

Mycotoxin Toxicity, Treatment and Prevention

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INTRODUCTION

Mycotoxins can increase disease incidence and reduce production efficiency in cattle. They exert their effects through three primary mechanisms: (1) alteration in nutrient content, absorption and metabolism, (2) changes in the endocrine and neuroendocrine function, and (3) suppression of the immune system (CAST, 1989). The resulting nonspecific symptoms may therefore be perplexing and make diagnosis difficult. Hesseltine (1986) and Schilfer (1990) discussed some of the problems encountered in diagnosing a mycotoxicosis which include:

- A lack of research reports, especially concerning some mycotoxins,
- Symptoms which are not specific or unique for the mycotoxin,
- Interaction of mycotoxins with other mycotoxins or other stress factors,
- Interaction of mycotoxins with immune suppression and thus, infectious diseases,
- Lack of feed samples or samples improperly collected, and
- Analysis which is complex and expensive.

Our experience suggests that while a definitive diagnosis cannot be made directly from symptoms, specific tissue damage, or even feed analyses, experience with mycotoxin affected herds greatly increases the probability of recognizing the problem. The following guidelines may be helpful in dealing with a possible mycotoxicosis:

- Mycotoxins should be considered as a possible primary factor resulting in production losses and increased incidence of disease.
- Documented symptoms in ruminants or other species can be utilized as a general guide to symptoms observed in the field; however there is a

lack of research data, and field observations may differ from those seen in controlled research studies.

- Systemic effects as well as specific damage to target tissues can be used as a guide to possible causes.
- Postmortem examinations may indicate no more than gut irritation, edema or generalized tissue inflammation.
- Ruling out other possible causes such as infectious agents or other toxins is essential.
- All feeds should be analyzed for common mycotoxins.
- Responses to simple treatments such as dilution or removal of the contaminated feed are helpful.
- Diagnosis may be impossible because the clinical situation may be complex and complicated due to interactions with other agents.

Dairy herds experiencing a mycotoxicosis, which is severe enough to reduce milk production, usually display other symptoms. Often there is intermittent diarrhea, sometimes with bloody or dark manure. Cows may not respond well to typical veterinary therapy. Symptoms may be nonspecific, be wide ranging, and include: reduced feed intake, feed refusal, unthriftiness, rough hair coat, undernourished appearance, subnormal production, increased abortions or embryonic mortalities, silent heats, irregular estrous cycles, expression of estrus in pregnant cows, and decreased conception rates. Fresh cows perform poorly and generally have an increased incidence of disease, particularly those that are most opportunistic in a dairy herd. There may be a higher incidence of displaced abomasum, ketosis, retained placenta, metritis, mastitis, and fatty livers. Only a few or many of these symptoms may be evident.

AFLATOXIN

The FDA limits aflatoxin (AF) in corn grain according to its intended use: no more than 200 ppb for breeding cattle, 300 ppb for finishing beef cattle, and

20 ppb for lactating dairy cattle. Aflatoxin is excreted into milk in the form of AFM₁ with residues of approximately 1.7% of the dietary level (Van Egmond, 1989). The FDA limits AFM₁ in milk to no more than 0.5 ppb. Since AF residues can be found in tissues, beef cattle should not be fed AF contaminated diets for three weeks prior to slaughter. Regulatory pressures and a widespread awareness have helped minimize AF problems. The GAO (1991) concluded that industry, federal and state programs are effective in detecting and controlling AF and that it is doubtful that additional programs or limits would reduce the risk of AF in the food supply. Thus, current surveillance programs aimed at reducing food residues, make it very unlikely for AF to have significant production or health effects on dairy herds.

