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Mold and Mycotoxin Issues in Dairy Cattle: Effects, Prevention and Treatment

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Summary

- Molds are filamentous (fuzzy or dusty appearing) fungi that occur commonly in feedstuffs, including roughages and concentrates.
- Molds can infect dairy cattle causing a disease referred to as mycosis. A mycosis is most likely when cows may be immune suppressed during stressful periods. A mycosis can occur in various locations such as the lungs, mammary gland, uterus or intestine. An intestinal infection may result in hemorrhagic bowel.
- Molds may also affect cattle by producing poisons called mycotoxins that affect animals when they consume contaminated feeds resulting in a mycotoxicosis.
- Molds are present throughout the environment and therefore, mycotoxins can be formed on crops in the field, during harvest, or during storage, processing, or feeding.
- Mold spores are in the soil and in plant debris lying ready to infect the growing plant in the field.
- Mold growth and the production of mycotoxins are usually associated with extremes in weather conditions leading to plant stress or hydration of feedstuffs, insect damage, poor storage practices, low feedstuff quality, and inadequate feeding conditions.
- Fungal field diseases are characterized by yield loss, quality loss, and mycotoxin contamination.
- Management of crop production can reduce, but not totally prevent, the occurrence and concentrations of mycotoxins.
- Excellent silage management can reduce the incidence of mycotoxins. Standard silage making practices should be followed to include hybrid selection, reduction of field and harvest stress, rapid filling of the silo, use of an effective silage additive, tight packing, covering, rapid feed out and discarding the spoilage.
- The U.N.'s Food and Agriculture Organization (**FAO**) estimated that worldwide, about 25% of crops are affected annually with mycotoxins.
- Because of mycotoxin degradation in the rumen, dairy cattle are more resistant to mycotoxins than are monogastrics, but because of greater feed consumption and production stresses, may be more susceptible to mycotoxins than are beef cattle.
- Because ruminants consume forages, byproduct feeds and wet feeds, they are exposed to a broader range of mycotoxins at concentrations that are perhaps higher than are found in dry grain mixtures.
- The mycotoxins of greatest concern to dairy cattle include: ergots produced in small grains, fescue and other grass; aflatoxin, which is generally produced by *Aspergillus* mold; deoxynivalenol, zearalenone, T-2 toxin, and fumonisin, which are produced by *Fusarium* molds; and ochratoxin, PR toxin, mycophenolic acid and roquefortine C produced by *Penicillium* molds.
- There are many other mycotoxins, some of which may also affect dairy cattle or co-occur with the more common mycotoxins in feeds.
- Contaminated feeds often contain multiple mycotoxins, altering the expected effects on the cow.
- A single large dose of a mycotoxin can cause an acute toxicity in cattle, but it is more likely that the effects are chronic, caused by low level consumption over time.

- Mycotoxins affect dairy cows by reducing feed consumption, reducing nutrient utilization, altering rumen fermentation, suppressing immunity, altering reproduction, irritating tissues and causing cellular death.
- Diagnosis can be difficult because mycotoxins residues are not easily detected in the cow, symptoms are often non-specific and may be the result of a series of events or opportunistic diseases.
- Feed analyses of mycotoxins are hindered by the difficulty in gathering representative feed samples. Obtaining representative feed samples is difficult because mold growth is inconsistent, and mycotoxins are non-uniformly distributed within a feedstuff.
- Feed analyses for mycotoxins is improving but continues to be slow and expensive and generally limited to only a few mycotoxins.
- Not all mycotoxins can be detected in routine testing by commercial laboratories.
- Mold spore counts and mold identification can be helpful to diagnosis.
- Diet management may reduce the impact of mycotoxins. Diets should be formulated and fed to reduce nutritional stress (such as transitional diets), and to supply sufficient protein, energy, fiber, antioxidant nutrients, and buffers.
- Experimentally, mycotoxins binders have been effective at partially reducing the effects of some mycotoxin, but at this time, no products are approved by the FDA for such claims.

Mycotoxins

Mycotoxins are toxic secondary metabolites produced by fungi (molds) that cause an undesirable effect (mycotoxicosis) when animals are exposed. Exposure is usually by consumption of contaminated feeds, but may also be by contact or inhalation. Biological effects include liver and kidney toxicity, central nervous system effects and estrogenic effects, to name a few. Only some molds produce mycotoxins and they are referred to as toxigenic. The fungal toxins are chemically diverse — representing a variety of chemical families — and range in molecular weight from about 200 to 500. There are hundreds of mycotoxins known, but few have been extensively researched and even fewer have good methods of analysis available. The primary classes of mycotoxins are aflatoxins, zearalenone, trichothecenes, fumonisins, ochratoxin A and the ergot alkaloids.

Molds Can Cause Disease

A mold (fungal) infection resulting in disease is referred to as a mycosis. Fungal pathogens include: *Aspergillus fumigatus, Candida albicans, Candida vaginitis,* certain species of *Fusarium* and others. *Aspergillus fumigatus* is known to cause mycotic pneumonia, mastitis and abortions and has been recently proposed as the pathogenic agent associated with mycotic hemorrhagic bowel syndrome (**HBS**) in dairy cattle (Puntenney et al., 2003). It is thought that *Aspergillus fumigatus* is a fairly common mold in both hay (Shadmi et al., 1974) and silage (Cole et al., 1977). While healthy cows with an active immune system are more resistant to mycotic infections, dairy cows in early lactation are immune suppressed and HBS is more likely in fresh cows (Puntenney et al., 2003). It is theorized that with a mycosis, mycotoxins produced by the invading fungi can suppress immunity; therefore increasing the infectivity of the fungus. *A. fumigatus* produces several mycotoxins, including gliotoxin and tremorgens that are toxic to cattle. *A. fumigatus* contaminated silage was found to contain fumigaclavine A and C and several fumitremorgens (Cole et al., 1977). Cattle consuming this silage demonstrated symptoms including generalized deterioration typical of protein deficiency, malnutrition, diarrhea, irritability, abnormal behavior and occasional death. The hay was fed to goats and rats and resulted in retarded growth and histopathological changes in the livers and kidneys. Gliotoxin, an immune suppressant, has been found to be present in animals infected with *A. fumigatus* (Bauer et al., 1989). Gliotoxin is also shown to be produced in mice associated with *A. fumigatus* (Eichner et al., 1988). Gliotoxin produced by *A. flavus* has immunosuppressive, antibacterial and apoptotic effects. Gliotoxin is shown to affect rumen fermentation, reducing digestibility and VFA production *in vitro* (Morgavi et al., 2004). Reeves et al. (2004) using an insect model demonstrated the significance of gliotoxin in increasing the virulence of *A. fumigatus*. Niyo et al. (1988a, b) demonstrated that in rabbits, T-2 toxin decreased phagocytosis of *A. fumigatus* conidia by alveolar macrophages and increased severity of experimental aspergillosis. It is possible that gliotoxin, T-2 toxin, or other mycotoxins suppress immunity and may be a trigger to increased infectivity by the fungus; ultimately resulting in HBS or other fungal infections. Perhaps reducing animal exposure to mycotoxins and moldy feeds may be a key to control of mycoses such as HBS. A commercial feed additive with anti-fungal and adsorbent properties appears to reduce HBS (Puntenney et al., 2003).

