Effects of Long Term Feeding Of Diets Containing Graded Levels of Fumonisin B1 (Fb1) to Laying Hens

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ABSTRACT

A 20- week experiment with laying hens was carried out to examine the effects of feeding graded levels of FB1 on performance, chemical parameters, antibody titers to Newcastle disease virus in serum and histopathological changes in different organs. The graded levels of FB1 are 100 mg FB1/kg diet (group2); 200 mg FB1/kg diet (group 3) and 400 mg FB1/kg diet (group 4), while group 1 fed diet uncontaminated with FB1. Each group included 16 hens. The increase of laying intensity and egg weight during the course of experiment was lower in hens of groups 2,3 and 4 than hens of group 1. While the body weight during the experimental period was lower in only hens of group 4 (fed on 400 mg FB1/kg diet) compared to those of groups 1, 2 and 3. A significant increase in alanine aminotransferase, aspartate aminotransferase, chloesterol, blood urea nitrogen and creatinine in FB1 treated groups compared to control one. While there was no significant changes in the level of the tumor marker Alphafeto protein (AFP) in FB1 treated groups compared to control one . Hens in groups 2, 3 and 4 have a significant decrease in serum titers to NDV.

Histopathological changes revealed thickening in the wall of blood vessels in different organs, fatty infiltration in heart and gizzard degeneration in proventriculus, nephrotoxic and hepatotoxic changes.

INTRODUCTION

Fumonisin B1 (FB1) is a mycotoxin produced by *fusarium verticillioides* (Formerly, *Fusarium moniliforme)* and is found in diverse crops such as corn, wheat and barley. Many diseases linked to FB1, such as porcine pulmonary edema, rat hepatic cancer and equine leukoencephalomalacia, which indicated a compromised immune system *(1-3).*

FB1 is hepatotoxic to all animal species tested, including mice, rats, equines, rabbits, pigs and non-human primates. With the exception Syrian hamsters, embryotoxicity or teratogenicity is only observed concurrent with or subsequent to maternal toxicity. It has hepatocarcinogenic and nephrocarcinogenic effects in rats and mice. Also, it inhibits cell growth and causes accumulation of free sphingoid bases and alteration of lipid metabolism in animals, plants and some yeasts *(4-6).*

The effects in humans are unclear, but epidemiolgic evidence suggests that consumption of fumonisin- contaminated corn was contributed to human esophageal cancer in Southern Africa and China *(7).* Moreover, there has been one report in India of a disease outbreak characterized by abdominal pain, borboryami and diarrhea., suspected to be associated with foodborne FB1 *(8).*

Although hens and broilers are regarded as very resistant to FB1 *(9-11),* it has been shown to cause feed refusal, poor growth, alter serum chemistry and organ lesions in poultry *(12-14).* Percentage of hen-day egg production was significantly lowered for the first 28 day laying period in ducklings fed 200 mg FB1/Kg diet *(14)* .

Limited information exists with respect to the FB1 effect on the immune system of chicks. FB1 is cytotoxic to chick macrophages *in vitro (15).*

Significant suppression in total IgM and IgG levels in chicks fed diet contained FB1, FB2 and moniliformin *(16).* Also immunosuppressive effect of FB1was evidenced by lowering HI or SN antibody titer in broiler chicks vaccinated against ND and IBD *(17).*

The purpose of this research was to investigate and describe the major effects of long-term feeding diets containing graded levels of FB1 to laying hens.

MATERIALS AND METHODS

Preparation of FB1 mycotoxin

Toxigenic *Fusarium verticillioides* was isolated and identified from commercial poultry ration *(18)* and FB1was produced by the isolated *F. verticillioides (19).* The produced toxin was measured using VICAM flourmetric method. *(20).*

Birds and experimental design

Sixty- Four lohmann brown female, 18 week age, were purchased from a local commercial grower.

