Effects of Feedborne *Fusarium* Mycotoxins on the Performance, Metabolism, and Immunity of Dairy Cows

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ABSTRACT

Little is known about the effects of feedborne *Fusarium* mycotoxins on the performance, metabolism, and immunity of dairy cattle. A total mixed ration (TMR) containing a blend of feedstuffs naturally contaminated with *Fusarium* mycotoxins was fed for 56 d to 18 midlactation Holstein cows (average milk production, 33 kg/d) in a completely randomized design with repeated measures that included 3 treatments: 1) a control diet, 2) a contaminated diet, and 3) a contaminated diet + 0.2% polymeric glucomannan mycotoxin adsorbent (GMA). Wheat, corn, and hay were the contaminated feedstuffs used in the study. Deoxynivalenol was the major contaminant and was found in the TMR at levels of up to 3.6 µg/g of dry matter. Body weight, body condition score, dry matter intake, net energy balance, milk production, milk composition, somatic cell count, blood serum chemistry, hematology, serum Ig concentrations, and coagulation profile were measured. Dry matter intake and body weight, as well as milk production, milk composition, and SCC, were not affected by diet. Total serum protein and globulin levels increased significantly in cows fed the contaminated TMR compared with cows fed the control diet at 42 d, whereas the albumin:globulin ratio decreased. Serum urea concentrations were significantly elevated throughout the experiment in cows fed the contaminated diet compared with those fed the control diet. Serum IgA concentrations decreased significantly in cows fed the contaminated TMR at 36 d of feeding. Feeding GMA prevented these effects. Serum sodium concentration and osmolality levels were increased throughout the experiment in all cows fed the contaminated diets. We concluded that feed naturally contaminated with *Fusarium* mycotoxins can affect the metabolic parameters and immunity of dairy cows and that GMA can prevent some of these effects.

Key words: dairy cow, *Fusarium* mycotoxin, deoxynivalenol, milk production

INTRODUCTION

There have been few reports regarding the sensitivity of dairy cattle to *Fusarium* mycotoxins. Charmley et al. (1993) observed that 4% FCM tended to exhibit a quadratic response to deoxynivalenol (DON) concentration in the diet (0, 6, and 12 µg/g of DON in concentrate DM), whereas Trenholm et al. (1985) recorded a trend toward decreased grain consumption in cows fed a DON (vomitoxin)-contaminated ration (6.4 µg/g in a grain mix). Whitlow et al. (1994) found that average milk production was correlated with the level of DON contamination of feedstuffs (500 to 900 ng/g, whereas Danicke et al. (2005) reported an elevation in rumen ammonia concentration and a reduction in duodenal flow of microbial protein in cows fed DON. A glucomannan mycotoxin adsorbent (GMA) has been shown to prevent some effects of mycotoxicoses in poultry (Chowdhury and Smith, 2004, 2005; Chowdhury et al., 2005a,b), swine (Swamy et al., 2002, 2003), and horses (Raymond et al., 2003). Therefore, an experiment was conducted to determine the effects of feedborne *Fusarium* mycotoxins on the performance, metabolism, and immunity of dairy cattle. The efficacy of a GMA in preventing *Fusarium* mycotoxicoses was also determined.

MATERIALS AND METHODS

Experimental Animals and Diets

A total of 18 midlactation Holstein cows of different parities (approximately 40% primiparous and 60% of multiparous animals, randomly assigned in groups) were used in the experiment (6 cows per treatment). Diets were fed for 56 d and included the following treatments: 1) control TMR, 2) contaminated TMR, and 3) contaminated TMR + 0.2% GMA (Mycosorb, Alltech Inc., Nicholasville, KY; Table 1). Wheat, corn, and hay were the sources of feedborne mycotoxins. Nutrient concentrations met nutritional requirements for lactating

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Table 1. Diet contents

Ingredient	Control TMR		Contaminated TMR		Contaminated + glucomannan mycotoxin adsorbent TMR	
	As fed, kg/cow per d	DM, kg/cow per d	As fed, kg/cow per d	DM, kg/cow per d	As fed, kg/cow per d	DM, kg/cow per d
Control first-mix hay (90.58% of DM)	1.5	1.25				
Contaminated first mix hay (90.58% of DM)			1.5	1.25	1.5	1.25
Haylage (33.76% of DM)	12.6	4.39	12.6	4.39	12.6	4.39
Corn silage (30.11% of DM)	22.8	6.61	22.8	6.61	22.7	6.60
Control corn (86.00% of DM)	6.0	5.16				
Control wheat (89.00% of DM)	2.5	2.23				
Contaminated corn (86.00% of DM)			6.0	5.16	6.0	5.16
Contaminated wheat (89.00% of DM)			2.5	2.23	2.5	2.23
TMR dairy supplement (91.52% of DM)	5.0	4.58	5.0	4.58	5.0	4.58
Glucomannan mycotoxin adsorbent					0.1	0.1
TMR total	50.4	24.22	50.4	24.22	50.4	24.22

dairy cows according to the NRC (2001). Cows were randomly assigned to tie stalls (180 × 130 cm) with individual feeders. Feed and water were provided ad libitum. Cows were milked twice a day in their stalls and received 2 h of exercise daily. The project was approved by the University of Guelph Animal Care Committee.

