverse in their host-associations and mycotoxin profiles, clearly identifying one species from another based on a range of morphological, molecular, and metabolic data is imperative given the need for proper control and precautionary measures that ensure a safe, valuable, high-quality, and high-yielding grain harvest. The taxonomic history of *Fusarium* species has been reviewed in great detail elsewhere (Gerlach and Nirenberg, 1982; Leslie and Summerell, 2006; Nelson et al., 1983, 1994; Nelson, 1992). The current review is intended as an update to the more recent taxonomic shifts among *Fusarium* species that are of particular agronomic and economic importance to the production of food and feed grain due to direct phytopathological interactions and indirect contamination by the various mycotoxins produced. The application of biological as well as phylogenetic species concepts, in addition to the traditional utilization of distinctive morphological differences, has resulted in numerous shifts in the taxonomy and systematics of *Fusarium* species within the last decade. The different species concepts and their relevant applications to *Fusarium* species are addressed in detail by Leslie and Summerell (2006).

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 will 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 important for long-term survival. Microconidia and macroconidia are important for wind and splash dispersal of the fungi. The conidia also are generally the propagules that result in infection of host plants. The impact of conidia and other factors on the ecology and phytopathology of *Fusarium* species will also be reviewed. Ecological and environmental parameters involving propagation, dispersal, host infection, disease development, mycotoxin production, and interaction with other organisms (plants, fungi, and bacteria) all influence the growth and physiological activity of *Fusarium* species. Understanding how the fungus interacts with its host and surrounding microbial community and how it responds to the various biological and climatic stimuli, especially as it relates to mycotoxin production, allows for more directed management strategies to be developed and implemented (reviewed in Jouany, 2007). For example, minimizing insect feeding damage to maize ears reduces ear rot and concurrently reduces mycotoxin contamination. Thus, implementation of strategies to reduce insect feeding, such as insecticide applications or

use of transgenic Bt maize that is resistant to European corn borer, results in decreased ear rot and decreased fumonisin contamination (Munkvold, 2003a,b).

The current review is outlined relative to the mycotoxins of interest. The *Fusarium* species producing each class of mycotoxins are discussed in turn. The species are listed in Table 1 along with their known sexual state (teleomorph), primary agronomic hosts, endemic regions, and major mycotoxins known to be produced. This is not an exhaustive review of all mycotoxins produced by *Fusarium* species or all *Fusarium* species that produce mycotoxins. Readers are directed to Desjardins (2006) and Leslie and Summerell (2006) for more extensive review and evaluation of the species and their associated mycotoxins. The goal of the current review is to address the major *Fusarium* species associated with feed grain and the major toxins of concern they are known to produce. Two main diseases are of primary concern: Fusarium head blight of small grains (primarily wheat, barley, and oats) and Fusarium ear rot of maize. Other grains such as rice, pearl millet, and sorghum are included as well because of their importance in some feed markets and geographical regions of the world.

2. Mycotoxin-producing *Fusarium* species

2.1. Trichothecenes

The first member of this toxin class was trichothecin, isolated from the fungus *Trichothecium roseum* in 1949. *Fusarium* trichothecenes were subsequently identified, including diacetoxyscirpenol from *F. scirpi*, nivalenol from *F. nivale* (now classified as *Fusarium kyushuense*), T-2 toxin from *F. tricinctum* (now classified as *Fusarium sporotrichioides*), and deoxynivalenol from *F. roseum* (now classified as *Fusarium graminearum*). Currently, more than 40 naturally occurring trichothecenes are known from *Fusarium* species (Desjardins, 2006), with a combined total of nearly 150 variants produced by species of *Fusarium*, *Cephalosporium*, *Cylindrocarpon*, *Myriothecium*, *Stachybotrys*, and *Trichoderma* (Grove, 1988). Deoxynivalenol, also commonly known as vomitoxin, is often the most prevalent trichothecene contaminating grain worldwide and is produced by *F. graminearum*, *Fusarium pseudograminearum*, and *Fusarium culmorum* (Table 1).

In addition to their animal toxicity (Pestka, 2007), trichothecenes also are phytotoxic to a range of plants, and production of the toxins enhances the virulence of some *Fusarium* species on some host plants but not others (Desjardins, 2006). Production of diacetoxyscirpenol by *F. sambucinum* was shown to enhance virulence toward parsnip roots, causing more rot if the fungus produced the trichothecene (Desjardins et al., 1992; Hohn and Desjardins, 1992). In contrast, diacetoxyscirpenol production was not necessary for *F. sambucinum* to cause potato tuber dry rot. In the case of *F. graminearum*, production of deoxynivalenol was shown to be a virulence factor enhancing disease development on several host species, including development of wheat head blight and corn ear rot (Bai et al., 2002; Desjardins et al., 1996; Harris et al., 1999; Nicholson et al., 1998; Proctor et al., 1995). Deoxynivalenol-nonproducing strains were less able to spread in wheat heads or maize ears after initial infection. The mechanism of phytotoxicity is thought to be based on binding to ribosomes and inhibition of peptidyltransferase resulting in inhibited protein synthesis.

Table 1
Fusarium species, known sexual state (teleomorph), primary agronomic hosts, endemic regions, and major mycotoxins known to be produced

Fusarium species	Teleomorph	Hosts of primary concern[a]	Endemic geographical region(s)	Mycotoxin(s)[b]
F. avenaceum	*Gibberella avenacea*	Maize; small grains	Worldwide	MON, BEA, FUS
F. crookwellense	Unknown	Small grains	Worldwide	NIV, ZEA, FUS
F. culmorum	Unknown	Maize; small grains	Worldwide	DON, ZEA, NIV, FUS
F. fujikuroi	*Gibberella fujikuroi*	Rice	Worldwide	GB, MON, BEA, FB[c]
F. globosum	Unknown	Maize	Africa	FB, BEA, FP[c]
F. graminearum	*Gibberella zeae*	Maize; small grains	Worldwide	DON, ZEA, NIV, FUS
F. kyushuense	Unknown	Wheat	Japan	NIV, T2, DAS
F. langsethiae	Unknown	Small grains	Europe	DAS, T2, HT2, BEA[c]
F. napiforme	Unknown	Millet, sorghum	Africa, Argentina	FB, MON
F. nygamai	*Gibberella nygamai*	Sorghum	Africa, Australia	FB, MON, BEA
F. poae	Unknown	Small grains	Worldwide	DAS, NIV, BEA, FUS, T2, HT2
F. proliferatum	*Gibberella intermedia*	Maize	Worldwide	FB, MON, BEA, FP
F. pseudoanthophilum	Unknown	Maize	Africa	BEA
F. pseudograminearum	*Gibberella coronicola*	Small grains	Africa, Australia, North America	DON, ZEA
F. pseudonygamai	Unknown	Millet	Africa	MON, FP
F. sporotrichioides	Unknown	Small grains	Worldwide	T2, HT2, DAS, BEA, FUS
F. subglutinans	*Gibberella subglutinans*	Maize	Worldwide	MON, BEA, FP
F. thapsinum	*Gibberella thapsina*	Sorghum	Worldwide	MON
F. verticillioides	*Gibberella moniliformis*	Maize	Worldwide	FB, FUS, MON[c]

[a] The most prevalent hosts are indicated. "Small grains" refers mainly to wheat, barley, and oats.