Hens were placed in laying cages (four per cage). Hens were fed on commercial laying diet, until the commencement of the experiment when the hens were 22- wk- old, hens were weighted and experimental diet were introduced. Percentage and weight of laid eggs were recorded daily. Water was supplied by nipple drinkers, the experiment continued for 20 weeks. The lighting regimen began with 13 hours of light and was increased 30 minute per week until 16 hours of light was reached. After of acclimation, the hens were randomly assigned to four dietary treatment group. Each treatment group consisted of 16 hens. Group1 (control diet with no added toxins) group 2 (100 mg FB1/Kg diet) group 3 (200 mg FB1/kg diet) and group 4 (400 mg FB1/kg diet).The doses were adopted after Ledoux *et al. (21).*

Blood samples

Blood sample were collected at 26,30,34, 38 and 42 weeks of age for immunological and clinico- chemical parameters. The blood was allowed to clot and sera were separated and inactivated at 56°C for 36 minutes and frozen at -20°C until serologically tested.

ND Vaccines

Hens were vaccinated intramuscularly with a killed NDV vaccine at the beginning of experiment (22 weeks of age) and vaccinated three times during the rearing period with living NDV vaccines.

Haemaggluatination test (HA)

It was carried out according to the standard method of examining poultry biologics *(22).*

Heamagglutination inhibition test (HI)

The test was carried out according to the standard method of examining poultry biologics *(22)*, the test was used for the measurements of HI antibody levels for ND.

Biochemical analysis

Serum Aspartate amino transferase (AST) Alanine amino transferase (ALT), Alpha-fetoprotein (AFP), cholesterol, Blood urea nitrogen and creatinine were determined according to Reitman and Frankel *(23).* Strickland, *et al., (2)* Thomas *(13)* Patton and Crouch *(25)* and Henry *(26)*, respectively.

Histopathological examination

Fresh tissue specimens were taken from lung, heart, liver, kidney, spleen, proventriculus and gizzard, fixed in 10% formalin solution. The specimens were dehydrated in alcohol, cleared in Xylol and embedded in paraffin wax. Sections of 4-6 micron thickness were prepared and stained by H&E *(27).*

Statistical analysis

Data are expressed as the mean ± SE. Differences between means were analyzed by T test. P value of less than 0.05 was considered significant according to Sendecor and Cochran *(23).*

RESULTS AND DISCUSSION

Laying intensity and egg weight increased significantly in the course of the experiment. This increase occurred at a lower level for hens of the group 2 (100 mg FB1/kg diet), group 3 (200 mg FB1/kg diet) and group 4 (400 mg FB1/kg diet) as shown in Table 1. These results partially agreed with results of Danicke *et al.(29)* who noticed that daily egg mass production, total egg production and egg weights significantly reduced in laying hens fed contaminated ration with FB1 (17.630 mg/kg diet) and zearalenone (1.580 mg/kg diet) for 16 weeks, while Prathapkumar *et*

al.(30), stated that egg production or egg variables had no significant change in laying hens fed ration contaminated with FB1 by dose of 8 and 16 mg/kg for one month. Diffencences in the present study with that of Prathapkumar *et al. (30)*, may be related to the dose and the period of exposure to FB1. The adverse effects of FB1 on performance was usually due to depression in feed intake. However this effect was especially pronounced at the beginning of the experiment. Our results disagree with results of LI *et al.(10)* who said that feed intake and body weight gain of chicks fed FB1 by dose of 200 mg FB1/kg diet for 3 or 4 weeks did not differ significantly from those of controls.

The body weight increased during the experimental period was significantly lowered only in hens fed 400 mg FB1/kg diet (group 4) as shown in Table 2. Our results are inconsistent to some extent with Kubena *et al.(12)* who recorded a lack of change in body weight in layers fed with 100 mg FB1/ kg diet and 200 mg FB1/ kg diet for 16 weeks.

Also LI *et al.(10)*, noticed that body weight gain of chicks fed FB1 by dose of 200 mg/kg diet for 3 or 4 weeks did not differ significantly from those of controls, while Prathapkumar *et al.*, *(30)*, recorded that a severe reduction in body weight gain in one-day-old cockerels by feeding diet containing 8.5 mg FB1/kg diet for 15 days.