Mold growth, mycotoxin formation

Many species of fungi produce mycotoxins in feedstuffs. Molds can grow and mycotoxins can be produced pre-harvest or during storage, transport, processing or feeding. Mold growth and mycotoxin production are related to plant stress caused by weather extremes, to insect damage, to inadequate storage practices and to faulty feeding conditions. In general, environmental conditions — heat, water and insect damage — cause plant stress and predispose plants in the field to mycotoxin contamination. Computer models to predict mycotoxin concentrations in corn prior to harvest are based on temperature, rainfall and insect pressure (Dowd, 2004).

Because feedstuffs can be contaminated pre-harvest, control of additional mold growth and mycotoxin formation is dependent on storage management. After harvest, temperature, water activity and insect activity are the major factors influencing mycotoxin contamination of feedstuffs (Coulombe, 1993). Molds grow over a temperature range of 10-40°C (50-104°F), a pH range of 4-8 and above 0.7 aw (equilibrium relative humidity expressed as a decimal instead of a percentage).

Molds can grow on feeds containing more than 12-15% moisture. In wet feeds such as silage, higher moisture levels allow mold growth if oxygen is available. Because most molds are aerobic, high moisture concentrations can exclude air and help prevent mold growth. The conditions most suitable for mold growth and for mycotoxin formation are not necessarily the same. For example, the *Fusarium* molds associated with Alimentary Toxic Aleukia have been reported to grow prolifically at 25-30°C without producing much mycotoxin, but at near-freezing temperatures, they produce large quantities of mycotoxins with minimal mold growth (Joffe, 1986). Field applications of fungicides may reduce mold growth, thus reducing production of mycotoxins. However, the stress or shock of the fungicide to the mold organism may reduce mold growth and yet not reduce the production of mycotoxins (Boyacioglu et al., 1992; Gareis and Ceynowa, 1994; Simpson et al., 2001).

Aspergillus species normally grow at lower water activities and at higher temperatures than the *Fusarium* species. Therefore, *Aspergillus flavus* and aflatoxin in corn are favored by the heat and drought stress associated with warmer climates. Aflatoxin contamination is enhanced by insect damage before and after harvest.

The individual *Penicillium* species have variable requirements for temperature and moisture, but are more likely to grow under post-harvest conditions, in cooler climates, in wet conditions and at a lower pH. *Penicillium* molds are a major contaminant of silage, probably because they are acid tolerant.

The *Fusarium* species are important plant pathogens that can proliferate pre-harvest, but continue to grow post-harvest. In corn, *Fusarium* molds are associated with ear rot and stalk rot, and in small grains, they are associated with diseases such as head blight (scab). In wheat, *Fusarium* is associated with excessive moisture at flowering and early grain-fill stages. In corn, *Fusarium graminearum* is referred to as a red ear rot and is more commonly associated with a cool, wet growing season and with insect damage. Fusarium ear rots that produce fumonisins are referred to as pink ear rots and vary in their environmental requirements. They are generally associated with dry conditions in mid-season followed by wet weather (CAST, 2003).

Mycotoxin occurrence

Worldwide, approximately 25% of crops are affected by mycotoxins annually (CAST, 1989), which would extrapolate to billions of dollars (Trail et al., 1995). Annual economic costs of mycotoxins to the U.S. agricultural economy is estimated to average $1.4 billion (CAST, 2003). Economic losses are due to effects on livestock productivity, losses in crops and the costs and effects of regulatory programs directed toward mycotoxins. In North Carolina feed samples submitted by North Carolina farmers over a nine-year period indicate that mycotoxins in feeds including corn silage and corn grain occur commonly at unsuitable concentrations (Whitlow et al., 1998).

Mycotoxin occurrence and concentrations are variable by year, which is expected because of the annual variation in weather conditions and plant stresses known to affect mycotoxin formation (Coulombe, 1993). It was concluded that mycotoxins occur frequently in a variety of feedstuffs and are routinely fed to animals. Sometimes, mycotoxins

occur at concentrations high enough to cause major losses in health and performance of animals. However, a more likely scenario is to find mycotoxins at lower levels interacting with other stressors to cause sub-clinical losses in performance, increases in incidence of disease and reduced reproductive performance. To the animal producer, these sub-clinical losses are of greater economic importance than losses from acute effects, but even more difficult to diagnose.

Mycotoxin effects

Although the potentially harmful effects of feeding moldy grain and foods has been known for many years (Matossian, 1989), mycotoxicology, the study of mycotoxins, really began in 1960 with the outbreak of Turkey-X disease in the U.K. This outbreak was linked to peanut meal imported from Brazil (Sargeant et al., 1961). Because of an intensive multidisciplinary research effort, a blue-fluorescent toxin was isolated and mycelia of *A. flavus* were observed. *A. flavus* was soon shown to produce the same toxic compound(s) found in the toxic peanut meal. The toxin was characterized chemically and biologically and was given the trivial name aflatoxin. Aflatoxin was shown to be very toxic and carcinogenic in some of the test animal species used, and it resulted in a toxic metabolite in milk of dairy cows (Allcroft and Carnaghan, 1962; 1963). The discovery of aflatoxin and elucidation of some of its effects led to research on other livestock health and production problems linked with moldy feedstuffs and to the discovery of additional mycotoxins.

Mycotoxins, in large doses, can be the primary agent causing acute health or production problems in a dairy herd. But more likely, mycotoxins are a factor contributing to chronic problems including a higher incidence of disease, poor reproductive performance, or suboptimal milk production. Ruminal degradation of mycotoxins helps to protect the cow against acute toxicity, but may contribute to chronic problems, associated with long term consumption of low levels of mycotoxins. Ruminal degradation of mycotoxins may have helped mask mycotoxin effects in dairy cows which were recognized in recent years as production stresses have increased and as the industry has paid more attention to management details.

Mycotoxins exert their effects through several means:
1) reduced intake or feed refusal;
2) reduced nutrient absorption and impaired metabolism;
3) altered endocrine and exocrine systems;
4) suppressed immune function;
5) altered microbial growth.

Recognition of the impact of mycotoxins on animal production has been limited by the difficulty of diagnosis. The progression and diversity of symptoms are confusing, making diagnosis difficult (Hesseltine, 1986; Schiefer, 1990). The difficulty of diagnosis is increased due to limited research, occurrence of multiple mycotoxins, non-uniform distribution, interactions with other factors, and problems of sampling and analysis. Because of the difficulty of diagnosis, the determination of a mycotoxin problem becomes a process of elimination and association. Certain basics can be helpful (Schiefer, 1990):

1) Mycotoxins should be considered as a possible primary factor resulting in production losses and increased incidence of disease.
2) Documented symptoms in ruminants or other species can be used as a general guide to symptoms observed in the field.
3) Systemic effects as well as specific damage to target tissues can be used as a guide to possible causes.
4) Post mortem examinations may indicate no more than gut irritation, edema, or generalized tissue inflammation.
5) Because of the immune suppressing effects of mycotoxins, increased incidence of disease or atypical diseases may be observed.
6) Responses to added dietary adsorbents or dilution of the contaminated feed may help in diagnosis.
7) Feed analyses should be performed, but accurate sampling is a major problem

Symptoms are often nonspecific and may be wide-ranging. Symptoms result from a progression of effects, or of opportunistic diseases, making a diagnosis difficult or impossible because of the complex clinical results with a

wide diversity of symptoms. Symptoms vary depending on the mycotoxins involved and their interactions with other stress factors and animals may exhibit few or many of a variety of symptoms. The more stressed cows, such as fresh cows, are most affected; perhaps because their immune systems are already suppressed. Symptoms may include: reduced production; reduced feed consumption; intermittent diarrhea (sometimes with bloody or dark manure); reduced feed intake; unthriftiness; rough hair coat; and reduced reproductive performance including irregular estrous cycles, embryonic mortalities, pregnant cows showing estrus, and decreased conception rates. There generally is an increase in incidence of disease; such as displaced abomasum, ketosis, retained placenta, metritis, mastitis, and fatty livers. Cows do not respond well to veterinary therapy.