Average BW of the experimental animals was 630 kg, and average daily milk production was 33 kg. Average DIM at the commencement of the experiment ranged from 112 to 160 d. Representative feed samples were taken every other day, and pooled samples were analyzed for nutrient content every 2 wk. Analyses were conducted according to the AOAC (1980).

Analysis of Feedborne Mycotoxins

Dietary contents of DON, 3-acetyl-DON, nivalenol, T-2 toxin, iso T-2 toxin, acetyl-T-2toxin, HT-2 toxin, T-2 triol, T-2 tetraol, fusarenon-X, diacetoxyscirpenol, scirpentriol, 15-acetoxyscirpentriol, neosolaniol, zearalenone (**ZEN**), and zearalenol were analyzed by GC-MS as described by Raymond et al. (2003) at the Veterinary Diagnostic Laboratory, North Dakota State University (Fargo, ND). The TMR was completely dried before extraction. The detection limit was 0.5 mg/kg. Corn and wheat were analyzed by the same laboratory, with a detection limit of 0.2 mg/kg. Hay was analyzed for DON and ZEN by ELISA at the AgTest Laboratory (Guelph, Ontario, Canada), with a detection limit of 0.2 mg/kg. Haylage and corn silage were not analyzed, but it is possible that these feedstuffs were contaminated. A mold count analysis was not performed because mold counts do not correlate well with actual mycotoxin contamination.

Parameters Measured

DMI. Amounts of TMR fed and orts remaining were individually recorded daily. Diets and orts were sampled 3 d/wk and weekly pooled samples were oven-dried at 105°C for 48 h and the percentage of DM calculated. Dry matter intake as a percentage of BW was also calculated.

Milk Yield. Milk yield for each cow was recorded every milking by an automatic milking system (Westfalia, Norwell Dairy Systems, Dayton, Ontario, Canada).

Milk Composition. Representative samples of milk were taken once a week at the morning milking using an automatic sampling unit. Milk was analyzed for fat, protein, lactose, lactose and other solids, freezing point, and SCC using a Foss MilkoScan System 4400 (Foss Food Systems, Minneapolis, MN). Analyses were performed by the University of Guelph Laboratory Services Division (Guelph, Ontario, Canada).

BW and BCS. Cows were weighed on an electronic scale on 2 consecutive days every week at the same time of day, and the average of 2 weights was calculated. Metabolic BW was calculated using the formula $BW^{0.75}$ (NRC, 2001). Body condition score was determined once every 2 wk with a 5-point scoring system (Ferguson et al., 1994).

Blood Biochemistry. Blood samples were collected from 0700 to 0900 h on d 0, 14, 28, 42, and 56 from a tail blood vessel. Serum concentrations of calcium, phosphorus, magnesium, sodium, potassium, chloride, total protein, albumin, globulin, albumin:globulin ratio, urea, creatinine, glucose, cholesterol, total bilirubin, conjugated bilirubin, free bilirubin, alkaline phosphatase, γ -glutamyltransferase, aspartate aminotransferase, creatine kinase, glutamic dehydrogenase, BHBA,

Table 2. Feedborne mycotoxin concentrations in feedstuffs and diets (mg/kg)

Mycotoxin	Corn	Wheat	Hay	Control TMR	Contaminated TMR	Contaminated + glucomannan mycotoxin adsorbent TMR
Analyzed mycotoxin level						
Deoxynivalenol	7.5	6.4	—	0.5	3.2	3.6
Calculated mycotoxin level						
15-Acetyl-deoxynivalenol	0.9	0.3	—		0.28	0.28
Zearalenone	0.7	0.5	0.31		0.24	0.24

NEFA, haptoglobin, Na:K ratio, and Ca:P ratio were determined (Hitachi 911 autoanalyzer, Roche Diagnostics, Hoffman-La Roche Ltd., Montreal, Quebec, Canada) by the Animal Health Laboratory of The University of Guelph, and osmolality was subsequently calculated.