Aflatoxin can reduce performance and impair health, but this occurs generally at dietary levels greater than the 25 to 50 ppb which can cause illegal milk residues. Although no level of AF is considered safe, the degree of toxicity is related to level of a toxin, duration of feeding, and the amount of other stresses affecting the animal. Levels of 300 to 700 ppb are considered toxic for beef cattle, depending on criteria for toxicity and other factors affecting toxicity (CAST, 1989). Garrett et al. (1968) showed that with beef cattle, gain and intake were affected at 700 ppb AF, but not at 300 ppb; however, levels of no effect can not be determined from such data with few animals. Trends in the data, especially for increased liver weights, would indicate potential toxicity at levels as low as 100 ppb. Guthrie (1979) showed a decline in reproductive efficiency when lactating dairy cattle in a field situation were consuming 120 ppb AF and an increase in milk production of over 25% when cows were changed to an AF-free diet. Patterson and Anderson (1982) and Marsi et al. (1969) also suggest that 100 ppb may reduce milk production. Applebaum et al. (1982) showed that impure AF produced by culture reduced production, but equal amounts of pure AF did not. Several studies indicate that naturally contaminated feeds are more toxic than would be expected from the concentrations of assayed mycotoxins, suggesting the presence of unidentified toxins.

FUMONISIN

Fumonisin (**FB₁**) was isolated by Gelderblom et al. (1988) and shown to be a cancer promoter. FB₁ has been shown to cause leukoencephalomalacia in horses (Marasas et al., 1988), pulmonary edema in swine (Harrison et al., 1990) and hepatotoxicity in rats (Gelderblom et al., 1991). While FB₁ is thought to be much less potent in ruminants than monogastrics, work by Kriek et al. (1981) suggested that FB was toxic to sheep. Osweiler et al. (1993) demonstrated that FB₁ in large amounts (148 ppm) can cause mild liver damage in cattle even when fed for a short term (31 days), without an effect on feed intake or weight gain. Whitlow (unpublished) has demonstrated that FB₁ is also toxic to dairy cattle. Fed for approximately 7 days prior to freshening and for 70 days thereafter, dietary FB₁ at 100 ppm significantly and dramatically reduced milk production (7 kg/cow/day) and affected serum enzyme levels indicative of liver disease. These results strongly suggest that FB₁ is toxic to dairy cattle and that FB₁ is less toxic to beef cattle than to dairy cattle, or perhaps FB₁ interacts with other factors to produce greatly different effects in beef and dairy cattle under different conditions.

Fumonisin carryover from feed to milk is thought to be negligible. Richard et al. (1996) fed about 75 ppm FB₁ to dairy cows and with no FB₁ or FB₂ detectable in milk (detection limit of 5 ng/ml). Scott et al. (1994) have confirmed this observation.

DEOXYNIVALENOL

Deoxynivalenol (**DON**) is the proper name for a commonly detected *Fusarium* produced mycotoxin often referred to as vomitoxin. Two independent Midwestern studies (Vesonder et al., 1978 and Côté et al., 1984) showed DON to be the primary mycotoxin associated with swine problems, including feed refusals, diarrhea, emesis, reproductive failure, and deaths. In cattle, DON has been associated with reduced feed intake (Trenholm et al., 1985) and lower milk production (Whitlow et al., 1991). Clinical data from 300 herds representing about 40,000 cow records showed that DON was associated with a loss in milk production but did not establish a cause and effect (Whitlow et al., 1991). Deoxynivalenol may simply be a marker for problem feeds. Field observations by others help substantiate these observations (Gotlieb, 1997 and Seglar, 1997).

Charmley et al. (1993), demonstrated a 13% (2.85 kg) numerical decrease in 4% fat corrected milk production (statistics not available) utilizing 18 mid-lactation dairy cows (average 19.5 kg milk) consuming diets shown to contain no common mycotoxins other than DON, which was at levels of 2.7 to 6.4 ppm in treatment diets. While the decrease in actual milk production (1.35 kg) was not statistically significant, the decrease in fat test (3.92% vs. 3.04%) was significant.