The FDA regulatory control program for mycotoxins is discussed by Wood and Trucksess (1999).

Safe levels of mycotoxins

Some of the same factors that make diagnosis difficult also contribute to the difficulty of establishing levels of safety. These include lack of research, sensitivity differences by animal species, imprecision in sampling and analysis, the large number of potential mycotoxins and interactions with stress factors or other mycotoxins (Hamilton, 1984; Schaeffer and Hamilton, 1991).

A mycotoxin provided by a naturally contaminated feed appears more toxic than the same level of a pure mycotoxin supplemented into a clean diet. Aflatoxin produced from culture was more toxic to dairy cattle than pure aflatoxin added to diets (Applebaum et al., 1982). In swine, Foster et al. (1986) demonstrated that a diet containing pure added deoxynivalenol (DON) was less toxic than diets with similar concentrations of DON supplied from naturally contaminated feeds. Smith and MacDonald (1991) have suggested that fusaric acid, produced by many species of *Fusarium*, occurs along with DON to produce more severe symptoms. Lillehoj and Ceigler (1975) gave an example where penicillic acid and citrinin were innocuous in laboratory animals when administered alone but were 100% lethal when given in combination. These studies strongly suggest the presence of other unidentified mycotoxins in naturally contaminated feeds and that mycotoxin interactions are important. It is well documented that several mycotoxins may be found in the same feed (Hagler et al., 1984). Abbas et al. (1989) demonstrated *Fusarium* species isolated from Minnesota corn produced multiple mycotoxins. Also, because animals are fed a blend of feedstuffs and because molds produce an array of mycotoxins, many mycotoxin interactions are possible. Speijers and Speijers (2004) have discussed the combined toxicity of mycotoxins and, therefore, suggest daily tolerable intake limits for groups of mycotoxins. Interactions of multiple mycotoxins are discussed in the CAST (2003) report.

Mycotoxin interactions with other factors make it difficult to determine safe levels of individual mycotoxins. Mycotoxin effects are affected by factors such as animal species, gender, age, duration of exposure and stresses of the environment and production. Animals under environmental or production stress may show the more pronounced symptoms. With fescue toxicity, more pronounced symptoms are expressed during heat stress (Bacon, 1995). Fumonisin at 100 parts per million has been shown to reduce milk production in dairy cattle (Diaz et al., 2000) and in a separate study did not affect average daily gain in beef cattle fed 148 ppm (Osweiler et al., 1993). While not a direct comparison, this difference in response may suggest a difference in stress levels of early lactation dairy cattle compared with growing beef cattle.

Jones et al. (1982) demonstrated that productivity losses in commercial broiler operations can occur when aflatoxin concentrations were below those levels of concern established by controlled research in laboratory situations. This suggests that conditions in commercial operations are different than laboratory conditions and that the toxicity of mycotoxins may be influenced by interactions with those conditions. The known dietary factors that interact with mycotoxins include nutrients such as fat, protein, fiber, vitamins and minerals (Brucato et al., 1986; Galvano et al., 2001; Smith et al., 1971). Dietary ingredients such as clay pellet binders adsorb some mycotoxins, reducing exposure of the animal. Thus, many factors and interactions make it difficult to relate field observations to those from controlled research.

Because of partial degradation in the rumen, mycotoxins are generally less toxic to ruminants than to most other animals. However, most mycotoxins are not completely degraded, and some of the degradation products remain toxic (Kiessling et al., 1984). Extent of ruminal degradation of mycotoxins appears to be variable and may be reduced in feeding situations where ruminal turnover rate is high or when rumen microbial population is reduced. Ruminal degradation of mycotoxins appears to be more dependent on protozoal than bacterial activity (Kiessling et al., 1984; Hussein and Brasel, 2001). Effects of mycotoxins in ruminants are reviewed by Jouany and Diaz (2005).

Conjugated mycotoxins in which a mycotoxin is bound to another substance, such as sugars, may be "masked" during laboratory analysis and yet toxic to animals. Both zearalenone (Gareis et al., 1990) and deoxynivalenol (Berthiller et al., 2005) are known to occur in "masked" forms. Therefore, mycotoxicoses cases may have occurred in situations where "masked" mycotoxins resulted in only low concentrations of mycotoxins detected in the laboratory, yet higher levels existed in the feed.

Toxicity of Individual Mycotoxins

Aflatoxin

Aflatoxins are extremely toxic, mutagenic, and carcinogenic compounds produced by *Aspergillus flavus* and *A. parasiticus*. Aflatoxin B1 is excreted in milk in the form of aflatoxin M1. The FDA limits aflatoxin to no more than 20 ppb in lactating dairy feeds and to 0.5 ppb in milk. A thumb rule is that milk aflatoxin concentrations equal about 1.7% (range from 0.8 to 2.0%) of the aflatoxin concentration in the total ration dry matter. Cows consuming diets containing 30 ppb aflatoxin can produce milk containing aflatoxin residues above the FDA action level of 0.5 ppb. Aflatoxin appears in the milk rapidly and clears within three to four days (Diaz et al., 2004 and Frobish et al., 1986).

Symptoms of acute aflatoxicosis in mammals include: inappetance, lethargy, ataxia, rough hair coat, and pale, enlarged fatty livers. Symptoms of chronic aflatoxin exposure include reduced feed efficiency and milk production, jaundice, and decreased appetite. Aflatoxin lowers resistance to diseases and interferes with vaccine-induced immunity (Diekman and Green, 1992). In beef cattle, Garrett et al. (1968) showed an effect on weight gain and intake with diets containing 700 ppb aflatoxin, but if increases in liver weights are used as the criteria for toxicity, 100 ppb would be considered toxic to beef cattle. Production and health of dairy herds may be affected at dietary aflatoxin levels above 100 ppb, which is considerably higher than the amount that produces illegal milk residues (Patterson and Anderson 1982, and Masri et al., 1969). Guthrie (1979) showed when lactating dairy cattle in a field situation were consuming 120 ppb aflatoxin, reproductive efficiency declined and when cows were changed to an aflatoxin free diet, milk production increased over 25%. Applebaum et al. (1982) showed milk production was reduced in cows consuming impure aflatoxin produced by culture, but production was not significantly affected by equal amounts of pure aflatoxin.

Aflatoxin is more often found in corn, peanuts and cottonseed grown in warm and humid climates. Aflatoxin can be found in more temperate areas, as was seen in the drought year of 1988 when aflatoxin was seen in 5% of corn grain in the Midwestern U.S. (Russell et al., 1991). The US General Accounting Office has concluded that industry, federal and state programs are effective in detecting and controlling aflatoxin and that it is doubtful that additional programs or limits would reduce the risk of aflatoxin in the food supply. Aflatoxin regulations worldwide have been reviewed by Van Egmond and Jonker (2005).