Complete Blood Count. Blood samples for complete blood count analyses were collected from 0700 to 0900 h on d 0, 14, 28, 42, and 56 from a tail blood vessel in EDTA-coated blood tubes. Analyses were performed by automated differentiation (Advia 120, Bayer Inc., Toronto, Ontario, Canada) for white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelets, mean packed volume, segmental neutrophil count, lymphocyte count, monocyte count, eosinophil count, and basophil count.

Coagulation Profile. Blood samples for coagulation measurements were collected from 0700 to 0900 h at d 0, 18, 36, and 54 in tubes containing citrate. Plasma was tested for prothrombin time, partial thromboplastin time, and fibrinogen (Amelung K4CA microanalyzer, Intermedico, Markham, Ontario, Canada).

Total Ig Count. Blood samples were taken on d 0, 18, 36, and 54, and serum was analyzed for total concentrations of IgA, IgG, and IgM by radial immunodiffusion (Mancini et al., 1965).

Statistical Analyses

Data were analyzed by analysis of covariance using the mixed model of SAS in a completely randomized design with repeated measures (Kuehl, 2000; SAS Institute, 2000). Pretreatment measurements were used as the covariate. If simple effects (diet $\times$ time interaction) were significant, time points were tested by multiple comparisons (Tukey's test). If main effects (among the diets) were significant, groups were compared by Dunnett's test (Kuehl, 2000). Statements of statistical significance were based on $P < 0.05$.

One of 5 model structures was used depending on the finite-sample corrected Akaike's information criterion

value for data that best fit the model. The structures were compound symmetry, heterogeneous compound symmetry, unstructured, autoregressive, and antedependence (Littell et al., 1998; Wang and Goonewardene, 2004). For each variable, the type of structure was chosen accordingly by using the smallest Akaike's information criterion value.

The statistical model used for the analysis was

$$y_{ijt} = y_o + \mu + d_i + \gamma_{j(i)} + \tau_t + (d\tau)_{it} + e_{ijt}$$

where y_{ijt} is the measurement taken at time t on the j th cow assigned to the i th diet, y_o is a covariate (pretreatment measurement), μ is the overall mean effect, d_i is the i th fixed diet effect, $\gamma_{j(i)}$ is the random effect of the j th cow within the i th diet, τ_t is the fixed t th time effect when the measurement was taken, $(d\tau)_{it}$ is the fixed interaction effect between diet and time, and e_{ijt} is the random error associated with the j th cow assigned to the i th diet at time t .

RESULTS

Analysis of Feedborne Mycotoxins

Deoxynivalenol was found to be the major contaminant. Zearalenone and 15-acetyl DON, which were found in dietary ingredients above detectable limits (0.2 mg/kg), did not exceed the detectable limits in the TMR (0.5 mg/kg). The control TMR contained 0.5 mg/kg of DON (DM), the contaminated TMR contained 3.2 mg/kg of DON, and the contaminated + GMA TMR contained 3.6 mg/kg of DON. Concentrations of feedborne mycotoxins in feedstuffs and diets are given in Table 2.

Performance

There was no effect of diet on DMI (Table 3), DMI as a percentage of BW, BW, metabolic BW, or BCS of cows. Milk production and milk composition were not affected by diet (Table 3).

Table 3. Effect of diet on DMI, milk production, milk composition, and SCC¹

Group	DMI, ² kg	Milk production, kg/cow per d	Milk fat, %	Milk protein, %	Lactose, %	SCC, cells/mL × 1,000
Control	23.8	30.0	4.0	3.5	4.7	60.0
Contaminated	24.8	31.1	3.8	3.4	4.7	57.8
Contaminated + glucomannan mycotoxin adsorbent	22.6	31.7	3.6	3.4	4.7	39.4
SEM	0.69	0.71	0.13	0.06	0.05	20.7
Control vs. contaminated	NS ³	NS	NS	NS	NS	NS
Control vs. contaminated + glucomannan mycotoxin adsorbent	NS	NS	NS	NS	NS	NS

¹Least squares mean.²Overall means.³ $P > 0.05$.

Blood Analysis

Total serum protein and globulin concentrations were increased after 42 d in cows fed the contaminated diet, whereas the albumin:globulin ratio decreased compared with cows fed the control diet (Table 4). Feeding the contaminated diet also elevated serum urea concentrations in the same cows throughout the experiment (Table 5). Serum sodium and serum osmolality were increased throughout the study in both groups fed contaminated diets compared with cows fed the control diet (Table 5).