A significant reduction in serum antibody to NDV was observed in the present study in groups 2, 3 and 4 as seen in Table 3, which is in accordance with the findings in growing chickens *(29)*, in laying lens *(31)* and in broilers *(17,32)*.

Mortality during the 140 days of the experimental period included one hens in the controls, 3 hens in the group 2, one hen in the group 3and two hens in the group 4. There is no obvious clinical signs in treated groups rather than blackish diarrhea. Blackish sticky diarrhea due to FB1 contaminated diet previously recorded *(21,33,34)*. While LI *et.al (10)* noticed that no signs of illness and mortality were observed in one-day-old chicks fed contaminated diets with FB1 by dose of 50 mg or 100mg or 200 mg FB1/kg diet for 3 to 4 weeks .

By the end of 42 weeks old age all hens were euthanized and gross lesions were recorded which were in the form of pale yellow colored livers with peripheral congestion, mild hemorrhage in proventriculus and watery accumulation in the intestine. These results are in agreement with results of Prathapkumar *et al.(30)*.

Fusarium species are common molds produce variety of toxic compounds that has a neurotoxic, immunotoxic and cytotoxic effects. The primary affected organs are liver and kidneys *(35)*.

The present study indicated that FB1 exhibited adverse hepatotoxic effects. The hepatotoxic effects of FB1 were evidenced by the significant increase of circulating alanine aminotransferase and aspartate aminotransferase. Oxidative damage caused by FB1 may be one of the underlining mechanisms of FB1-induced hepatic cell injury *(36)*. Histopathological lesions appeared approximately the same in all groups of the experiment but the difference is the severity of these lesions between the experimental groups. As the histopatholgical changes appear mild, moderate and severe in groups 2, 3 and 4 respectively. Liver of group 2 showed infiltration with inflammatory cells and beginning of thrombus formation in hepatic blood vessels (Fig.1), also there is distortion in hepatocytes and pyknosis (Fig.2).

Hepatocytes in group 3 were arranged in the form of solid clusters, other revealed aciner form (Fig.3). While liver of group 4 showed individualization of hepatocytes, pyknosis in nuclei and disarrangement of hepatocytes (Fig.4). The toxic effects of FB1 are attributed to the disruption of sphingolipid metabolism as a result of ceramide synthase inhibition *(37)*.

Table 1. Performance of laying hens (weeks 22 to 42 weeks of age) fed on contaminated and non contaminated feed with FB1.

Experimental period (week)	Groups	Laying intensity %	Egg weight (gm)	Daily feed intake (gm/hen)
1-4	Group 1	88.5	54.6	100.1
	Group 2	86.0	49.7	100.1
	Group 3	82.8	49.8	89.3
	Group 4	79.5	49.1	85.7
5-8	Group 1	98.1	57.7	115.0
	Group 2	94.3	54.5	114.2
	Group 3	89.9	53.9	113.0
	Group 4	87.2	52.5	113.0
9-12	Group 1	98.0	59.8	120.4
	Group 2	92.0	57.2	119.2
	Group 3	86.5	56.1	118.0
	Group 4	85.5	55.2	119.1
13-16	Group 1	97.1	61.4	118.3
	Group 2	89.7	59.3	118.0
	Group 3	85.1	57.1	116.0
	Group 4	76.5	55.9	116.5
17-20	Group 1	95.0	62.0	120.2
	Group 2	87.5	59.1	121.0
	Group 3	84.2	56.3	118.0
	Group 4	76.0	56.0	118.0

ANOVA test indicated significant differences (< 0.05) as a result of experimental weeks and groups.

Table 2. Effects of Fumonisin B1 on body weight of laying hens

Treatment	Period*					Body weight change
Fumonisin B1	1	2	3	4	5	
Mg/Kg diet	Gm					
Group 1 (Control)**	1425	1505	1620	1750	1803	378
Group 2 (100 mg/kg)	1427	1510	1618	1727	1805	378
Group 3 (200 mg/kg)	1421	1506	1619	1746	1804	273
Group 4 (400 mg/kg0	1411	1423	1503	1601	1650	239

* Period = 28 days ** significant differences (< 0.05).