Deoxynivalenol (DON) or Vomitoxin

Deoxynivalenol is a *Fusarium* produced mycotoxin, commonly detected in feed. It is sometimes called vomitoxin because it was associated with vomiting in swine. Surveys have shown DON to be associated with swine disorders including: feed refusals, diarrhea, emesis, reproductive failure, and deaths. The impact of DON on dairy cattle is not established, but clinical data show an association between DON and poor performance in dairy herds (Whitlow et al., 1994). Dairy cattle consuming diets contaminated primarily with DON (2.5 ppm) have responded favorably (1.5 kg milk, $P<.05$) to the dietary inclusion of a mycotoxin binder, providing circumstantial evidence that DON may reduce milk production (Diaz et al., 2001). Field reports help substantiate this association (Gotlieb, 1997 and

Seglar, 1997). Results from a Canadian study using 6 first-lactation cows per treatment during mid-lactation (average 19.5 kg milk) showed that cows consuming DON contaminated diets (2.6 to 6.5 ppm) tended ($P<0.16$) to produce less milk (13% or 1.4 kg) than did cows consuming clean feed (Charmley et al., 1993). DON had no effect on milk production in 8 cows fed over a 21 day period (Ingalls, 1996). DON has been associated with altered rumen fermentation (Seeling et al., 2006) and reduced flow of utilizable protein to the duodenum (Danicke et al., 2005). Beef cattle and sheep have tolerated up to 21 ppm of dietary DON without obvious effects (DiCostanzo et al., 1995).

Like other mycotoxins, pure DON added to diets, does not have as much toxicity as does DON supplied from naturally contaminated feeds, perhaps due to the presence of multiple mycotoxins in naturally contaminated feeds. These mycotoxins can interact to produce symptoms that are different or more severe than expected. For example, it is now known that fusaric acid interacts with DON to cause the vomiting effects, which earlier was attributed to DON alone and resulted in use of the trivial name of vomitoxin for DON (Smith and MacDonald, 1991). It is believed that DON serves as a marker, indicating that feed was exposed to a situation conducive for mold growth and possible formation of several mycotoxins.

The U.S. Food and Drug Administration advisory level for deoxynivalenol in wheat and wheat derived products destined for dairy cattle diets is for no more than 5 ppm DON and to be used at levels below 40%.

T-2 Toxin (T-2)

T-2 toxin is a very potent *Fusarium* produced mycotoxin that occurs in a low proportion of feed samples (<10%). Russell et al. (1991) found 13% of Midwestern corn grain contaminated with T-2 toxin in a survey of the 1988 drought damaged crop. Effects of T-2 are less well established in cattle than in laboratory animals. In dairy cattle, T-2 has been associated with gastroenteritis, intestinal hemorrhages (Petrie et al., 1977; Mirocha et al., 1976) and death (Hsu et al., 1972 and Kosuri et al., 1970). Dietary T-2 toxin at 640 ppb for 20 days resulted in bloody feces, enteritis, abomasal and ruminal ulcers, and death (Pier et al., 1980). Weaver et al. (1980) showed that T-2 was associated with feed refusal and gastrointestinal lesions in a cow, but did not show a hemorrhagic syndrome. Kegl and Vanyi (1991) observed bloody diarrhea, low feed consumption, decreased milk production, and absence of estrous cycles in cows exposed to T-2. Serum immunoglobulins and complement proteins were lowered in calves receiving T-2 toxin (Mann et al., 1983). Gentry et al. (1984) demonstrated a reduction in white blood cell and neutrophil counts in calves. McLaughlin et al. (1977) demonstrated that primary basis of T-2 reduced immunity is reduced protein synthesis. Guidelines for T-2 toxin are not established, but avoiding levels above 100 ppb may be reasonable. Diacetoxyscirpenol, HT-2 and neosolaniol may occur along with T-2 toxin and cause similar symptoms.

Zearalenone (ZEA)

Zearalenone is a *Fusarium* produced mycotoxin that has a chemical structure similar to estrogen and can produce an estrogenic response in animals. Zearalenone is associated with ear and stalk rots in corn and with scab in wheat. Controlled studies with ZEA at high levels have failed to reproduce the degree of toxicity that has been associated with ZEA contaminated feeds in field observations. A controlled study with non-lactating cows fed up to 500 mg of ZEA (calculated dietary concentrations of about 25 ppm ZEA) showed no obvious effects except that corpora lutea were smaller in treated cows (Weaver et al., 1986b). In a similar study with heifers receiving 250 mg of ZEA by gelatin capsule (calculated dietary concentrations of about 25 ppm ZEA), conception rate was depressed about 25%; otherwise, no obvious effects were noted (Weaver et al., 1986a). Several case reports have related ZEA to estrogenic responses in ruminants including abortions (Kellela and Ettala, 1984; Khamis et al., 1986; Mirocha et al., 1968; Mirocha et al., 1974; and Roine et al., 1971). Symptoms have included vaginitis, vaginal secretions, poor reproductive performance, and mammary gland enlargement of virgin heifers. In a field study, (Coppock et al., 1990) diets with about 660 ppb ZEA and 440 ppb DON resulted in poor consumption, depressed milk production, diarrhea, increased reproductive tract infections, and total reproductive failure. New Zealand workers (Towers et al., 1995) have measured blood ZEA and metabolites ("zearalenone") to estimate ZEA intake. Dairy herds with low fertility had higher levels of blood "zearalenone". Individual cows within herds examined by palpation and

determined to be cycling had lower blood "zearalenone" levels than did cows that were not cycling. In this study, reproductive problems in dairy cattle were associated with dietary ZEA concentrations of about 400 ppb.

Fumonisin (FB)

Fumonisin B1 produced by *F. verticillioides*, was first isolated in 1988. It causes leukoencephalomalacia in horses, pulmonary edema in swine, and hepatotoxicity in rats. It is carcinogenic in rats and mice and is thought to be a promoter of esophageal cancer in humans (Rheeder et al., 1992). Fumonisins are structurally similar to sphingosine, a component of sphingolipids, which are in high concentrations in certain nerve tissues such as myelin. Fumonisin toxicity results from blockage of sphingolipid biosynthesis and thus degeneration of tissues rich in sphingolipids.

While FB1 is much less potent in ruminants than in hogs, it has now been shown toxic to sheep, goats, beef cattle, and dairy cattle. Osweiler et al. (1993) fed 18 young steers either 15, 31, or 148 ppm of fumonisin in a short term study (31 days). With the highest feeding level, there were mild liver lesions found in two of six calves, and the group had lymphocyte blastogenesis and elevated enzymes indicative of liver damage. Dairy cattle (Holsteins and Jerseys) fed diets containing 100 ppm fumonisin for approximately 7 days prior to freshening and for 70 days thereafter demonstrated lower milk production (6 kg/cow/day), explained primarily by reduced feed consumption (Diaz et al., 2000). Increases in serum enzyme concentrations suggested mild liver disease. Because of greater production stress, dairy cattle may be more sensitive to fumonisin than are beef cattle.

Fumonisin carryover from feed to milk is thought to be negligible (Scott et al., 1994). A USDA, APHIS survey of 1995 corn from Missouri, Iowa, and Illinois found that 6.9% contained more than 5 ppm fumonisin B1. Fumonisin was prevalent in Midwestern corn from the wet 1993 season as well. Corn screenings contain about 10 times the fumonisin content of the original corn.

U.S. Food and Drug Administration guidance for industry on fumonisin levels in human foods and animal feeds recommends that corn used for dairy purposes should contain no more than 30 ppm of total fumonisins and limited to 50% of the diet.

Ergot alkaloids, including fescue toxicity

One of the earliest recognized mycotoxicoses is ergotism caused by a group of ergot alkaloids. They are produced by several species of *Claviceps*, which infect the plant and produce toxins in fungal bodies called sclerotia or ergots, which are small black colored bodies similar in size to the grain. Ergotism primarily causes a gangrenous or nervous condition in animals. Symptoms are directly related to dietary concentrations and include reduced weight gains, lameness, lower milk production, agalactia and immune suppression (Robbins et al., 1986). Sclerotia concentrations above 0.3% are related to reproductive disorders.