Hematology parameters and coagulation profiles were not affected by diet (data not shown). Total IgA concentrations decreased significantly after 36 d of feeding the contaminated diet compared with the control group (Table 5), whereas serum concentrations of total IgM and IgG (data not shown) were not affected by diet.

DISCUSSION

Feedborne Mycotoxins Concentrations

Three feedstuffs in the experimental diets were naturally contaminated with mycotoxins, corn, wheat, and hay. The grain mix contained DON as the major contaminant, with 15-acetyl-DON and ZEN as minor con-

taminants. Only ZEN was detected in hay in low concentrations, and only DON exceeded detectable limits (0.5 mg/kg) in the TMR. The contaminated diet and the contaminated diet + GMA had similar DON concentrations (3.2 and 3.6 mg/kg, respectively). The control diet consisted of feedstuffs expected to be relatively free of mycotoxins, but low levels of DON (0.5 mg/kg) were found. The reason for feeding blends of naturally contaminated feeds was that minor components, unidentified mycotoxins, and their metabolites could contribute additive and synergistic effects to mycotoxicoses, even if the concentration of a major toxin was not high. Conjugated mycotoxins, in which the toxin is usually bound to a more polar substance such as glucose, are referred to as “masked” mycotoxins. These mycotoxins can escape routine detection methods but can be released after hydrolysis *in vivo*. Berthiller et al. (2005) recently published the first report on the natural occurrence of a glycoside of DON in *Fusarium*-infected wheat and corn.

Effect of Diet on Performance

There was no effect of diet on cow performance. Dry matter intake, BW, BCS, milk production, and milk composition did not change because of mycotoxin exposure. These results are in agreement with previous

Table 4. Effect of diet on serum protein concentrations (g/L) at d 42¹

Group	Total protein	Globulin	Albumin: globulin ratio
Control	80.0	39.0	1.08
Contaminated	89.2*	49.3*	0.82*
Contaminated + glucomannan mycotoxin adsorbent	85.5	44.7	0.93
SEM	1.51	1.55	0.044
Control vs. contaminated	0.0130*	0.016	0.0074
Control vs. contaminated + glucomannan mycotoxin adsorbent	NS	NS	NS

¹Least squares mean.* $P < 0.05$.

Table 5. Effect of diet on serum urea, sodium, osmolality and IgA levels¹

Group	Serum urea, mmol/L	Serum sodium, mmol/L	Serum osmolality, mmol/L	Serum IgA, g/L
Control	5.3	137.2	272.0	0.35
Contaminated	6.1*	140.9*	279.7*	0.19*
Contaminated + glucomannan mycotoxin adsorbent	5.6	139.0*	276.0*	0.23
SEM	0.16	0.48	0.8	0.029
Control vs. contaminated	0.0121*	0.0005	<0.0001	0.0095
Control vs. contaminated + glucomannan mycotoxin adsorbent	NS	0.0245	0.0018	NS

¹Values are least squares mean.**P* < 0.05.

studies performed in dairy cows fed naturally contaminated feed (Charmley et al., 1993; Ingalls, 1996). The reasons for this might be the low mycotoxin concentrations in TMR, short-term exposure, or high-quality environmental conditions at the research facility. A commercial farm environment, as well as different feed-borne mycotoxin combinations, could result in unpredictable effects on animal performance.

Effect of Diet on Serum Protein Concentrations

Proteins serve as structural components, enzymes, antibodies, coagulation factors, and transporters. Albumin and most of the α - and β -globulins are synthesized in the liver, but immunoglobulins are synthesized in the lymphoid organs. Serum protein abnormalities can reflect many diseases and dysfunctions, depending on which class of globulins is affected (Duncan and Prasse, 1986). In the current study, serum total protein and globulin concentrations increased, whereas the albumin:globulin ratio decreased in cows fed the contaminated diet for 42 d. *Fusarium* mycotoxins might affect the synthesis of globulins of hepatic origin as well as globulins of lymphoid origin. Rotter et al. (1994) suggested that *Fusarium* mycotoxins can directly affect α -globulin synthesis in the liver. Changes in serum protein concentration did not appear to be indicative of acute inflammation in the current study, because there was no elevation of other markers of inflammation, such as fibrinogen or haptoglobin. The increase in serum protein was also not likely due to clinical dehydration, because there were no clinical signs of excessive water loss.

These results are in contrast to those of Tryphonas et al. (1986), who fed purified DON to mice, resulting in a significant reduction in serum concentrations of α_1 - and α_2 -globulins and an increase in concentrations of total serum albumin. In another study, serum concentrations of total protein and globulin were decreased in pigs fed diets containing a high level of *Fusarium* mycotoxin-contaminated grains, whereas the albumin:globulin ratio increased (Swamy et al., 2003).