[b] BEA, beauvericin; DAS, diacetoxyscirpenol; DON, deoxynivalenol or its acetylated derivatives; FB, fumonisin B1, B2, and B3; FP, fusaproliferin; FUS, fusarin C; GB, gibberellins; HT2, HT-2 toxin; MON, moniliformin; NIV, nivalenol or its acetylated derivatives; T2, T-2 toxin; ZEA, zearalenone.

[c] Production of this toxin is rare among strains of the species.

2.1.1. F. graminearum and F. pseudograminearum

F. graminearum (teleomorph, *Gibberella zeae*) has long been recognized as a variable species in terms of the mycotoxin profile, morphology, and *in vitro* characteristics of various strains. Two populations of *F. graminearum* were previously recognized based on morphological and cultural characteristics. The key diagnostic feature for distinguishing Group 1 from Group 2 populations was the ability of Group 2 strains to form abundant homothallic perithecia in single-spore derived cultures (Francis and Burgess, 1977). Group 1 strains did not form perithecia unless one strain was mated in a heterothallic fashion with another compatible Group 1 strain (Aoki and O'Donnell, 1999a,b). Additionally, the associated pathology of the two populations on small grains was distinctive (Desjardins, 2006; Francis and Burgess, 1977; Leslie and Summerell, 2006). Group 1 strains were soil-borne pathogens of wheat, barley, oats and *Medicago* causing crown rot and foot rot in Australia, South Africa, and the Pacific northwest of the United States. In contrast, Group 2 strains typically caused ear rot of maize and head blight of wheat, barley, and oats in northern temperate regions of the Northern Hemisphere.

Within recent years the application of phylogenetic analyses based on DNA sequence comparisons of various genetic loci have allowed for further refinement of the species and resulted in recognition of several new species. Combined morphological and molecular analyses of Group 1 and Group 2 strains previously identified as *F. graminearum* have recognized the Group1 population as the distinct species *F. pseudograminearum* (Aoki and O'Donnell, 1999a; Scott and Chakraborty, 2006). In fact, while the Group 2 *F. graminearum* strains were phenotypically most similar to *F. pseudograminearum*, they were more closely related to *Fusarium crookwellense* (syn. *Fusarium cerealis*) and *F. culmorum* based on phylogenetic analysis of β-tubulin sequence data. *F. pseudograminearum* was the sister taxon to the clade formed by the other four species. *Gibberella coronicola* is the name given to the heterothallic teleomorph of *F. pseudograminearum* (Aoki and O'Donnell, 1999b). A recent multilocus phylogenetic analysis indicated *F. pseudograminearum* is a single phylogenetic species without development of geographically structured lineages (Scott and Chakraborty, 2006). Although studies are limited, one metabolic distinction between *F. pseudograminearum* and *F. graminearum* is that only the latter species produces the trichothecene nivalenol (Blaney and Dodman, 2002). Strains of both species produce the trichothecene deoxynivalenol (and its derivatives), as well as the polyketide estrogenic metabolite zearalenone (Table 1).

O'Donnell et al. (2000, 2004) have proposed additional taxonomic revisions to homothallic *G. zeae*/*F. graminearum* populations based on extensive molecular phylogenetic analyses of 11 nuclear genes. Nine phylogenetically distinct biogeographically structured lineages were identified and formally recognized as distinct species. In addition to *F. graminearum* (lineage 7), the new phylogenetic species are *F. austroamericanum* (lineage 1), *F. meridionale* (lineage 2), *F. boothii* (lineage 3), *F. mesoamericanum* (lineage 4), *F. acaciae-mearnsii* (lineage 5), *F. asiaticum* (lineage 6), *F. cortaderiae* (lineage 8), and *F. brasilicum* (lineage 9). Putative geographical regions of endemism are South America for *F. austroamericanum*, *F. brasilicum*, *F. cortaderiae*, and *F. meridionale*; Central America for *F. mesoamericanum*; Asia for *F. asiaticum*; and Australia and perhaps Africa for *F. acaciae-mearnsii* (O'Donnell et al., 2004). The endemic areas of *F. boothii* and *F. graminearum* are more broadly distributed globally. The primary species in temperate areas of the northern

hemisphere associated with Fusarium head blight appears to be lineage 7 (*F. graminearum sensu stricto*).

Strains of the *G. zeae* species complex (*F. graminearum* and the other phylogenetic lineages) are homothallic and do not require obligatory outcrossing to produce perithecia, yet mating between different strains can be performed such that *G. zeae* perithecia containing recombinant ascospore progeny can be produced (Bowden and Leslie, 1999). Such outcrossing has facilitated extensive genetic analyses including creation of a genetic map (Jurgenson et al., 2002). The capacity for interbreeding among the nine phylogenetic species given above was assessed by crossing representative strains of each species with three female tester strains of *F. graminearum* lineage 7 (Bowden et al., 2004). While cross fertility was highly variable and differed among the three tester strains, all males from all the lineages successfully fertilized at least one of the female tester strains. The resulting perithecia produced viable ascospores, suggesting fertility barriers between the lineages do not exist. Given such cross fertility, Jurgenson et al. (2002) have suggested that "... these [*F. graminearum*] strains are members of geographically separated and genetically distinct populations rather than distinct species." Given the ongoing discussion regarding species delineation, I will refer to the full collection of lineages as the *G. zeae*/*F. graminearum* species complex.

2.1.2. *F. crookwellense (syn. F. cerealis)*

F. crookwellense is also commonly referred to as *F. cerealis*, and the taxonomic history for this synonymy is summarized in detail elsewhere (Desjardins, 2006; Nirenberg, 1990). In brief, *F. crookwellense* was described from extensive collections of strains mainly from temperate climates of eastern Australia, northern United States and Canada, Europe, South Africa, and China (Burgess et al., 1982), but the description of this species was later determined by Nirenberg (1990) to be predated by the description of *F. cerealis*, thus relegating *F. crookwellense* as a synonym of *F. cerealis*. However, due to the lack of proper type material, some authors believe the name *F. crookwellense* is preferable for isolates that fit its description (Leslie and Summerell, 2006).

As noted above, *F. crookwellense* is phylogenetically related to *F. graminearum* and *F. culmorum* (Aoki and O'Donnell, 1999a; O'Donnell et al., 2000). Like those species, *F. crookwellense* can be a component of corn ear rot and wheat head blight in Europe and Canada, though it is typically occurs at lower frequencies than *F. avenaceum*, *F. culmorum*, and *F. graminearum* (Bottalico and Perrone, 2002; Logrieco et al., 2002; Xue et al., 2004). Although *F. crookwellense* has not been associated with any disease outbreaks among animals or humans, strains are capable of producing the trichothecene nivalenol as well as zearalenone and fusarin C (Table 1) (Desjardins, 2006).

2.1.3. *F. culmorum*

F. culmorum is morphologically similar to *F. graminearum* and *F. crookwellense*, all three of which are phylogenetically closely related as already mentioned above. *F. culmorum* and *F. crookwellense* also share similar geographical distribution and climate preferences (Desjardins, 2006). Host range for *F. culmorum* is very broad, with the fungus often causing root and stem rots (Leslie and Summerell, 2006; Marasas et al., 1984). Among the *Fusarium* species causing head blight of wheat and other cereals, *F. culmorum* has a high frequency of

association in areas having cool weather during the growing season (Bottalico and Perrone, 2002; Waalwijk et al., 2004a). The species has also been associated with corn ear rot in Europe (Logrieco et al., 2002). Animal toxicoses associated with the consumption of feed contaminated with *F. culmorum* and *F. graminearum* are known (Marasas et al., 1984), but since the two species have very similar toxin production capabilities (Table 1), direct association of *F. culmorum* with animal toxicity is not known but is considered probable and worth further study, especially since culture material of *F. culmorum* is reported to be toxic to laboratory animals (Marasas et al., 1984).