Fescue infected with *Neotyphodium* or *Epichloe* may contain toxic alkaloids associated with “fescue toxicity” (CAST, 2003). Symptoms include lower weight gains, rough hair coat, increased body temperature, agalactia, reduced conception, and gangrenous necrosis of the extremities such as the feet, tail and ears. Fescue is a major pasture grass in the U.S., growing widely throughout the lower Midwest and upper South. More than 20% of US beef cattle graze fescue and more than half of the fescue is endophyte infected, making this a serious problem for cattle producers. Endophyte-free varieties are available, but they are not as hardy as infected varieties. Fescue infected with a nonpathogenic endophyte appears to be more field hardy and less toxic.

Ochratoxin A

Ochratoxin A (OTA) is produced by species of *Penicillium* and *Aspergillus* and is a causative agent of kidney disease in pigs that has been referred to as mycotoxin porcine nephropathy (Krogh, 1979). The primary toxic effect is inhibition of protein synthesis (Creppy et al., 1984). In cattle, OTA is rapidly degraded in the rumen and thus thought to be of little consequence unless consumed by young pre-ruminant calves (Sreemannarayana et al., 1988). With high-grain diets, less of the dietary ochratoxin may be degraded in the rumen and thus be more toxic in those situations (Hohler, et al., 1999). Moldy alfalfa hay containing *A. ochraceus* was implicated as producing OTA

associated with abortions in cattle (Still et al., 1971). OTA in moldy forage has also been implicated in cattle deaths (Vough and Glick, 1993).

PR toxin

PR toxin is one of the several mycotoxins produced by *Penicillium* molds. Penicillium grows at a low pH and in cool damp conditions and has been found to be a major contaminant of silage. PR toxin, produced by *P. roquefortii*, has been suggested as the causative agent associated with moldy corn silage problems (Seglar 1997 and Sumarah et al., 2005). Surveys of grass and corn silage in Europe have found an occurrence of *P. roquefortii* in up to 40% of samples (Auerbach, 2003) and associated with cattle disorders (Boysen et al., 2000). PR toxin, caused acute toxicity in mice, rats and cats by increasing capillary permeability resulting in direct damage to the lungs, heart, liver and kidneys (Chen et al., 1982) and was the suspected vector in a case study with symptoms of abortion and retained placenta (Still et al., 1972). Other *Penicillium* produced mycotoxins in silages, such as roquefortine C, and mycophenolic acid have been associated with herd health problems (Auerbach, 1998; Scudamore and Livesay, 1998, and Sumarah et al., 2005).

Patulin

Patulin is produced by *Penicillium*, *Aspergillus* and *Byssochlamys* (Dutton et al., 1984; Hacking and Rosser, 1981). Patulin is most likely to occur in moldy fruits such as apples, but may also be found in grains, especially wet grains, and silage. Patulin is antibiotic against gram-positive bacteria. Added to rumen continuous cultures at 0, 20, 40 or 80 mg per day, patulin reduced VFA production, fiber digestion and bacterial yield (Tapia et al., 2005). The potential for patulin toxicity of livestock is thought to be low, but there are reported case studies of toxicity (Sabater-Vilar et al., 2004).

Citrinin

Citrinin can co-occur with OTA, is produced by both *Penicillium* and *Aspergillus* and like OTA, citrinin targets the kidney (Kitchen et al., 1977). The toxicity of citrinin was reviewed, indicating that it is a parasympathomimetic agent, causes necrosis of tubular epithelial cells in the kidney, and in some cases, hepatotoxicity (Hanika and Carlton, 1994).

Forage Mycotoxins

Many other mycotoxins may affect ruminants but there is less information about them or they are of less consequence. There is much less information available about mycotoxins in forages. The array of mycotoxins found in forages may be different than those found in grains, and are of major importance in mycotoxicoses of ruminants. Mycotoxins in forages and associated mycotoxicoses in cattle have been reviewed (Lacey, 1991; Gotlieb, 1997; Scudamore and Livesay, 1998; Seglar, 1997; Whitlow, 1997). El-Shanwany et al. (2005) isolated 43 fungal species belonging to 17 genera from 40 silage samples collected in Egypt. The most prevalent genera were *Aspergillus* and *Penicillium* followed by *Fusarium* and *Gibberella.* Molds were found in 206 of 233 grass or corn silage samples collected in Germany during 1997-98 (Schneweis et al., 2000). *Penicillium* was the dominant genus followed by *Mucoraceae, Monascus* and *Aspergillus.* Mycophenolic acid was present in 32% of samples. In 25 hay and silage samples collected in Minnesota, Wisconsin and Illinois, there was a high incidence of cyclopiazonic acid, DON, FB, PR toxin and alternaria TA toxin (Yu et al., 1999). It appears that *A. flavus* does not grow well in hay or silage; however, aflatoxin concentrations of up to 5 ppm have been reported (Kalac and Woolford, 1982). The most important pasture-induced toxicosis in the U.S. is tall-fescue toxicosis caused by endophytic alkaloids (Bacon, 1995). Other forage toxicosis of fungal origin include ergotism, perennial ryegrass staggers, slobbers syndrome, a hemorrhagic disease associated with dicoumarol produced in fungal-infected sweet clover and sweet vernal grass and syndromes of unthriftiness and impaired reproduction associated with *Fusarium* (Cheeke, 1995).

Mycotoxin Testing

Analytical techniques for mycotoxins are improving. Several commercial laboratories are available and provide screens for an array of mycotoxins. Cost of analyses has been a constraint but can be insignificant compared with the economic consequences of production and health losses related to mycotoxin contamination. Newer immunoassays have reduced the cost of analyses.

Collection of representative feed samples is a problem, because molds can produce large amounts of mycotoxins in small areas, making the mycotoxin concentrations highly variable within the lot of feed (Whittaker, 2003). Variability of mycotoxins from core samples of horizontal silos confirms that mycotoxins can be highly variable throughout the silo. Because mycotoxins can form in the collected sample, samples should be preserved and delivered to the lab quickly. Samples can be dried, frozen or treated with a mold inhibitor before shipping.

The accurate determination of mycotoxin concentrations in feedstuffs depends on a number of factors. First, a statistically valid sample must be drawn from the lot (Whittaker, 2003). Because mycotoxins are not evenly distributed in grains and other feedstuffs, most of the error in a single analysis is due to sampling — as much as 90% of the error is associated with the taking of the initial sample. Proper collection and handling of representative feed samples is essential. Since molds grow in "hot" spots, mycotoxins are not uniformly distributed within a feed, making it difficult to obtain a representative sample, especially from whole seed, course feeds or feeds not adequately mixed. Once collected, samples should be handled properly to prevent further mold growth. Wet samples may be frozen or dried before shipment, and transit time should be minimized.

The collected sample must should be finely ground and subsampled for analysis; this step is the second-largest source of error in an analysis. Finally, the subsample is extracted, the extract purified using one of several techniques, and then the mycotoxins are measured. Toxin determination may be by thin-layer chromatography plates, high-performance liquid chromatography, gas-liquid chromatography, enzyme-linked immunosorbent assays, and spectrophotometer or by other techniques.

Mold spore counts may not be very useful but their presence is a gross indication of the potential for toxicity. Mold identification can be useful to suggest which mycotoxins may be present. Because tests for some potentially important mycotoxins such as PR toxin are not generally available, it is currently recommended to analyze silages for mold spore count and mold identification to provide some insight to possible problems.