Effect of Diet on Serum Urea Concentrations

The high concentrations of serum urea in cows fed contaminated TMR may be a result of 1) increased ammonia absorption caused by altered protein turnover in the rumen microflora, or 2) altered protein metabolism in bovine tissues. In ruminants, serum urea levels are affected by protein digestion and metabolism by the rumen biomass. A large portion of dietary protein is hydrolyzed and deaminated by rumen microflora, giving rise to peptides and free ammonia in the rumen (Herd, 2000). A portion of the free ammonia is absorbed and is metabolized to urea in the liver. The remainder is incorporated into microbial protein in the rumen. If microbial protein synthesis in the rumen is inhibited by mycotoxins, more free ammonia remains in the rumen, is absorbed into the blood, and is metabolized to urea, resulting in elevated blood urea concentrations. Danicke et al. (2005) observed that postprandial rumen fluid ammonia concentrations were consistently higher when *Fusarium* mycotoxin-contaminated wheat was fed to cows. Moreover, the flow of microbial protein and utilizable protein at the duodenum were simultaneously reduced. These results suggest that diets naturally contaminated with DON as the major mycotoxin can alter microbial protein turnover in the rumen.

Another source of urea in the blood is the Krebs-Henseleit cycle in the liver. Ammonia appears in the tissues as a result of AA catabolism. Ammonia and other nitrogen-containing substances are converted to urea in the liver during the Krebs-Henseleit cycle. The hypothesis is therefore that inhibition of protein synthesis results in elevated concentrations of free AA that are used for energy utilization, resulting in increased serum urea. The results of this study are in agreement with those of Chowdhury and Smith (2004), who observed that excessive serum concentrations of uric acid in laying hens were a result of feeding feedborne *Fusarium* mycotoxins. Moreover, in a subsequent study with laying hens, they found that feeding contaminated grains led to reduced hepatic fractional protein synthesis rates (Chowdhury and Smith, 2005). Danicke et al.

(2006) also observed a reduction in fractional protein synthesis rates in the kidneys, spleen, and ileum of pigs exposed to DON.

Effect of Diet on Serum Sodium and Serum Osmolality

Serum sodium concentrations and osmolality are mainly affected by the relative water balance (Kaneko, 1989). In the current study, these parameters were elevated throughout the experiment in cows fed the contaminated diet as well as in cows fed the contaminated diet + GMA. These changes normally reflect a level of hydration, but there were no clinical signs of dehydration. No excess Na intake was attributable to diet formulation. The reason for these changes may be a subclinical decrease in water intake (which was not measured). Reduced water intake was previously reported in mice exposed either to DON or T-2 toxin in the drinking water (Burmeister et al., 1980) or to DON-contaminated feed (Khera et al., 1984).

Effect of Diet on Total Serum IgA Concentrations

The reduction in concentrations of serum IgA in cows fed the contaminated diet illustrates the immunosuppressive effect of *Fusarium* mycotoxins. Immunoglobulin A has a short metabolic half-life of 5.5 d. Serum IgA concentrations started to decline shortly after the beginning of feeding the contaminated diet. Immunoglobulin A is the major Ig in external secretions. In serum it functions as a second line of defense, mediating the elimination of pathogens that have breached the mucosal surface (Woof and Kerr, 2004). Depression of serum IgA might be a potential sign of a reduction in secretory IgA concentrations as well. The effect of mycotoxins on secretory IgA levels in cattle needs to be investigated in more detail. The current result is in agreement with Mann et al. (1982), in which declines in total serum IgA were observed in T-2 toxin-treated calves. However, the current result is in contrast with the experiments of Green et al. (1994), in which dramatic elevations in serum IgA levels occurred in mice fed diets containing DON, resulting in immunopathology that closely mimicked the common human glomerulonephritis (IgA nephropathy). Biliary IgA concentrations decreased in laying hens and increased in turkeys fed grains naturally contaminated with *Fusarium* mycotoxins (Chowdhury et al., 2005a,b). No effect was seen on serum IgA. The feeding of grains contaminated with *Fusarium* mycotoxins increased serum IgM and IgA concentrations in swine (Swamy et al., 2002).

CONCLUSIONS

It was concluded that feed naturally contaminated with *Fusarium* mycotoxins can adversely affect some metabolic and immune parameters of dairy cows. Contaminated feedstuffs should be fed to high-producing dairy cows only with caution. The feeding of GMA can prevent many of these adverse effects if the mycotoxins cannot be eliminated from the feed.

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