2.1.4. Fusarium poae, F. sporotrichioides, F. kyushuense, and Fusarium langsethiae

These four species are phylogenetically related in historically what has been referred to as section *Sporotrichiella* (Knutsen et al., 2004; Nelson et al., 1983; Schmidt et al., 2004; Yli-Mattila et al., 2004), though such sectional classifications are avoided by some because of phylogenetic incongruence (Aoki and O'Donnell, 1998). All four are known to infect small grains such as wheat, barley, and oats in temperate climates. *F. poae* and *F. sporotrichioides* have worldwide distribution, while *F. kyushuense* is known from Japan and *F. langsethiae* is currently restricted to Europe (Table 1). *F. poae* is a major species associated with the head blight complex of small grains in Europe (Bottalico and Perrone, 2002) and has been identified as a minor component of corn ear rot in Europe (Logrieco et al., 2002). *F. sporotrichioides* is a minor component of both head blight of small grains and corn ear rot in Europe. *F. langsethiae* is also likely to be a minor component of head blight.

All four species are of unique concern among *Fusarium* species infecting food and feed grain because they produce diacetoxyscirpenol and the T-2 and HT-2 toxins (Table 1). *F. langsethiae* and *F. sporotrichioides* share a more similar mycotoxin profile in that neither is known to produce nivalenol (Thrane et al., 2004), while *F. kyushuense* and *F. poae* both produce the trichothecenes nivalenol, diacetoxyscirpenol, and T-2 toxin (Aoki and O'Donnell, 1998; Marasas et al., 1984; Thrane et al., 2004). The full mycotoxin profile of *F. kyushuense* is uncertain (Thrane et al., 2004).

F. poae and *F. sporotrichioides* have been associated with disease outbreaks among humans and animals. Both species were isolated from the grain associated with the outbreak of alimentary toxic aleukia in Russia as well as outbreaks of hemorrhagic syndrome in cattle, swine, and poultry in the midwestern United States (Desjardins, 2006; Marasas et al., 1984). Feeding experiments with pure cultures of each species suggested *F. sporotrichioides* may be the more toxic of the two species (Marasas et al., 1984).

2.2. Zearalenone

First isolated and characterized from *G. zeae* by Urry et al. (1966), zearalenone is a unique mycotoxin both structurally and functionally. The history, toxicology and chemistry of zearalenone are detailed elsewhere in this special issue (Morgavi and Riley, 2007; Fink-Gremmels and Malekinejad, 2007; Krska et al., 2007).

2.2.1. F. crookwellense, F. culmorum, F. graminearum, and F. pseudograminearum

These four species were introduced above since all produce trichothecenes in addition to zearalenone (Table 1). Production of zearalenone currently is restricted to these species plus

F. equiseti and *F. semitectum*, which are not included in this review because they are generally secondary invaders more commonly associated with soils (Desjardins, 2006; Leslie and Summerell, 2006). The restriction of zearalenone production to a few trichothecene producers demonstrates the need for accurate species identification of *Fusarium* species as well as for integrated mycotoxin sampling, monitoring, and management strategies.

2.3. Fumonisins

Fumonisins are a family of mycotoxins originally characterized from culture material of *Fusarium verticillioides* strain MRC826 (Bezuidenhout et al., 1988; Gelderblom et al., 1988). The history, toxicology and chemistry of fumonisins are detailed elsewhere in the current special issue (Morgavi and Riley, 2007; Voss and Haschek, 2007; Krska et al., 2007). Fumonisins are sphinganine analog mycotoxins bearing a structural resemblance to free sphingoid bases found in all classes of sphingolipids, which are a diverse class of lipids comprising over 300 distinct compounds (Merrill et al., 1997). The structural similarity between free sphinganine and fumonisins lead to the discovery that fumonisins are potent and specific inhibitors of the mammalian acyl CoA-dependent ceramide synthase (Wang et al., 1991), a key enzyme in the *de novo* sphingolipid biosynthesis pathway. Such inhibition of ceramide synthase also occurs in plants (Abbas et al., 1994; Riley et al., 1996; Williams et al., 2006).

2.3.1. F. verticillioides

Animal toxicity associated with mouldy maize has been documented for more than 100 years in the United States. Toxic syndromes were reported for a range of animals, with horses and mules being particularly prone to staggers, tremors, paralysis, convulsions, and death [reviewed in this issue by Morgavi and Riley (2007) and Voss and Haschek (2007)]. Butler (1902) was able to induce equine leucoencephalomalacia in horses fed naturally contaminated mouldy maize. Identification of the causal fungus remained unknown until Sheldon (1904) described *Fusarium moniliforme* as the pink mold growing on maize implicated in a toxicosis event. Much taxonomic confusion has centered on this name, and a number of distinct species have been segregated out and formally recognized, including *Fusarium proliferatum* and *F. subglutinans*, two other species that are often associated with maize (Marasas et al., 1984; Nelson et al., 1983; Nirenberg, 1989). In addition to traditional morphological criteria, refinement in the delineation of species was based on application of a biological species concept relative to distinct mating populations (Hsieh et al., 1977; Kuhlman, 1982; Leslie, 1991; Leslie, 1995), as well as subsequent application of a phylogenetic species concept based on analyses of DNA sequences (Nirenberg and O'Donnell, 1998; O'Donnell et al., 1998). Additionally, the formal recognition of *F. moniliforme* as a valid specific epithet was disputed for the maize-associated species producing simple phialides with long chains of conidia. The accepted taxonomically valid name for this fungus is *F. verticillioides* (Gerlach and Nirenberg, 1982).

The discovery of mating populations and application of the biological species concept was possible because of the heterothallic formation of perithecia in culture when strains of opposite mating type were grown together (Hsieh et al., 1977; Leslie, 1991, 1995; Yun et

al., 2000). Perithecia are the fruiting bodies formed during sexual reproduction and contain the asci and resulting ascospores. Several of the various species segregated out of *F. moniliforme* now have a known sexual state, including *F. verticillioides* (Desjardins, 2003; Samuels et al., 2001). As dictated by nomenclatural rules, a fungal sexual state (teleomorph) is recognized with its own scientific binomial independent of the name assigned its asexual state (anamorph). Thus, the anamorph *F. verticillioides* is associated with its teleomorph *G. moniliformis*, previously known as *G. fujikuroi* mating population A. At least nine such mating populations are now known within the *G. fujikuroi* species complex (Britz et al., 1999; Klaasen and Nelson, 1996; Leslie, 1995; Leslie et al., 2005b; Nirenberg and O'Donnell, 1998; Samuels et al., 2001; Zeller et al., 2003). The species *G. fujikuroi sensu stricto* is associated with the anamorph *Fusarium fujikuroi*, which is mating population C in the species complex.