Blacklighting for bright-greenish-yellow fluorescence (BGYF) is often used as a screening technique for aflatoxin in corn grain, but it is very inaccurate. Newer and better methods should be used. As far as we are aware, blacklighting is completely inappropriate for other mycotoxins.

Generally, laboratories provide analysis for only a limited number of mycotoxins, perhaps including aflatoxin, ochratoxin, DON, ZEA, fumonisin and T-2 toxin. Minimum detection levels may be limited because the purpose of the laboratory is often directed at finding high levels that cause acute toxicity and serious animal disease rather than low levels associated with chronic effects such as production losses, impaired immunity and significant economic losses. Analytical techniques for mycotoxins are improving, costs are decreasing and several commercial laboratories are available that provide screens for an array of mycotoxins. The Federal Grain Inspection Service (USDA-GIPSA) provides a list on the internet of approved mycotoxin tests for grains and provides excellent background materials for the feed industry (at www.usda.gov/gipsa/pubs/mycobook.pdf). Laboratory methods can be found in "Official methods of analysis of AOAC International" (Horwitz, 2000). Analytical protocols for mycotoxins are published (Trucksess and Pohland, 2000).

Standards for acceptable concentrations of mycotoxins should be conservatively low due to non-uniform distribution, uncertainties in sampling and analysis, the potential for multiple sources of mycotoxins in the diet, and interacting factors affecting toxicity (Hamilton, 1984).

Prevention and Treatment

Prevention of mycotoxin formation is essential since there are few ways to completely overcome problems once mycotoxins are present. Drought and insect damage are most important in instigating mold growth and mycotoxin formation in the field. Therefore, varieties with resistance to fungal disease or to insect damage (Bt hybrids) have fewer field produced mycotoxins. Varieties should be adapted to the growing area. Irrigation can reduce mycotoxin formation in the field. When harvesting, avoid lodged or fallen material, because contact with soil can increase mycotoxins. Mycotoxins increase with delayed harvest, and with late season rain and cool periods. Damaged grains have increased mycotoxin levels, thus for dry grain storage, harvesting equipment should be maintained to avoid kernel damage. Mycotoxin concentrations are greatest in the fines, and in broken and damaged kernels, thus cleaning can greatly reduce mycotoxin concentrations in the feedstuff.

After harvest, grains should not be allowed to remain at moisture levels greater than 15 to 18%. While there is little mold growth in grain below 15% moisture, drying to levels below 14% and preferably to <13% help to compensate for non-uniform moisture concentrations throughout the grain mass. High temperatures increase the amount of free moisture (water activity) in the grain which is the primary cause of mold growth in storage. Storage should be sufficient to eliminate moisture migration, moisture condensation or leaks. Grain stored for more than two weeks should be kept aerated and cool. Aeration is critical because as molds start to grow in isolated spots, the moisture produced by metabolism is sufficient to stimulate spread of the mold growth. Aeration reduces moisture migration and non-uniform moisture concentrations. Commodity sheds should protect feedstuffs from rain or other water sources. They should be constructed with a vapor barrier in the floor to reduce moisture. If wet feeds are stored in commodity sheds near dry feeds, a method must be devised to prevent moisture contamination of the dry feed. Bins, silos and other storage facilities should be cleaned to eliminate source of inoculation. Check stored feed at intervals to determine if heating and molding are occurring. Organic acids can be used as preservatives for feeds too high in moisture for proper storage.

It can be difficult to make hay at moisture levels low enough to prevent mold growth. Mold will grow in hay at moisture levels above 12 to 15%. Hay harvested at high moistures will tend to equilibrate to moisture contents of 12 to 14%, but rate of moisture loss is dependent on moisture at harvest, air movement, humidity, air temperature, bale density and the storage facility. Rate of dry down is enhanced by ventilation, creation of air spaces between bales, reduced size of stacks, alternated direction of stacking and avoidance of other wet products in the same area. As molds and other microorganisms grow, they produce heat and cause deterioration. Heating can be great enough to cause spontaneous combustion and hay fires.

Prevention of mycotoxins in silage includes following accepted silage making practices aimed at preventing deterioration primarily by quickly reducing pH and eliminating the oxygen. Accepted silage making practices emphasize ●harvesting at the proper moisture content; ●chopping uniformly at the proper length, ●filling the silo rapidly; ●packing the silage sufficiently to exclude air; ●using an effective fermentation aide; and ●covering completely and well. Infiltration of air after ensiling can allow growth of acid tolerant microorganisms, an increase in the pH and then mold growth. *Penicillium* molds are acid tolerant and may grow if any air is present. Microbial or other additives that reduce pH rapidly can reduce mold growth and mycotoxin formation. Ammonia, propionic acid, sorbic acid and microbial or enzymatic silage additives are shown to be at least partially effective at inhibiting mold growth. Added ammonia may prevent silage from reaching a low pH, but it can reduce mold growth through direct inhibition. Organic acids provide some of the acidity needed for preservation without sole reliance on microbial produced acids. Organic acids may be used to treat the entire silage mass, or to selectively treat the outer layers of the silo. Organic acids are sometimes used during feedout to treat the silo feeding face and/or the TMR in an effort to reduce deterioration of the feeding face and to reduce heating in the feed bunk. Silo size should be matched to herd size to insure daily removal of silage at a rate faster than deterioration. In warm weather, it is best to remove a foot of silage daily from the feeding face. The feeding face of silos should be cleanly cut and disturbed as little as possible to prevent aeration into the silage mass. Silage (or other wet feeds) should be fed immediately after removal from storage. Spoilage should not be fed and feed bunks should be cleaned regularly.

As with silage, high moisture grains or byproduct feeds must be stored at proper moisture content to exclude air and stored in a well maintained and managed structure. Wet feeds must be handled in quantities which allow them to be fed out within 7 to 10 days. Organic acids are very helpful in preventing mold in wet commodity feeds and can extend storage life. Discard any spoilage.

Obviously moldy feed should be avoided. Spoilage or deteriorated silage can reduce feed consumption, fiber digestibility and production. If unacceptably high levels of mycotoxins occur, dilution or removal of the contaminated feed is preferable; however, it is often impossible to completely replace some feeds in the ration, particularly the forage ingredients. Cleaning or ammoniation of grains can reduce mycotoxin concentrations, but there is no practical method to detoxify affected forages. Chemical, physical, and biological methods are reviewed along with other methods for management and detoxification of mycotoxins (Lopez-Garcia and Park, 1998; Sinha, 1998).

Management strategies to reduce mycotoxins in animal feeds have been reviewed by Trenholm et al. (1988). Dietary strategies to counteract the effects of mycotoxins have been reviewed (Galvano et al., 2001). Increasing dietary levels of nutrients such as protein, energy and antioxidants may be advisable. Animals exposed to aflatoxin show marginal responses to increased protein. In some situations, poultry respond to water soluble vitamins or to specific minerals, but data is lacking for cattle. Acidic diets seem to exacerbate effects of mycotoxins, and therefore adequate dietary fiber and buffers are recommended. Because mycotoxins reduce feed consumption, feeding management to encourage intake can be helpful. Dry cows, springing heifers and calves should receive the cleanest feed possible. Transition rations can reduce stress in fresh cows and reduce effects of mycotoxins. Strategic use of mold inhibitors can be beneficial.

Mycotoxin binders

Reviews of mycotoxin binders have been published (Avantaggiato *et al.*, 2005;Ramos *et al.*, 1996a; Ramos and Hernandez, 1997; Huwig *et al.* 2001, Whitlow 2006).