Table 3. Results of mean HI antibody titer in laying with ND vaccines and treated with FB1.

Group	Experimental weeks			
	28 weeks of age	30 weeks of age	34 weeks of age	38 weeks of age
1	8.51	9.00	8.55	8.00
2	8.00	8.00	7.82	7.00
3	7.54	7.00	6.36	5.71
4	7.51	7.00	5.63	4.71

*Anova test indicated significant differences between the experimental weeks and various groups as a result of experimental weeks.

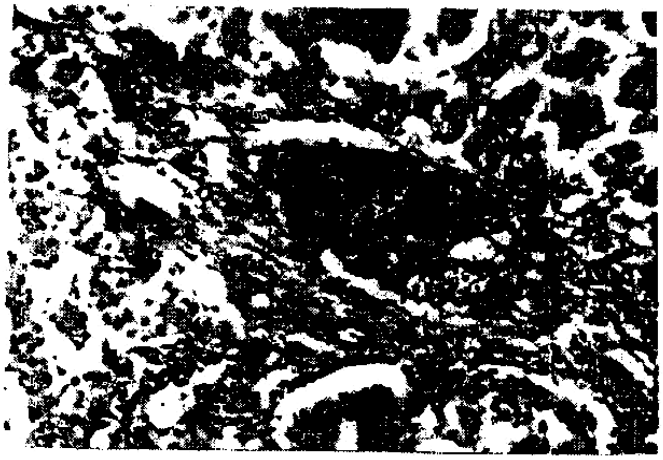

Fig. 1. Section in the liver of group (2) showing infiltration with ionflammatory cells and beginning of Thrombus formation in hepatic blood vesscls (H&E stain x 400)

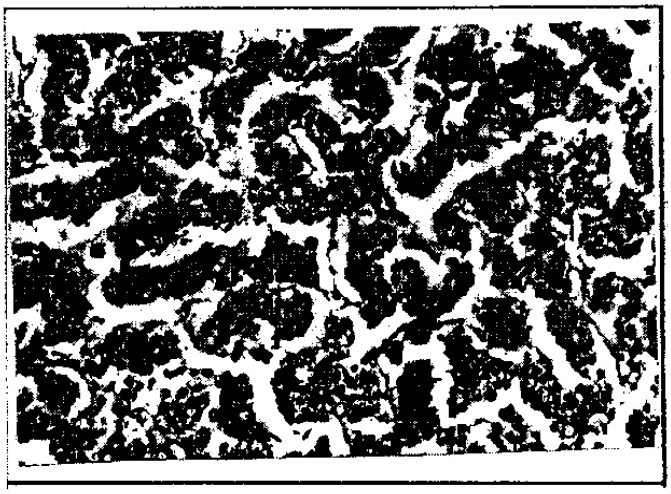

Fig. 2. Section in the liver of group (2) showing distortion in hepatocyte and pyknosis in nuclei (H&E stain x 400)

Fig. 3. Section in the Liver of group (3) showing heptocytes arranged in the form of solid clusters other revealed acinar form (H&E stain x 200)

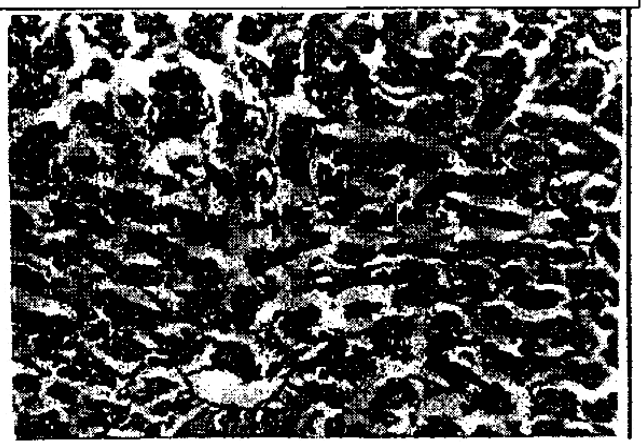

Fig. 4. Section in the liver of group (4) showing unididualization of heptocyte, pyknosis in nuclei and disarrangement of heptocyte (H&E stain x 400)