F. verticillioides is a cosmopolitan ascomyceteous fungus consistently associated with maize worldwide. The fungus is not host specific and has been reported to exist in association with many plant species in addition to maize (Bacon et al., 1996), though the exact number may be confounded by historical confusion over fungal species delineation and taxonomy (Kerenyi et al., 1999; Leslie, 1995). While several major diseases of maize, including seed rot, seedling blight, root rot, stalk rot, and ear rot, are attributed to *F. verticillioides* (Kommedahl and Windels, 1981; Limber, 1927; White, 1999), the fungus often systemically colonizes vegetative tissues without causing disease symptoms (Bacon and Hinton, 1996; Foley, 1962). Such symptomless infections are of concern because of the potential for fumonisin contamination of high grade maize that is visually sound. Maize kernels are generally known to be frequently infected with *F. verticillioides*, indicating that seed transmission is common and may be an important mechanism of dispersal and persistence in a maize-field environment.

The role fumonisin production plays in pathogenic interactions with maize seems to vary based on the specific disease interaction and maize genotype. In relation to corn seedling blight, fumonisins were suggested to increase the virulence of *F. verticillioides* but were not necessary or sufficient for disease development (Desjardins et al., 1995). More recent assessments indicate fumonisin B_1 is necessary for development of the full suite of seedling blight disease symptoms and is sufficient for inhibition of root development, stunting, and leaf lesion development, although the severity of disease development is dependent on the maize genotype (Glenn and Riley, personal observation). In contrast, detailed studies have shown that fumonisin production is not necessary for *F. verticillioides* to cause ear rot (Desjardins et al., 1998, 2002; Desjardins and Plattner, 2000).

Fumonisin production by *F. verticillioides* is dependent upon possession and proper function of a 42.3 kb biosynthetic gene cluster located on chromosome 1. This cluster of 15 co-expressed genes encodes a number of biosynthetic enzymes necessary for formation and modification of the polyketide backbone of the fumonisins (Bojja et al., 2004; Butchko et al., 2003a,b; Proctor et al., 1999, 2003, 2006; Seo et al., 2001). The key gene is *FUM1* (formerly designated *FUM5*) which encodes a polyketide synthase, and targeted deletion of *FUM1* by homologous recombination eliminated fumonisin production in the mutants (Proctor et al., 1999). Deletion of *FUM6* or *FUM8*, which encode for a cytochrome P450 monooxygenase and an aminotransferase, respectively, also eliminated fumonisin production (Bojja et al., 2004; Seo et al., 2001). Deletion of other genes in the cluster resulted in

no obvious phenotype or the deletion strains had modified biosynthesis of fumonisin B_1, B_2, B_3, and B_4 (Butchko et al., 2003a,b; Proctor et al., 2003).

2.3.2. F. proliferatum and F. fujikuroi

F. proliferatum is another species commonly found infecting maize, and it too produces fumonisins (Bacon and Nelson, 1994; Leslie et al., 1990; Leslie, 1995; Logrieco et al., 2002; Pascale et al., 2002; Ross et al., 1990). The teleomorph is *G. intermedia* (=*G. fujikuroi* mating population D) (Samuels et al., 2001). Considered a generalist, *F. proliferatum* has an unusually broad host range across agricultural crops (*e.g.*, banana, maize, fig, mango, pine, sorghum, and wheat) as well as native prairie grasses (Leslie, 1995; Leslie et al., 2004a; O'Donnell et al., 1998). This species is intriguing in that it also produces a broad array of mycotoxins. In addition to the fumonisins, *F. proliferatum* produces moniliformin, beauvericin, and fusaproliferin, all at significant levels (Bacon and Nelson, 1994; Desjardins et al., 2000b; Leslie et al., 2004a; Logrieco et al., 2002; Pascale et al., 2002; Shephard et al., 1999). Some strains of *F. proliferatum* produced significantly greater quantities of fumonisins than strains of *F. verticillioides* (Leslie et al., 2004a). Interestingly, comparative genomic analysis of the fumonisin biosynthetic gene clusters from *F. proliferatum* and *F. verticillioides* found them to be completely syntenic (*i.e.*, the position of each gene and direction of transcription relative to each other were conserved), yet the regions flanking the fumonisin gene clusters were highly dissimilar suggesting that the cluster has been inserted at different genome locations in both species (Waalwijk et al., 2004b). Thus, the common occurrence of *F. proliferatum* with *F. verticillioides* in maize, and their ability to cause ear rot as well as produce fumonisins and additional mycotoxins, suggests both fungi should be considered when assessing fungal population dynamics in relation to minimizing risks to the quality of maize produced.

F. proliferatum is morphologically similar to *F. verticillioides*, and the two were once lumped together into *F. moniliforme* as noted earlier. Yet, *F. proliferatum* can be distinguished based on its production of conidia in false heads and chains from polyphialides (Leslie and Summerell, 2006). *F. proliferatum* is phylogenetically closely related to the rice pathogen *F. fujikuroi* (teleomorph, *G. fujikuroi*; mating population C) (Malonek et al., 2005a; O'Donnell et al., 1998; O'Donnell and Cigelnik, 1997), and the two have been shown to be interfertile, though the level of fertility is generally reduced compared to intraspecific crosses (Desjardins et al., 1997; Leslie et al., 2004b). Within the context of the biological species concept, such interfertility suggests the two species may actually represent variants of the same species (Leslie et al., 2004b). However, the mycotoxin profiles of the two species are very distinct. Most notably *F. fujikuroi* is the only species in the *G. fujikuroi* species complex that produces gibberellins, even though *F. proliferatum* and other members of the species complex do have part or all of the gibberellin biosynthetic gene cluster (Desjardins et al., 2000a; Malonek et al., 2005a). Gibberellins are plant hormones that contribute to the Bakanae disease of rice (Sun and Snyder, 1981). While some strains of *F. fujikuroi* produce low levels of fumonisins, most strains are fumonisin non-producers that produce significant quantities of moniliformin and beauvericin (Desjardins et al., 2000a; Proctor et al., 2004). Thus, the distinctive host preferences and mycotoxin profiles of *F. proliferatum* and *F. fujikuroi* argue against recognizing them as the same biological species. Interestingly, *F. proliferatum* does not produce gibberellins yet does have all seven biosynthetic

genes organized in the same order and orientation as the *F. fujikuroi* genes (Malonek et al., 2005a). Gibberellin production could be restored in *F. proliferatum* by heterologous complementation of three mutated genes encoding enzymes responsible for the initial steps in the biosynthetic pathway with functional homologs from *F. fujikuroi* (Malonek et al., 2005b,c). Their interfertility does suggest a practical concern regarding outcrossing in natural environments and potential derivation of hybrid progeny producing a novel spectrum of mycotoxins (Desjardins et al., 1997; Leslie et al., 2004a,b). Leslie et al. (2004b) suggest the broad host range and geographical distribution of *F. proliferatum*, along with its relatively broad array of mycotoxins produced, are indicative of the species representing hybrid swarms of heterogeneous populations. Restriction fragment length polymorphism (RFLP) analysis of mitochondrial DNA also indicated *F. proliferatum* strains were highly diverse (Láday et al., 2004).

2.3.3. *Fusarium globosum*

F. globosum has close morphological association with *F. verticillioides* and *F. proliferatum* given its production of ellipsoidal microconidia in chains from monophialides and polyphialides but differs in that it also produces abundant globose microconidia singly or in botryose clusters on phialides (Rheeder et al., 1996). *F. proliferatum* and *F. fujikuroi* are closely related to *F. globosum* within the Asian clade based on multilocus phylogenetic analyses (O'Donnell et al., 1998). Rheeder et al. (1996) originally isolated *F. globosum* from naturally infected maize kernels harvested in the Transkei region of South Africa, an area with abnormally high incidences of oesophageal cancer and neural tube birth defects correlated with higher levels of fumonisin contamination of maize (Marasas et al., 2004; Rheeder et al., 1992; Sydenham et al., 1990). Sydenham et al. (1997) subsequently assessed 17 isolates of *F. globosum* cultured on maize and found that all produced fumonisin B_1 (5–325 μg/g) while none produced detectable levels of moniliformin. Proctor et al. (2004) assessed a smaller number of strains and also found that they produced fumonisins (>500 μg/g) and that the strains possessed four representative biosynthetic genes (*FUM1*, *FUM8*, *FUM12*, and *FUM19*) as detected by low stringency Southern hybridizations using probes designed from the *F. verticillioides* genes.