The addition of mycotoxin binders to contaminated diets has been considered the most promising dietary approach to reduce effects of mycotoxins (Galvano *et al.*, 2001). The theory is that the binder decontaminates mycotoxins in the feed by binding them strongly enough to prevent toxic interactions with the consuming animal and to prevent mycotoxin absorption across the digestive tract. Therefore, this approach is seen as prevention rather than therapy.

Potential absorbent materials include activated carbon, aluminosilicates (clay, bentonite, montmorillonite, zeolite, phyllosilicates, etc.), complex indigestible carbohydrates (cellulose, polysaccharides in the cell walls of yeast and bacteria such as glucomannans, peptidoglycans, and others), and synthetic polymers such as cholestryamine and polyvinylpyrrolidone and derivatives.

Binder Evaluations and Concerns

Research with mycotoxin binders has been conducted for over 20 years, and yet products are not yet approved for the marketplace and information for producers is limited. Mycotoxin binders have been evaluated using both in vitro and in vivo systems. In vitro evaluations have been useful as a screening method for potential binder products, providing an idea of binding affinity and capacity. In vitro methods are not standardized and therefore are not comparable across all laboratories. The in vitro techniques have not produced results that correlate well with in vivo results. Therefore, in vitro data should not be used to make decisions about products to use in practice (Doll *et al.*, 2004; Diaz *et al.*, 2004; Garcia *et al.*, 2003). In vivo studies have generally used performance responses or biological markers such as tissue residues or changes in biochemical parameters to determine effectiveness of binders. These measurements can only estimate binding indirectly. Because many factors and conditions of the study affect results, binders need to be evaluated with different inclusion rates; with different mycotoxins; across animal species, ages, and genders; and under different environmental conditions. However, if comparisons are to be made across studies, experimental criteria must be standardized. Even with standardization, products may vary significantly by lots, resulting in different results in vitro or in vivo and from study to study (Bailey *et al.* 1998). Any negative effects of the binder should also be evaluated. Gathering the definitive information is complex, expensive, time-consuming, and thus frustrating to an industry waiting for solutions.

Charcoal or activated carbon

Activated carbon is a general adsorptive material with a large surface area and excellent adsorptive capacity. It has been recommended as a general toxin adsorbing agent and is routinely recommended for various digestive toxicities (The Merck Veterinary Manual, Eighth Edition, Merck & Co., Inc.,
Whitehouse Station, NJ). In one of the first studies to test the concept of mycotoxin binding, activated charcoal at a high dosage was shown to reduce aflatoxicosis in goats (Hatch *et al.*, 1982). In subsequent studies, the effects of activated charcoal have been variable. Galvano *et al.* (1996) showed reduced aflatoxin residues in milk of cows consuming different sources of charcoal, but responses to charcoal did not exceed that seen with a clay based binder (a hydrated sodium calcium aluminosilicate or HSCAS). Likewise, Diaz *et al.* (2004) showed that low levels (45 g/cow daily) of activated carbon did not significantly reduce milk aflatoxin residues, whereas clay type binders (225 g/cow daily) or an organic polymer of esterified glucan (10 g/cow daily) significantly reduced milk aflatoxin. Responses to charcoal with broilers (Edrington *et al.*, 1997), turkey poults (Edrington *et al.*, 1996), rats (Abdel-Wahhab *et al.*, 1999) and mink (Bonna *et al.*, 1991) also suggest that charcoal may not as effective in binding aflatoxin as are clay based binders. Activated charcoal may be important in binding zearalenone and/or deoxynivalenol (Doll *et al.*, 2004; Bueno *et al.*, 2005). In an in vitro gastrointestinal model, activated carbon reduced availability of deoxynivalenol and nivalenol (Avantaggiato *et al.*, 2004).

Silicate binders

Silicates are divided into subclasses, not by their chemistries, but by their structures. Minerals in different subclasses may have similar chemistries. The silicate subclasses include neosilicates (single tetrahedrons), sorosilicates (double tetrahedrons), inosilicates (single and double chains), cyclosilicates (rings), phyllosilicates (sheets), and tectocilicates (frameworks). Silicates investigated as adsorbent materials are classified primarily as phyllosilicates and tectosilicates. Perhaps the most extensively studied of these materials is one designated a hydrated sodium calcium aluminosilicate (**HSCAS**). Several reviews are available (Bingham *et al.*, 2003; Kubena *et al.*, 1987; Phillips, 1999; Phillips *et al.*, 1991; Ramos and Hernandez, 1997). It is suggested that this specific silicate minerals can bind with aflatoxin by chelating the β-dicarbonyl moiety in aflatoxin with uncoordinated metal ions in the clay materials (Phillips *et al.*, 1991). Other silicates that have been studied include bentonites, zeolites, clinoptilolites and various others that are often not completely characterized. The clay group is a subcategory of the phyllosilicates. Bentonite is a general clay material originating from volcanic ash and containing primarily montmorillonite as the main constituent. Montmorillonite clay is a hydrated sodium calcium aluminum magnesium silicate hydroxide. Clays are silica sheets that are similar to other phyllosilicates but contain a high concentration of water. Zeolites are classified as tectosilicates consisting of interlocking tetrahedrons. The zeolite structure provides vacant spaces that form channels of various sizes allowing movement of molecules into and out of the structure. Zeolites can lose and absorb water without damage to their crystal structures. A reference to minerals may be found at Amethyst Galleries, Inc. (http://mineral.galleries.com/minerals/silicate/class.htm).
Clearly much of the pioneering work with mycotoxin binders was done with silicates and specifically with the HSCAS material studied at Texas A&M University. Phillips *et al.* (1988) screened a large number of silicates and selected one of the better materials for further study. That specific HSCAS included at 0.5% to 2.0% of the diet is well documented to adsorb aflatoxin and to prevent aflatoxicosis across species, including chickens (Huff *et al.*, 1992, Kubena *et al.*, 1987, 1990a,b, 1992, 1993; Ledoux *et al.*, 1999; Phillips *et al.*, 1988; Scheideler, 1993), turkeys (Kubena *et al.*, 1991), swine (Colvin *et al.*, 1989; Harvey *et al.*, 1989; Lindemann *et al.*, 1993), lambs (Harvey *et al.*, 1991a), dairy cows (Harvey *et al.*, 1991b), dairy goats (Smith *et al.*, 1994) and mink (Bonna *et al.*, 1991). Responses to HSCAS appear to be dose dependent (Smith *et al.*, 1994).

This HSCAS is characterized as an "aflatoxin-selective clay," is not a good adsorbent of other mycotoxins (Phillips *et al.*, 1999), and therefore, is not expected to be protective against feeds containing multiple mycotoxins. Cyclopiazonic acid, which has co-occurred with aflatoxin, is not adsorbed by HSCAS (Dwyer *et al.*, 1997). Garcia *et al.* (2003), using a silicate material, failed to show reduced ochratoxin toxicity but did demonstrate reduced T-2 toxicity. Huff *et al.* (1992) also failed to see a benefit to adding HSCAS to diets containing ochratoxin. Watts *et al.* (2003) showed that 1% HSCAS was not protective to chicks and poults receiving diets containing 1 mg deoxynivalenol, 5 mg moniliformin, 5 mg fumonisin B1, 100 μg aflatoxin B11 mg zearalenone and 0.5 mg ochratoxin per kg of diet. HSCAS was protective to mink against zearalenone (Bursian *et al.*, 1992). Patterson and Young (1993) failed to see a benefit to the addition of HSCAS in pig diets containing deoxynivalenol. Huebner *et al.* (1999) and Chestnut *et al.* (1992) found that clays bind well with ergotamine in vitro; however, in vivo studies with sheep showed that an HSCAS added at 2% of the diet did not reduce fescue toxicity (Chestnut *et al.*, 1992).