Noller et al. (1979) utilized 54 lactating dairy cows in a 21 day feeding experiment using corn grain contaminated with *Gibberella zeae* and containing 500 ppb of zearalenone (**ZEN**). DON was probably present, but it was not analyzed directly. Grain harvested earlier from the same field was contaminated with DON at 12 to 13 ppm. Neither dry matter intake (**DMI**) nor milk production (average 22.9 kg) were affected by additions of this grain to the diet. However, compared with controls, cows which received this grain at either 10% (about 1.25 ppm DON and 50 ppb ZEN) or 20% (about 2.50 ppm DON and 100 ppb ZEN) of their diet gained significantly less weight during the study (5.8 kg or 8.1 kg less weight gain for cows consuming the 10% or 20% diets over 21 days).

DiCostanzo et al. (1995a) cites results by Ingalls (1994) where lactating dairy cows were fed 0, 3.6, 10.9 and 14.6 ppm of DON for 21 days, without apparent effects on feed intake or milk production, which averaged about 30 kg daily.

Beef cattle and sheep appear to tolerate relatively large amounts of DON without obvious deleterious effects. Reports from Nebraska, indicated similar feed intakes, average daily gains (**ADG**) and feed efficiencies when sheep (8.5 ppm dietary DON) or cattle (1 ppm dietary DON) consuming DON contaminated diets, were compared with those consuming control diets containing no detectable DON (DeHaan et al., 1984). Nelson et al. (1984) fed feedlot steers and heifers, diets containing either 0.2, 2.3 or 10 ppm of DON for 126 days. The low DON diet was corn based, while the other two contained wheat. Results reported for the low, medium and high DON diets were similar for DMI (9.4, 8.7 and 7.8 kg/day), ADG (1.54, 1.64, and 1.34 kg/day) and feed efficiency (6.2, 5.6, and 5.7 kg DMI/kg gain). Results for carcass characteristics, serum biochemistry and tissue histology were similar across treatments. DiCostanzo et al. (1995_{a,b}) indicated that feeding up to 18 ppm dietary DON did not affect

intake, daily gain, feed efficiency or carcass characteristics of 415 kg steers fed for 166 days. Other recent feeding experiments with beef cattle suggest they can tolerate large concentrations of DON in a feedlot situation without effects on DMI, ADG, or feed to gain ratio (Boland et al., 1994, and Windels et al., 1995).

These data suggest that cattle are relatively tolerant of DON. While not compared directly, it appears that beef cattle and sheep may be less sensitive to DON than dairy cattle. Differences could be related to level of production stress, since mid-lactation, low producing dairy cattle also appear to be more tolerant to DON than high producing dairy cattle in early lactation. Mycotoxins may interact with immune suppression in early lactation to produce more severe effects than would otherwise be expected. Heat or other environmental stresses may be involved. Thus, the early lactation, high producing cows which experience greater stress, lower immunity, marginal nutrient deficiencies and a faster rumen turnover (less mycotoxin degradation in the rumen) may be more vulnerable to mycotoxin effects.

Deoxynivalenol is but one causative agent that may be present. DON may serve as a marker for feed exposed to a situation conducive to mold growth and mycotoxin formation, and thus the possible presence of other mycotoxins or factors more toxic than DON itself. The differences in response to DON may be due to other mycotoxins. Experiments with beef cattle have generally utilized DON contaminated corn or barley. Deoxynivalenol from contamination of a different feed source, such as silage, could result in interactions of different mycotoxins. Mycotoxin interactions are discussed more fully in the section *Safe Levels of Mycotoxins*.