Fumonisin B1 is carcinogenic in rats and mice and many studies have linked consumption of fumonisin contaminated maize with oesophageal cancer in human populations *(38)*; in the present study there was an abnormal arrangement of hepatocytes in groups or clusters with or without lumen in few cases. However there is no significant changes in the level of the tumor marker Alphafetoprotein (which detect hepatocellular carcinoma) in Fumonisin B1 treated groups compared to control one.

Cholesterol level showed high significant increase in Fumonisin B1 treated groups, this result agree with Gelderblom, *et al (39)* who found that Fumonisin B1 increased the concentration of the phospholipid and th total cholesterol levels. Cholesterol is closel associated with the fatty acids and hence it i important in determining membrane fluidity Altered lipid biosynthesis is a possibl mechanism for liver damage and cance promotion

Nephrotoxic effect of FB1 wa represented by necrosis and sloughing of som renal tubular cells and shrinkage of th glomeruli especially in high dose of FB (Figures 5,6,7). Significant increase was als found in blood urea nitrogen and creatinin levels. Minor histopathological changes in th kidney accompanied by increases in bloo urea nitrogen was reported by severa

investigators *(35,40)* .

Histopathological examination showed thickening in the blood vessel wall with thrombus in renal and hepatic blood vessels, meanwhile Wanda and Coling *(41)* recorded that FB1 caused vascular injury, interstitial pneumonia, (Fig 8) depletion of spleen lymphoid follicles, (Fig.9) edema, necrosis and desquamation of epithelial cells in proventriculus (Fig.10). These similar findings were recorded by Howard *et al. (42).* Group 3, showed necrosis and fattey infiltration in between cardiac muscle fiber (Fig.11) Edema and necrosis observed in different organs were attributed to vascular injury induced by FB1 which cause edema followed by necrosis *(41)*

Nephrotoxic, hepatotoxic, carcinogenic and immunosuppressive were observed in animals and man *(43)*. Sharma *et al. (44)* heptotoxicity was attributed to FB1 caused localized activation of cytokines in liver that modulate FB1 to induced heptic apoptosis. also accumulation of sphingoid bases and leads to increase tumor necrosis factor alpha. FB1 is hepatic carcinogen in mice *(42).*

Wanda and coling *(41)* the histopathologocal changes were seen in different organs of chickens fed FB1. Increased sphinganine, sphinosine ratio, also enhance membrane damage and oxidative stress of macrophage contributing to pathogensis induced toxicity. Similar results were recorded by several authers *(21,37,46-48).*

Therefore exposure of chickens to mycotoxins should be avoided. This is achievable by the use of good agricultural and good manufacturing practices.

Table 4. Effect of Fumonisin B1 on some bio-chemical parameters.

	AFP ng/mlk	AST U/L	ALT U/L	Cholesterol mg/dl	Urea mg/dl	Creatinine mg/dl
Control	< 0.60	18.37± 1.13	27.00 ± 1.93	89.37 ± 5.81	18.62± 1.71	0.68 ± 0.03
Group A (100 mg)	<0.60	45.35±5.60***	67.81 ±7.34***	142.36±5.30***	20.68±1.32 *	1.40± 0.08**
Group B (200 mg)	<0.60	66.65 ± 4.82***	83.37± .37***	182.10 ± 5.23 ***	25.36±2.6*	1.50± 0.05**
Group C (400 mg)	<0.60	69.66 ± 5.63***	88.3 ± 7.10 ***	200.70 ± 2.50***	28.35±3.2*	1.52± 0.02**