Abdel-Wahhab *et al.* (2005) showed that montmorillonite binds well with sterigmatocystin, a mycotoxin chemically similar to aflatoxin. A clinoptilolite was effective in reducing the effects of aflatoxin in quail (Parlat *et al.*, 1999). Various clay products including a calcium bentonite were similar in effectiveness to a HSCAS in restoring performance to pigs consuming aflatoxin (Schell *et al.*, 1993a; Schell *et al.*, 1993b). Diaz *et al.* (2004) studied the efficacy of several clay types to reduce aflatoxin residues in milk of dairy cows. Several products were effective; however, a sodium bentonite reduced milk aflatoxin more than a similar amount of calcium bentonite. Diatomaceous earth has shown the potential in vitro to bind aflatoxin, sterigmatocystin, T-2 toxin, zearalenone and ochratoxin (Natour and Yousef, 1998). Zeolites have not proven to reduce the toxicity of T-2 toxin (Kubena *et al.*, 1998; Devorska and Surai, 2001).

A number of studies have examined chemically modified silicates. Doll *et al.* (2004) examined a chemically modified aluminosilicate that showed good binding with zearalenone in vitro confirming previous work (Lemke *et al.*, 1998; Tomasevic-Canovic *et al.*, 2003). Others have shown that chemical modifications have increased the binding of HSCAS with zearalenone (Pimpukdee *et al.*, 2004). Dakovic, *et al.* (2005) demonstrated adsorption of aflatoxin, ochratoxin and zearalenone by an octadecyldimethylbenzyl ammonium treated zeolite.

Organic polymers as binders

Some complex indigestible carbohydrates (cellulose, polysaccharides in the cell walls of yeast and bacteria such as glucomannans, and peptidoglycans, and others) and synthetic polymers such as cholestryamine and polyvinylpyrrolidone can adsorb mycotoxins.
Indigestible dietary fiber has adsorbance potential for mycotoxins. Alfalfa fiber has reduced the effects of zearalenone (James and Smith, 1982; Stangroom and Smith, 1984) in rats and swine and T-2 toxin in rats (Carson and Smith, 1983).

Saccharomyces cerevisiae live yeast was shown to reduce the detrimental effects of aflatoxin in broiler diets (Stanley *et al.*, 1993). The aflatoxin protective effect of live yeast was confirmed in rats, but thermolysed yeast was shown ineffective (Babtista *et al.*, 2002). Fibrous material from the yeast cell wall was shown to have a potential to bind several mycotoxins (Devegowda *et al.* 1998). Esterified glucomannan polymer extracted from the yeast cell wall was shown to bind with aflatoxin, ochratoxin and T-2 toxin, individually and combined (Raju and Devegowda 2000). Additions of esterified glucomannan at 0.5 or 1.0 g/kg to diets supplying 2 mg of total aflatoxin resulted in dose dependent responses in broiler chicks (Basmacioglu *et al.* 2005). Addition of esterified glucan polymer to aflatoxin contaminated diets of dairy cows has significantly reduced milk aflatoxin residues (Diaz *et al.*, 2004) and yet the same product failed to reduce milk aflatoxin in a subsequent study (Stroud et al., 2006).

The esterified glucan polymer may have the capability to bind several mycotoxins. Yiannikouris, *et al.* (2004) demonstrated the mechanism of binding with zearalenone. A glucan polymer bound both T-2 toxin and zearalenone in vitro (Freimund *et al.*, 2003). The glucan polymer product was protective against depression in antioxidant activities resulting from T-2 toxin consumed by growing quail (Dvorska and Surai, 2001). A glucan polymer product has protected swine (Swamy *et al.*, 2002), broilers (Swamy *et al.*, 2004) and hens (Chowdhury and Smith, 2004) against some of the detrimental effects of multiple mycotoxins, but without restoring growth rate. Aravind *et al.* (2003) using dietary additions of 0.5% esterified glucomannan, alleviated growth depression in broilers associated with naturally contaminated diets containing aflatoxin, ochratoxin, zearalenone and T-2 toxin. A glucan polymer product was effective in preventing aurofusarin toxicity in quail (Dvorska *et al.*, 2003). A glucan polymer product did not alleviate the toxic effects on mink consuming diets contaminated with fumonisin, ochratoxin, moniliformin and zearalenone (Bursian *et al.*, 2004).

Certain bacteria, particularly strains of lactic acid bacteria, propionibacteria and bifidobacteria, appear to have the capacity to bind mycotoxins, including aflatoxin and some Fusarium produced mycotoxins (El-Nezami *et al.*, 2000, 2002a, 2002b; Haskard *et al.*, 2001 and Oatley *et al.*, 2000; Yoon *et al.*, 1999). The binding appears to be physical with deoxynivalenol, diacetoxyscerpenol, nivalenol, and other mycotoxins associated with hydrophobic pockets on the bacterial surface. Research reports on the subject are limited.

Other Binders

A synthetic water soluble polymer, polyvinlypyrrolidone (PVP) has been investigated as a binder of mycotoxins. Insufficient information is available to make any recommendations. PVP is reported to bind with aflatoxin and

zearalenone in vitro (Alegakis *et al.*, 1999). PVP did not alleviate the toxicity of deoxynivalenol seen in pigs (Friend *et al.*, 1984).

Cholestyramine resin is used in human medicine for the reduction of cholesterol and functions through adsorption of bile acids. Cholestyramine has proven to adsorb zearalenone (Ramos *et al.*, 1996b; Doll *et al.*, 2004) and fumonisins (Solfrizzo *et al.*, 2001). In rats consuming ochratoxin, cholestyramine reduced plasma ochratoxin and increased fecal ochratoxin excretion (Kerkadi *et al.*, 1998). In another in vivo study, cholestyramine did not bind ochratoxin (Bauer, 1994). Because of cost, cholestyramine use is questionable.

An enzyme from a pure bacterial strain has been isolated that can de-epoxidize some trichothecenes (Binder *et al.*, 2000).

Desirable Characteristics of a Binder

A binder must be effective at sequestering the mycotoxin(s) of interest. In some cases, it may be of value to bind one specific mycotoxin and in others, to bind multiple mycotoxins. A binder should significantly prevent animal toxicity. There should not be serious detrimental effects on the animal, or at least detrimental effects should not outweigh the benefits. Costs should render its use practical and profitable. Animal/product residues of mycotoxins should not increase. There should be no detrimental effects on the animal food product. Mycotoxins in feeds should not be masked such that feed contamination cannot be verified. The binder should be physically usable in commercial feed manufacturing situations. Binder use and efficacy should be verifiable.

Binder – Conclusions

There is an excellent potential for binders to help manage the mycotoxin problem. Various materials can bind mycotoxins in feed and thus reduce toxic exposure to consuming animals. No product currently meets all the characteristics for a desirable binder. Mycotoxin control measures may require many approaches. In addition to binders or multiple binders, diets may be treated with other decontamination products. Animals may also be supplemented with antioxidants and other beneficial substances. Responses in dairy cattle to some of these products have been very encouraging. Overall results are variable by type and amount of binder, specific mycotoxins and their amounts, animal species, and interactions of other dietary ingredients. No adsorbent product is approved by the FDA for the prevention or treatment of mycotoxicoses. Several of these adsorbent materials are recognized as safe feed additives (GRAS) and are used in diets for other purposes such as flow agents, pellet binders, etc.

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