T-2 TOXIN

T-2 toxin (**T-2**), a *Fusarium* produced mycotoxin, has been associated with gastroenteritis, intestinal hemorrhages (Petrie et al., 1977 and Mirocha et al., 1976) and death (Hsu et al., 1972 and Kosuri et al., 1970). Weaver et al. (1980) demonstrated that T-2 was associated with feed refusal and gastrointestinal lesions in a cow, but failed to show a hemorrhagic syndrome. Serum immunoglobulins and certain complement proteins were lowered in calves receiving T-2 (Mann et al., 1983). Other data demonstrated a reduction in white blood cell and neutrophil counts in calves (Gentry et al., 1984). A calf intubated with T-2

developed severe depression, hindquarter ataxia, knuckling of the rear feet, listlessness and anorexia (Weaver et al., 1980).

While data with cattle are limited, the toxicity of T-2 in laboratory animals is well documented (Wannemacher et al., 1991). Our experience suggests that T-2 is a severe gastrointestinal irritant, which can cause hemorrhage and necrosis of the intestinal tract. Diarrhea is usually present but may not be hemorrhagic. With high levels of T-2, there can be congestion and irritation to the liver, lungs and heart. Two dairy herds were observed to receive T-2 contaminated feed from the same supplier and on similar dates. Early lactation cows were more severely affected, showing a lack of appetite, severe and prolonged weight loss, low peak milk production, higher levels of morbidity, and death. In another field case, with corn produced on the farm, resulted in approximately 350 ppb T-2 in the diet. Cows exhibited diarrhea, which moved in a wave over time through a dairy herd of about 150 Jersey cows. Milk production was erratic for two to three days and then dropped by 15%. The addition of a clay product to the diet appeared to restore production to previous levels after about three weeks. Removal of the clay resulted in an immediate loss in milk production and the clay was again fed with a positive response.

ZEARALENONE

Zearalenone (ZEN) is a *Fusarium* produced mycotoxin which elicits an estrogenic response in monogastrics (Sundlof and Strickland, 1986). However, ZEN is rapidly converted to α - and β -zearalenol in rumen cultures (Kiessling et al., 1984) and has been less toxic to ruminants. Ruminal degradation of ZEN was found to be about 30% in 48 hours (Kellela and Vasenius, 1982). A controlled study with cows fed up to 22 ppm ZEN showed no obvious effects except that corpora lutea were smaller in treated cows (Weaver et al., 1986b). In a similar study with heifers receiving about 13 ppm ZEN, conception rate was depressed about 25%; otherwise, no obvious effects were noted (Weaver et al., 1986a).

Several case reports have related ZEN to an estrogenic response in ruminants (Khamis et al., 1986; Mirocha et al., 1968; and Roine et al., 1971). Large doses are associated with abortions in cattle (Kellela and Ettala, 1984 and Mirocha et al., 1974).

Mirocha et al. (1968) isolated ZEN from hay associated with infertility in dairy cattle. Other cattle responses may include vaginitis, vaginal secretions, poor reproductive performance and mammary gland enlargement of virgin heifers. In a field study, (Coppock et al. 1990), diets with about 750 ppb ZEN and 500 ppb DON resulted in poor consumption, depressed milk production, diarrhea, and total reproductive failure.

New Zealand workers (Towers et al., 1995^{a,b}; Sprosen and Towers, 1995; and Smith et al., 1995) have related urinary ZEN and ZEN metabolites (ZEN, zearalanone, α - and β -zearalenol and α - and β -zearalanol) which they refer to as *zearalenone* to intake of *zearalenone* and to reproductive disorders in sheep and dairy cattle. In sheep, *zearalenone* was related to lower conception, reduced ovulation, and increased twinning rates. With dairy cattle, herds with low fertility were found to have higher levels of blood and urinary *zearalenone* and consumed pastures containing higher levels of *zearalenone*. In addition, within herds, individual cows were examined by palpation and those that were determined to be cycling had lower blood *zearalenone* levels than did cows that were not cycling. Differences in *zearalenone* levels were attributed to selective grazing behavior. The reproductive problems in dairy cattle were noted with *zearalenone* concentrations of about 400 ppb in the pasture samples.