2.3.4. *Fusarium napiforme*

F. napiforme is phylogenetically related to *F. verticillioides* and other species within the African clade of the *G. fujikuroi* species complex (O'Donnell et al., 1998). This species was first identified from millet and sorghum grain in South Africa and Namibia (Marasas et al., 1987) but has also been identified from sorghum grain and poultry feed in Argentina (González et al., 1997; Magnoli et al., 1999). It is morphologically distinguished by its production of napiform and lemon-shaped microconidia. Nelson et al. (1992) found that 5 of 33 strains from Africa and Australia produced fumonisin B_1 (16–479 μg/g). The Southern hybridization analysis by Proctor et al. (2004) mentioned above detected none of the *FUM* genes in the one strain of *F. napiforme* that was assessed. Further confirmation is needed regarding fumonisin production and possession of the necessary genes, especially considering that strains of *F. napiforme* were able to produce moniliformin (16–388 μg/g) (Marasas et al., 1991), therefore increasing potential concern over contaminated feed grain.

2.3.5. *Fusarium nygamai and Fusarium pseudonygamai*

F. nygamai is also phylogenetically related to *F. verticillioides* and *F. napiforme* (O'Donnell et al., 1998). The species *F. pseudonygamai* was segregated from *F. nygamai* based on strains of the former lacking chlamydospores and having slightly longer microconidial chains (Nirenberg and O'Donnell, 1998). The two species are phylogenetically distinct lineages within the African clade (O'Donnell et al., 1998). Additionally, while *F. nygamai* produces fumonisins and moniliformin, *F. pseudonygamai* produces high amounts of moniliformin but no fumonisins (Leslie et al., 2005a). Southern hybridization assessment indicated that representative strains of *F. nygamai* possessed the *FUM* biosynthetic genes (Proctor et al., 2004). *F. pseudonygamai* was not assessed. *F. nygamai* is common in hot, dry areas and has been most often reported from sorghum plant tissue or sorghum field soil in Australia and South Africa (Leslie et al., 2005a). *F. pseudonygamai* is described from pearl millet grain in Africa (Leslie et al., 2005a; Leslie and Summerell, 2006; Marasas et al., 1991; Nirenberg and O'Donnell, 1998).

2.4. *Moniliformin, beauvericin, fusarin C, and fusaproliferin*

Moniliformin, a hydroxycyclobutenedione, was initially characterized as a culture extract from *F. proliferatum* strain NRRL 6322, which was identified at the time as *F. moniliforme*, hence the name moniliformin (Burmeister et al., 1979). The metabolite is only known to be produced by species of *Fusarium*, and while moniliformin is known to be toxic to poultry based on laboratory toxicity studies (Burmeister et al., 1979; Leslie et al., 1996, 2005a; Marasas et al., 1991; Rabie et al., 1982), it has not been associated with any acute or chronic disease outbreaks among animals.

In addition to *F. proliferatum*, the *Fusarium* species known to produce significant amounts of moniliformin include *F. avenaceum*, *F. fujikuroi*, *F. nygamai*, *F. pseudonygamai*, *F. subglutinans*, and *F. thapsinum* (Table 1) (Desjardins et al., 1997; Leslie et al., 1996). The literature concerning production of moniliformin by *F. verticillioides* is confounded by misidentification of the strains examined (Burmeister et al., 1979; Leslie et al., 2005a; Marasas et al., 1988a,b). Due to taxonomic refinement, it seems clear that the species now recognized as *F. verticillioides* does not generally produce significant levels of moniliformin even though some occasional strains may produce the mycotoxin when grown on maize (Rabie et al., 1982). The confusion mainly centers on *F. proliferatum* and *F. thapsinum*, which were previously lumped with *F. verticillioides* in the species *F. moniliforme* (Leslie et al., 1996).

A genetically homogeneous population of banana-associated isolates were recently characterized and shown to have phylogenetic affinity with *F. verticillioides* despite having a range of clearly distinct phenotypes (Hirata et al., 2001; Mirete et al., 2004; Moretti et al., 2004). Most notably, the banana isolates produced moniliformin (100–1400 μg/g) but did not produce fumonisin B_1 or B_2 (Moretti et al., 2004). In contrast, the *F. verticillioides* isolates from maize in that study produced fumonisin B_1 (20–5645 μg/g) and B_2 (25–850 μg/g) but did not produce moniliformin. Phylogenetic analyses indicated the banana isolates formed a homogeneous cluster that could be considered as a distinct, geographically restricted, clonally reproducing population within *F. verticillioides* (Mirete et al., 2004). While fertile, crosses between members of the banana population and the more

heterogeneous maize-associated population produced perithecia that were abnormally large and slow to reach maturity (Moretti et al., 2004). Glenn et al. (2004) found similar results. The combined observations suggest that reproductive isolation of the banana population from the maize population may be occurring, and the banana population may represent a cryptic sibling species to *F. verticillioides*.

Assessment of the ex type strain of *F. pseudoanthophilum* for production of beauvericin, moniliformin, fusaproliferin, and fumonisins B_1 and B_2 found that it produced only beauvericin (2.2 ± 0.2 μg/g) (Fotso et al., 2002). Mubatanhema et al. (1999) recovered five isolates of *F. pseudoanthophilum* from a survey of fungal species infecting maize collected in Zimbabwe, and all five produced moniliformin and fumonisin B_1. The authors did not indicate how species determinations were made, nor did they provide quantitative data on the amounts of each toxin produced by these five isolates. More validated strains of *F. pseudoanthophilum* need examination for their capacity to produce various mycotoxins in order to more clearly evaluate potential contamination of maize.

Beauvericin is a nonribosomal, cyclohexadepsipeptide cation chelating agent and ionophore with insecticidal properties (Logrieco et al., 1998). It was first isolated from the entomopathogenic fungus *Beauveria bassiana*, from which the metabolite's name is derived, and is highly toxic to a range of insects (Desjardins, 2006). While beauvericin can accumulate in *Fusarium*-infected maize kernels, it has not been associated with any animal disease outbreaks or disease in experimental animals (Desjardins, 2006; Logrieco et al., 2002). However, beauvericin has been shown to induce apoptosis in mammalian cell lines (Logrieco et al., 2002). Potential synergistic effects on animal health of beauvericin with other co-occurring *Fusarium* mycotoxins have not been addressed. In addition to *F. pseudoanthophilum*, other beauvericin-producing species include *F. avenaceum*, *F. fujikuroi*, *F. globosum*, *F. nygamai*, *F. poae*, *F. proliferatum*, and *F. subglutinans* (Table 1).