Values are the mean ± S.E., n =16 *P<0.05 **P<0.01 ***P<0.001 vs. control group

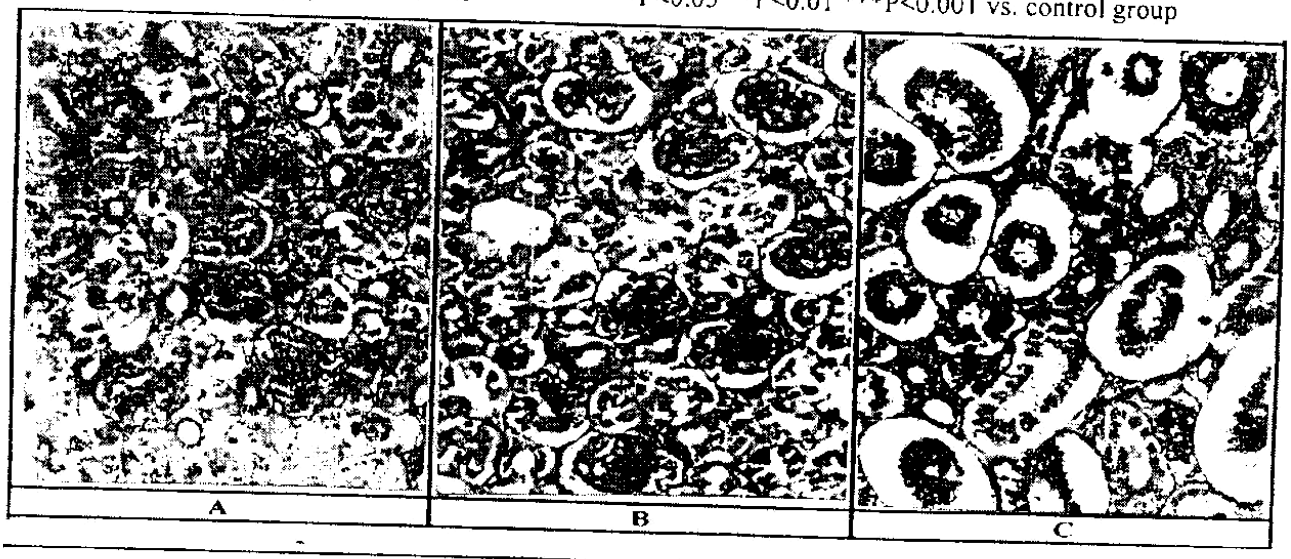

Fig. 5. Section in the kidney of group (2) showing : A): hypercellularity in gromeuli (H&E stain x 200)
B): Periglomerular edema and necrosis in renal tubule (H&E stain x 400) .
C):Desqumamation of Epithelium lining renal tubule (H&E stain x 400)

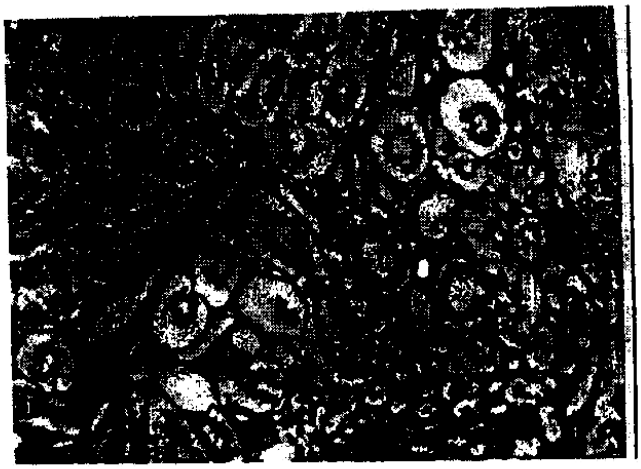

Fig. 6. Section in the kidney of group (3) showing renal tubule denuded epithelium lining into lumina, the epithelium of few tubules appeared completely lysed (H&E stain x 100)