Our observations suggest that ZEN may be associated with poor conception, early embryonic mortalities and increased reproductive tract infections. In most cases, cows have appeared well nourished with average body condition scores but poor reproductive performance. The differences may be attributed to the presence of other mycotoxins or interaction with other factors.

SAFE LEVELS OF MYCOTOXINS

Guidelines for acceptable levels of mycotoxins should be conservatively low due to:

- Nonuniform distribution,
- Uncertainties in sampling and analysis,
- The potential for more than one source in the diet, and
- The limited amount of research. All these factors make it impossible to declare levels of safety.

Hamilton (1984) and Schaeffer and Hamilton (1991) have reviewed the topic of safe levels of mycotoxins. They conclude that epidemiological studies coupled with laboratory studies to elaborate the underlying principles may be the best approach to determining safe levels. They state that any level of mycotoxin carries a risk of loss with it and that it is impossible to define a safe level under laboratory conditions that will be accurate under field conditions, primarily because of three reasons: (1) difficulties in conceptualizing and executing experiments to investigate multiple interacting factors simultaneously; (2) the unappreciated fact that the frequency and level of contamination with AF and other mycotoxins vary unpredictably under field conditions; and (3) animal facilities currently available to investigators do not permit experiments under controlled conditions with the number of animals commonly at risk under field conditions. They conclude that establishing usable or tolerable levels of mycotoxins may be acceptable only when all concerned parties are aware of levels and the risks associated.

Interactions with other factors make recommendations difficult. Not only is concentration of a mycotoxin important but duration of exposure is extremely important. Levels of environmental and production stresses are important. Sex and age of the animal are important. The known dietary factors which interact with mycotoxins include most nutrients for which rations are formulated: fat, protein, fiber, vitamins and minerals. Dietary pellet binders (clay) 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.

Lillehoj and Ceigler (1975) give an example where penicillic acid and citrinin were innocuous when administered alone, but were 100% lethal when given in combination. Aflatoxin produced from culture was more toxic to dairy cattle than pure AF

added to diets (Applebaum et al., 1982). In swine, Foster et al. (1986) demonstrated that pure DON added to diets was less toxic than diets with similar concentrations of DON supplied from naturally contaminated feeds. Smith and MacDonald (1991) suggested that fusaric acid may occur along with DON to produce more severe symptoms. Fusaric acid has been demonstrated to potentiate the toxicity of FB (Porter et al., 1995). A variety of such interactions are possible since *Fusarium* molds produce many mycotoxins, and it is well documented that several mycotoxins may be found in the same feed (Hagler et al., 1984). Abbas et al. (1989) demonstrated that *Fusarium* species isolated from Minnesota corn produces an array of mycotoxins. Scott (1990) states that screening methods are needed for the *Fusarium* produced mycotoxins and that one approach is to test for DON, diacetoxyscirpenol (**DAS**), T-2 and nivalenol, because other *Fusarium* mycotoxins seldom occur without one of these four also present.

There are distinct species differences in tolerance to mycotoxins. The rat is much more sensitive to both AF and T-2 than is the mouse (Wannemacher et al., 1991). Cattle are more tolerant to most mycotoxins than many other animals, probably due to some mycotoxin degradation in the rumen (Kiessling et al., 1984). Fumonisin at 100 ppm has reduced milk production in dairy cattle (Whitlow et al., 1994), but a higher FB concentration of 148 ppm did not affect ADG in beef cattle (Osweiler et al., 1993). DON appears to be more toxic to dairy than to beef cattle.