Fusarin C is one of several fusarins produced by *Fusarium* species and is of most concern due to its mutagenicity (Desjardins, 2006; Gelderblom et al., 1984). Fusarins all have the same polyketide backbone but differ in the structure and substitution of the 2-pyrrolidone moiety (Desjardins, 2006). Fusarin C differs in that the pyrrolidone possesses a C-13,14 epoxide and an ethanolic side chain. The C-13,14-epoxide group may be necessary for the mutagenic properties (Gelderblom et al., 1984). Fumonisin-producing and trichothecene-producing *Fusarium* species are known to also produce fusarin C (Table 1), but fusarin C has not been directly implicated in any disease outbreaks in either humans or animals. Assessments of experimental carcinogenicity using *F. verticillioides* culture material and DNA adduct formation with extracts of culture material showed no link with fusarin C (Bever et al., 2000; Jaskiewicz et al., 1987). Feed grain-associated *Fusarium* species known to produce fusarin C include *F. avenaceum*, *F. crookwellense*, *F. culmorum*, *F. graminearum*, *F. poae*, *F. sporotrichioides*, and *F. verticillioides* (Desjardins, 2006).

Fusaproliferin is a sesterterpene metabolite produced by only a few *Fusarium* species within the *G. fujikuroi* species complex (Table 1). In relation to feed grain, *F. proliferatum* and *F. subglutinans* are of most significance since they are common pathogens of maize, and isolates of these two species consistently produce high levels of fusaproliferin (Desjardins, 2006; Shephard et al., 1999). Indeed, 40–50% of maize ear and feed samples infected with *F. proliferatum* and *F. subglutinans* in Italy and Iowa were positive for fusaproliferin (Logrieco et al., 2002; Munkvold et al., 1998). Surveillance of fusaproliferin contamination of food

and feed grain has been limited because the metabolite has not been linked to any animal or human disease outbreaks. Experimental analysis found fusaproliferin was cytotoxic to mammalian and insect cell lines (Fornelli et al., 2004; Logrieco et al., 1996). Some strains of *F. globosum* and *F. pseudonygamai* also are able to produce fusaproliferin (Fotso et al., 2002; Shephard et al., 1999).

2.5. Ecological and environmental factors associated with mycotoxin contamination of feed

Elimination of mycotoxigenic fungi from grain is unlikely due to the intimate biological associations they have with their varied hosts. Management of the amount of mycotoxins produced during epidemics of corn ear rot and Fusarium head blight of wheat and barley should be the practical objective rather than elimination of the toxins. Management and food safety concerns are magnified by the frequent complexes of mycotoxigenic species associated with either ear rot or head blight (Bottalico and Perrone, 2002; Logrieco et al., 2002). The mixture of species potentially results in mixtures of mycotoxins contaminating the grain. Additional discussion of the prevention of plant contamination with *Fusarium* species and their associated mycotoxins at the field level and other management strategies can be found in Jouany (2007) in this issue.

The factors contributing to development of Fusarium head blight and ear rot and subsequent mycotoxin contamination include fungal and host genotypes, temperature, relative humidity, amount and timing of rainfall, fungal sporulation, wind patterns, niche competition, insect damage to the plant, and cultural practices. For example, management of crop residue can have a significant impact on severity of disease and mycotoxin contamination. Wheat, maize, and other grain crop residues are generally regarded as the primary source of inoculum for *Fusarium* species (Cotten and Munkvold, 1998; Shaner, 2003). For Fusarium head blight caused by *F. graminearum*, data suggest severity of disease and deoxynivalenol contamination can be managed by crop rotation and reduction of crop residues harboring inoculum (Dill-Macky and Jones, 2000). Deoxynivalenol levels were 50% lower when wheat followed soybeans in rotation compared to when wheat followed maize. Furthermore, plowing under crop residue also lowered head blight and deoxynivalenol contamination. Data indicate that crop rotation and tillage is less effective with maize for controlling ear rot (Flett et al., 1998), probably because of the long-term survival of *Fusarium* species on maize residue. *F. verticillioides*, *F. proliferatum*, and *F. subglutinans* survived for at least 630 days in maize stalk residue that was either buried or left on the soil surface (Cotten and Munkvold, 1998). The long-term integrity and rate of decomposition of crop residue may be important for allowing the fungi to persist and proliferate until wheat or maize is planted again.

The differing efficacies of crop rotation and tillage on wheat head blight and maize ear rot support other observations that the type of primary spore inoculum is important in the disease cycle. The primary infection pathway leading to corn ear rot is by asexual conidia landing on the silks and growing down to the developing kernels (Munkvold et al., 1997b). Therefore, growth and proliferation of *Fusarium* species on maize stubble would result in an increase in the number of airborne conidia that land on silks. No specialized fungal development is needed other than general mycelial growth and conidiation. In contrast, the primary spore

inoculum for development of wheat head blight appears to be ascospores produced from the homothallic reproduction of *G. zeae* (=*F. graminearum*) and formation of perithecia on the residue of wheat or maize (Shaner, 2003). Such *G. zeae* sexual reproduction commonly occurs in the field, but since wheat is susceptible to infection when it is flowering, the timing of perithecial development and ascospore discharge must coincide with anthesis. In contrast to the common occurrence of *G. zeae* perithecia, the heterothallic sexual reproduction of *G. moniliformis* (=*F. verticillioides*) occurs enough to contribute to genetic recombination but is nonetheless relatively rare (Leslie and Klein, 1996).

Similar to *F. verticillioides* and other ear rot pathogens, *F. graminearum* is thought to overwinter in crop residue as a mycelium, but *F. graminearum* then forms perithecia in spring and early summer as wheat anthesis occurs (Shaner, 2003). Ascospores are then forcibly discharged and wind dispersed (Trail et al., 2002). Utilizing ascospores as primary inoculum could be unique to *G. zeae*. Other species such as *F. culmorum* must utilize asexual macroconidia as primary inoculum (Shaner, 2003) since they are not known to sexually reproduce (Table 1) and therefore cannot produce ascospores. *G. zeae* ascospore discharge occurs between 10 and 30 °C with an optimal temperature of approximately 16 °C and is triggered by a drop in air temperature accompanied by a rise in relative humidity (60–95%), although subsequent dry periods may be required for forcible discharge from the perithecia (Doohan et al., 2003; Paulitz, 1996). For comparison, production of *F. graminearum* macroconidia is severely inhibited below 16 °C. Air sampling for spores showed that ascospore discharge had a diurnal periodicity, with few spores collected between 08:00 and 16:00 h (<20 spores/150 L of air) and a sharp increase in the number of spores from 18:00 to 23:00 h (650 spores/150 L of air) (Paulitz, 1996). Ascospore discharge was greatest 1–4 days after rainfall exceeding 5 mm. Moisture was required in the form of high relative humidity but saturation suppressed ascospore discharge (Paulitz, 1996).

The influence of climatic parameters on *Fusarium* species and incidence and severity of disease and mycotoxin contamination has been reviewed in detail (Doohan et al., 2003). In general, optimal conditions for development of Fusarium head blight of small grains requires moderately warm temperatures and wet weather at anthesis. The same general conditions are necessary for development of *F. graminearum* ear rot or maize, including high rainfall during the maturation period (Munkvold, 2003b). In comparison, optimal conditions for development of corn ear rot by *F. verticillioides* requires warm to hot temperatures and dry conditions at silking and during grain-filling (Doohan et al., 2003; Munkvold, 2003b). Additionally, drought stress is associated with increased frequency of *F. verticillioides* infection and fumonisin accumulation in kernels (Miller, 2001; Munkvold and Hellmich, 1999). Late season rainfall is also associated with elevated ear rot (Kommedahl and Windels, 1981).