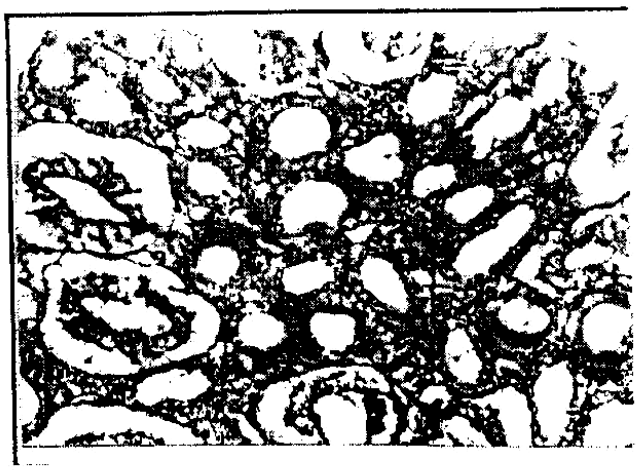

Fig. 7. Section in the kidney of group (4) showing stuffing tubular epithelium degeneration and necrosis of renal tubule (H&E stain x 200)

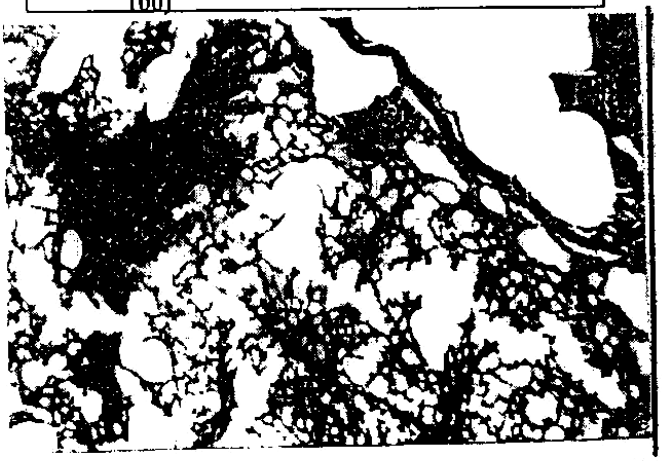

Fig. 8. Section in the lung of group (2) showing thickning in wall of blood vessels and focal area of haemorrhage (H&E stain x 400)

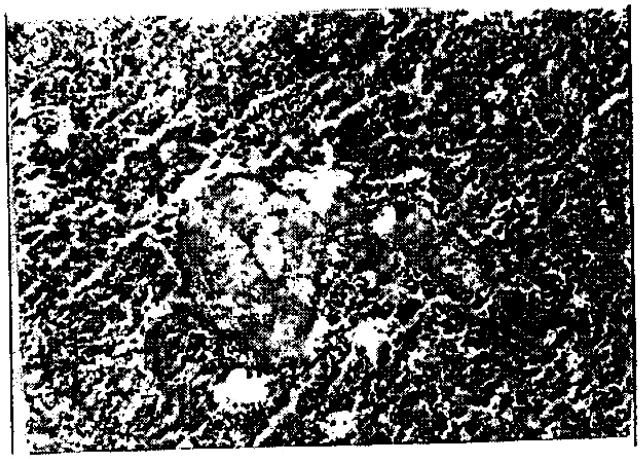

Fig. 9 Section in the spleen of group (2) showing atlectasis, compensatory emphysema and dilatation in bronchiol (H&E stain x 200)

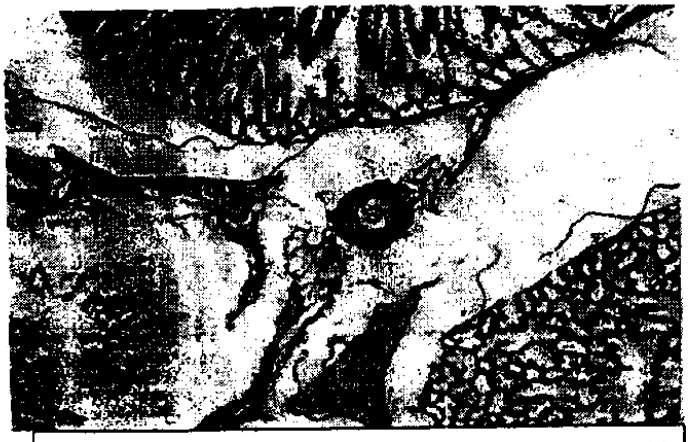

Fig. 10. Section in the proventriculus of group (3) showing desquamation of epithelium lining gland, thickening in wall of blood vessel and edema in inter lobular connective tissue (H&E stain x 100)