PREVENTION AND TREATMENT

Prevention of mycotoxin formation is essential since there are few ways to completely overcome problems once mycotoxins are present. Prevention of mycotoxins begins with selection of crop varieties more resistant to fungal foliar diseases, along with use of agronomic practices which reduce fungal infection of the crop. Prevention of mycotoxins in silage includes following accepted silage making practices aimed at enhancing proper fermentation and eliminating oxygen. Silages should be harvested at the correct moisture content, the silo filled rapidly, the silage packed tightly and the silo sealed completely. Silo size should be matched to herd size to insure daily removal of silage at a rate faster than deterioration (4 to 6 inches daily, depending on weather). The face of horizontal silos should be cut cleanly while avoiding loosening more silage than is to be fed. Secondary

fermentation can occur very rapidly after loosened silage is exposed to the air. Therefore, silage should be fed directly after removal from the silo and feed bunks should be cleaned regularly. Care should be taken to ensure that high moisture grains are stored at proper moisture contents and in a well-maintained structure. Grains or other dry feed such as hay should be stored at a moisture content <14%, below which molds do not readily grow. Aeration of grain bins is important to reduce moisture migration and to keep the feedstuffs dry.

Some additives may be beneficial in reducing mycotoxins because they are effective in reducing mold growth. Ammonia, propionic acid and microbial or enzymatic silage additives have all shown effectiveness as mold inhibitors. It seems reasonable that additives which enhance fermentation may be added at ensiling; while those which inhibit mold growth may be added as surface treatments when capping off the silo or daily after silage feed-out to reduce molding of the exposed silage surface.

If unacceptably high levels of mycotoxins occur, dilution or removal of the contaminated feed is preferable; however, it is usually impossible to completely replace major forage ingredients. Ammoniation of grains can destroy some mycotoxins, but there is no practical method to detoxify affected forages already in storage. Increasing nutrients such as protein, energy and antioxidant nutrients may be advisable (Brucato et al., 1986 and Chandler, 1992). In some situations, poultry respond to water soluble vitamins. Acidic diets may exacerbate effects of mycotoxins. Additional research on treatments is needed.

Materials which bind mycotoxins and thus prevent absorption by the animal's digestive tract are not approved by the FDA for the prevention or treatment of mycotoxicoses. However, favorable research results have been seen when binding agents

such as clays (bentonites) are added to mycotoxin contaminated diets of rats, poultry, swine and cattle (Diaz et al., 1997; Galey et al., 1987; Harvey, 1988; Lindemann et al., 1991; Scheideler, 1990; Hayes, 1990 and Smith, 1980, 1984). In most cases, clay was added to the diet at about 1%. Considerable data is also available for other binding materials such as charcoal, fiber, and yeast cell components. A

mannanoligosaccharide product (MTB-100, Alltech, Inc.) was shown (Diaz, et al., 1999) to reduce milk AF concentrations by 58% in dairy cows consuming AF contaminated diets when MTB-100 was included at 0.05% of the diet dry matter. Diaz et al., 1997 demonstrated that three bentonite products (AB-20, Prince Agri-Products ; Flow Guard, Laporte Biochem, Inc.; and Mycosorb, American Colloid Co.) reduced milk aflatoxin residues by an average of 58%. The reduction of milk AF was similar to that seen for a sodium bentonite product included at 1.1% of the diet dry matter. The reduction in milk AF may be a good indicator of strong binding with dietary AF, reducing AF absorption through the intestine of the cow.

CONCLUSIONS

Research evidence is being gathered to substantiate the detrimental effects of mycotoxins on dairy cattle. Field observations have suggested that mycotoxin contaminated feeds are more toxic than is indicated from controlled research with pure mycotoxins. Interactions with other mycotoxins and other stress factors may explain those discrepancies. Products and management practices to reduce the toxic effects of mycotoxins are showing promise. Opportunities for meaningful research are bountiful.

The Council for Agricultural Science and Technology published a list of major needs for mycotoxin research (CAST, 1989). Included in their list are:

- Surveillance of feeds for mycotoxin presence and quantity,
- Assessment of control methods,
- Development of resistant plants,
- Improvement of sampling and analysis,
- Improved understanding of effects on animals particularly on immunosuppression,
- Toxicological evaluation of newly discovered mycotoxins and
- Assessment of economic effects.

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