Not surprisingly the incidence of the *Fusarium* species causing head blight of small grains or corn ear rot is generally dependent on geographical location and regional climatic conditions. *F. culmorum*, *F. avenaceum*, and *F. poae* generally are more common head blight pathogens in cooler regions such as northern and central Europe, while *F. graminearum* is common across Europe from north to south and is also the dominant head blight species in North America (Bottalico and Perrone, 2002; Doohan et al., 2003). Major corn ear rot pathogens are also geographically correlated, with *F. verticillioides* being dominant in the United States and often associated with *F. proliferatum* and *F. subglutinans*, while in Europe

F. verticillioides and *F. proliferatum* are more common in the south with *F. subglutinans* more common in northern and central regions (Doohan et al., 2003; Logrieco et al., 2002; Munkvold, 2003b). *F. graminearum*-associated ear rot is more common in cooler northern regions such as Canada and northern Europe. Congruent with these observations, *in vitro* experiments found that *F. graminearum* had a competitive advantage over *F. verticillioides* and *F. proliferatum* at 15 °C, while at 25–30 °C the species appeared to coexist (Marin et al., 1998; Velluti et al., 2000).

Plant breeding and genetic modification both attempt to alter host genotypes to be more resistant to the fungus or to insect feeding damage. Identification and incorporation of genetic resistance to fungal infection and mycotoxin contamination by breeding programs has had some success as reviewed by Munkvold (2003a). However, achieving high levels of resistance has proven difficult. In contrast, use of commercially available transgenic hybrids with Bt insect resistance has proven very successful for managing mycotoxin contamination since incidence of ear rot caused by *F. verticillioides* is positively correlated with European corn borer damage to kernels (Munkvold et al., 1997a). Transgenic maize hybrids expressing the *cryIA*(*b*) genes in kernels consistently exhibited reduced ear rot and *Fusarium* infection of kernels compared with their nontransgenic counterparts (Munkvold et al., 1997a; Munkvold, 2003a; Munkvold and Hellmich, 1999). CryIA(b) expression in kernels resulted in greatly reduced kernel damage by European corn borer larvae, apparently resulting in reduced infection by *F. verticillioides*. Over a 3-year field study, ear rot severity was reduced by 54–96% and incidence of kernel infection by *Fusarium* species was reduced by 17–38%. Overall, transgenic maize resulted in grain of a higher quality, which is significant since other studies have found that symptomatic kernels (*i.e.*, visibly mouldy, darkened, streaked, or chalky in appearance) contained higher concentrations of fumonisins compared to asymptomatic, undamaged kernels (Desjardins et al., 1998; Ross et al., 1991). For example, a batch of maize screenings associated with an outbreak of equine leucoencephalomalacia had 553 μg/g fumonisin B_1 in damaged kernels compared to <1 μg/g in undamaged kernels (Ross et al., 1991). Clearly, maize intended for feed should be managed for minimal insect damage and even screened post-harvest for removal of diseased or damaged kernels, thus significantly reducing exposure of the animals to fumonisin contamination.

Interestingly, the presence of *F. verticillioides* in maize may promote infestation of the plant by lepidopteran and coleopteran pests. Data suggest the fungus may actually attract insect pests to the plant and enhance their survival (Cardwell et al., 2000; Schulthess et al., 2002). Such attraction may be by release of volatiles from the fungus and/or plant as *F. verticillioides* infects and colonizes the kernels. Bartelt and Wicklow (1999) found that *F. verticillioides* cultures on autoclaved maize produced various small alcohols, esters, aldehydes, and other compounds that were attractive to nitidulid beetles, and similar types and quantities were produced on inoculated ears. They concluded that *F. verticillioides* growing naturally on wounded kernels in field maize could easily produce volatiles at a rate that is significantly attractive to nitidulid beetles. Such attraction could enhance insect damage to the ears, thus providing *F. verticillioides* with bountiful carbohydrates for saprophytic growth resulting in rot and mycotoxin production. Movement of the insects from ear to ear could also vector *F. verticillioides* and potentially impact local fungal population structure among maize-associated species. In relation to tritrophic interactions, it is worth

noting again that several *Fusarium* species produce beauvericin (Table 1), which is toxic to a range of insects. What impact, if any, beauvericin has on maize–*Fusarium*–insect interactions is unknown.

Production of mycotoxins is energetically draining for fungi. They have complex biosynthetic pathways involving many genes that must be expressed, transcribed and translated into functional proteins that then catalyze various additions and modifications to produce the mycotoxins. At the genomic scale, evolutionary pressures have clustered together the genes encoding for the biosynthetic pathways, suggesting that gene clustering provides some sort of genetic and/or biochemical advantage (Lawrence, 1999; Lawrence and Roth, 1996; Walton, 2000). Maintaining the integrity of these gene clusters and the mycotoxins for which they encode may provide the fungi with enhanced fitness for suppressing or otherwise out-competing other fungi or bacteria. For example, fumonisin B_1 was able to suppress the growth of some fungi, including *F. graminearum*, but had no effect on growth of fumonisin-producing species *F. verticillioides*, *F. globosum*, and *F. proliferatum* or the growth of *F. subglutinans*, which does not produce fumonisins but commonly co-occurs in maize with *F. verticillioides* and *F. proliferatum* (Keyser et al., 1999; Leslie et al., 1990; Logrieco et al., 2002). Similarly, colonization of maize by a bacterial endophyte, *Bacillus mojavensis*, was reduced due to fusaric acid (Bacon et al., 2004), which is another *Fusarium* mycotoxin that is not discussed in this review due to its low toxicity to animals (Bryden et al., 2001). *Fusarium* secondary metabolites such as fumonisin and fusaric acid may impact niche competition and microbial community structure in the soil or in the host plant.

Given that mycotoxins often impact cellular functions across a broad spectrum of eukaryotic organisms, several studies have investigated whether mycotoxin production by *Fusarium* species enhances virulence toward their respective hosts. In relation to corn seedling blight, Desjardins et al. (1995) found that fumonisin production increased the virulence of *F. verticillioides* but was not necessary or sufficient for disease development. Williams et al. (2006) reported a significant positive correlation between leaf lesion development on maize seedlings and the production of fumonisin B_1 in soils by *F. verticillioides*. Recent assessments using fumonisin-nonproducing mutants created by targeted gene deletions indicate fumonisin B_1 is necessary for development of the full suite of seedling blight disease symptoms, most notably the development of leaf lesions and other foliar symptoms (Glenn and Riley, personal observation). Additionally, fumonisin B_1 caused a significant dose-dependent reduction in maize seedling root and shoot development (Lamprecht et al., 1994) and had similar dose-dependent inhibition of maize callus growth (van Asch et al., 1992). Another study showed fumonisin had no effect on seed germination but did inhibit radicle elongation by up to 75% (Doehlert et al., 1994). In contrast, spraying maize seedlings of two cultivars with fumonisin B_1 (1000 μg/mL) did not produce any symptoms of disease (Abbas and Boyette, 1992).

However, interpretation of these various experiments must take into consideration the maize lines used in the experiments. Maize genotype will impact the phenotypic response when germinating seed or seedlings are challenged with fumonisin B_1 (Desjardins et al., 2005). In regard to ear rot, use of a gene deletion mutant that did not produce any fumonisins clearly showed that production of the mycotoxin was not necessary for *F. verticillioides* to cause ear rot (Desjardins et al., 1998, 2002; Desjardins and Plattner, 2000).