Fig. 11. Section in the heart of group (3) showing necrosis and fatty infiltration between cardiac muscle fiber (H&E stain x 200)

CONCLUSION

From our results we can conclude that Fumonisin B1 alter the performance and immune response in broiler chickens as it lower the intensity, egg weight, body weight and serum titer to NDV but increase in serum ALT, AST, cholesterol, blood urea, and creatinine. Moreover, there is no significant changes in the level of AFP. It produced a histopathological changes in different organs of broiler chickens. This imply that chickens exposed to FB1 may be susceptible to infecious diseases.

RECOMMENDATIONS

1-Limitation of human dietary exposure should be established with special consideration to populations consuming a high level of calories as maize meal.

2-Measures should be taken to limit fumonisin exposure and maize contamination by

a)Developing maize - resistant to Fusarium kernel rot.

b) Practisizing better crop management.

c) Segregating mouldy kernels.

3-Improving communication between veterinarians and public health officials on outbreaks of mycotoxicosis in domestic animals for inducing early awareness of potential food contamination.

4-Undoubtedly, *in vivo* investigations in rodents will continue to provide insignt into the effects and modes of action of these important mycotoxins.

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الملخص العربي

تأثير التغذية لفترات طويلة على علائق تحتوى على مستويات متدرجة من الفيومنسين (FB1) على الدجاج البياض

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تم أجراء هذه التجربة لمدة ٢٠ أسبوع لدراسة تأثير التغذية بمستويات متدرجة من الفيومنسين ب١ على الأداء ، القياسات الكيميائية ، مستوى الأجسام المناعية لفيروس النيوكاسيل فى السيرم والتأثيرات الباثولوجية في الأعضاء المختلفة للدجاج البياض، وكانت الجرعات المتدرجة من الفيومنسين ب١ على النحو التالي:

-١٠٠ مجم FB1 / كجم علف (المجموعة ٢)

-٢٠٠ مجم FB1 / كجم علف (المجموعة ٣)

-٤٠٠ مجم FB1 / كجم علف (المجموعة ٤)

بينما المجموعة (١) تمت تذيتها على علف غير ملوث بالفيومنسين ب١ وتركت كمجموعة ضابطة واحتوت كل مجموعة على ١٦ دجاجة.

وقد لوحظ أن الزيادة فى قوة إنتاج البيض ووزن البيض خلال فترة التجربة كانت أقل فى دجاج المجموعات ٢،٣،٤ عنها فى المجموعة الأولى. كذلك كانت الزيادة فى وزن الجسم خلال فترة التجربة أقل فى المجموعة الرابعة بالمقارنة بالمجموعات ١،٢،٣.

كما لوحظت زيادة معنوية فى الألانين أمينو ترانسفيريز ، أسبارتات أمينوترانسفيريز ، كوليستيرول ، نيتروجين يوريا الدم ، والكرياتينين فى المجموعات المجرعة بالفيومنسين ب١ مقارنة بالمجموعة الضابطة. بينما لم توجد زيادة معنوية فى مستوى دلالة الأورام الألفافيتوبروتين (AFP) فى المجموعات المجرعة بالفيومنسين ب١ مقارنة بالمجموعة الضابطة. كذلك لوحظ نقص معنوي في مستوى فيروس النيوكاسيل فى سيرم الدم فى المجموعات ٢،٣،٤.

كما أثبتت التغيرات الباثولوجية زيادة فى سمك الأوعية الدموية فى مختلف الأعضاء ، تجمع دهنى فى خلايا عضلة القلب والقانصة وتغيرات بجدار المعدة وتأثيرات سامة على الكلى والكبد.