The toxicity of trichothecenes to plants and their impact on fungal virulence was recently reviewed in detail by Desjardins (2006). Several studies have detailed the acute phytotoxicity of trichothecenes, from their inhibition of seed germination and seedling growth, to their chlorotic and necrotic effects. Use of trichothecene-nonproducing mutants created by targeted deletion of the *TRI5* gene have shown that trichothecene production by *F. sambucinum* enhanced the virulence of this fungus on parsnip roots, but even nonproducing mutants were as virulent as trichothecene-producing strains on potato tubers (Desjardins et al., 1992; Hohn and Desjardins, 1992). Similar *TRI5* gene deletion in *F. graminearum* resulted in loss of deoxynivalenol production with a concurrent reduction in development of wheat head blight and corn ear rot (Bai et al., 2002; Desjardins et al., 1996; Harris et al., 1999; Nicholson et al., 1998; Proctor et al., 1995). Deoxynivalenol-nonproducing strains had decreased virulence and were less able to spread in wheat heads or maize ears after initial infection.

Plants possess a variety of defensive mechanisms exhibited in response to challenges by plant-pathogenic fungi. One strategy is to release low molecular weight compounds that either kill or inhibit the growth of invading fungi (Osbourn, 1999; VanEtten et al., 1994). Maize, wheat and rye produce a class of antimicrobial compounds as part of their normal developmental routine (Niemeyer, 1988). These cyclic hydroxamic acids are DIMBOA (2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3-one) and DIBOA (2,4-dihydroxy-2H-1,4-benzoxazin-3-one). In maize, DIMBOA is produced in higher quantity than DIBOA, and their concentrations are greatest during the first 6–8 days after germination, with absolute amounts continuing to increase through plant maturity (Klun and Robinson, 1969; Niemeyer, 1988). Wheat also produces both of these compounds, while rye produces just DIBOA (Villagrasa et al., 2006; Zuniga et al., 1983). Other grains, such as rice, sorghum, and pearl millet, do not produce benzoxazinoids.

Free DIMBOA and DIBOA are highly reactive and spontaneously degrade to the corresponding benzoxazolinones, 6-methoxy-2-benzoxazolinone (MBOA) and 2-benzoxazolinone (BOA), respectively (Hashimoto and Shudo, 1996). The half-life for DIMBOA or DIBOA is 24 h or less in aqueous solution (pH 5–7.5) at 25 °C (Woodward et al., 1978). Many insects, fungi, and bacteria are deterred or inhibited by these compounds, resulting in increased plant resistance (Argandona et al., 1980; Corcuera et al., 1978; Hansen, 2006; Klun and Robinson, 1969; Niemeyer, 1988), yet, *F. verticillioides*, the main fungal inhabitant of maize, detoxifies MBOA and BOA within 24 h by actively metabolizing them into *N*-(2-hydroxy-4-methoxyphenyl) malonamic acid (HMPMA) and *N*-(2-hydroxyphenyl) malonamic acid (HPMA), respectively (Glenn et al., 2001, 2002, 2003; Richardson and Bacon, 1995; Yue et al., 1998). A screen of 29 *Fusarium* species found that 11 had some level of tolerance to MBOA and BOA (Glenn et al., 2001). The most tolerant species, in decreasing order, were *F. verticillioides*, *F. subglutinans*, *F. crookwellense*, and *F. graminearum*, all of which are associated with maize and/or wheat (Table 1). Each of the four was able to metabolize MBOA and BOA.

Recent ecotoxicological studies have indicated that microbial transformation of MBOA and BOA can result in degradation products, such as HPMA and 2-aminophenoxazin-3-one (Glenn et al., 2003), that were as toxic or more toxic to test organisms than the parent compounds (Fomsgaard et al., 2006; Fritz and Braun, 2006). These data suggest a BOA-tolerant *Fusarium* species may alter the antimicrobial environment surrounding

its mycelium such that a toxic compound is metabolized to form another compound that is benign to the *Fusarium* but inhibitory to other organisms. To do so would enhance the fitness of *Fusarium* and increase its niche colonization success. In terms of phytopathological interactions, detoxification of BOA is not thought to significantly increase the virulence of *F. verticillioides* toward maize seedlings (Glenn et al., 2002), but whether such metabolism provides an ecological advantage by increasing fitness for niche competition needs further examination. Such metabolic activity may contribute to the dominance of these BOA-tolerant fungi in maize and wheat field environments.

3. Conclusions

Great potential exists for infection of cereal grains with multiple *Fusarium* species, probably resulting in contamination of feed with multiple *Fusarium* mycotoxins. The trichothecenes, zearalenone and fumonisins are of greatest concern due to their effects on animals and the worldwide distribution of the fungi. The synergistic effects of these toxins with other metabolites such as beauvericin, fusaproliferin and fusarin C may pose additional risks to animal health. Having a clear understanding of the taxonomic identity and mycotoxigenic potential of the various *Fusarium* species and their associated phytopathology is critical for development and implementation of strategies for monitoring and managing mycotoxin contamination of grain.

Taxonomic identity and proposed evolutionary relationships among *Fusarium* taxa have undergone extensive revision and clarification within the last 10 years due to identification of biological species as well as application of molecular phylogenetics. *F. graminearum* Group 1 is now recognized as the biologically distinct species *F. pseudograminearum*. The once confusing species conglomeration *F. moniliforme* now is segregated into *F. verticillioides*, *F. subglutinans*, and *F. proliferatum*. The taxonomy now more accurately reflects the biology and host-associations of the differing species.

Most recently, analyses of multilocus and genomic sequence data are advancing our understanding of organismal and genomic evolution. Comparative analyses are elucidating details of genomic architecture and synteny between species, such as observed for the fumonisin biosynthetic gene cluster between *F. verticillioides* and *F. proliferatum*. Furthermore, the distribution of genes necessary for the production of fumonisins among various species has been assessed. *F. proliferatum*, which is closely related to the gibberellin-producing *F. fujikuroi*, was found to possess an inactive gibberellin biosynthetic gene cluster. Finally, hypotheses regarding biogeographical distributions and origins of phylogenetic lineages have been proposed for the *F. graminearum* complex. Molecular phylogenetics also allows for assessment of convergent evolution by evaluating possible independent losses or acquisitions of traits, such as the capacity to produce specific mycotoxins or specific associations with host plants.

Much attention is being focused on utilizing the available molecular genetic and genomic resources to elucidate how mycotoxigenic *Fusarium* species respond to environmental and biotic stimuli that contribute to mycotoxin production. Even with recent significant advancements in basic understanding of how ecological and environmental factors impact mycotoxin contamination of grain, many biological questions remain. While insects play an

apparent role in corn ear rot severity and increased fumonisin contamination, the dynamics of tritrophic interactions between insects, *F. verticillioides*, and maize are unclear. Does the fungus alter insect behavior through release of volatile attractants and secondary metabolites that may facilitate plant damage and nutrient availability or vectoring and dispersal of the fungal spores? The release of secondary metabolites, including mycotoxins such as fumonisins and deoxynivalenol, may actually enhance fungal fitness and niche colonization by inhibiting competing fungi or even compromising the health of the host plant to facilitate necrotrophic growth of the fungus and colonization of plant tissues. Much also remains to be learned regarding how temperature, moisture, and host genotype impact geographical distribution of *Fusarium* species, their sympatric interactions, and development of cereal diseases and mycotoxin production.

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