Tropical and Subtropical Agroecosystems

REVIEW [REVISIÓN]

AFLATOXINS IN RABBIT PRODUCTION: HAZARDS AND CONTROL

[AFLATOXINAS EN LA PRODUCCIÓN DE CONEJOS: RIESGOS Y CONTROL]

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SUMMARY

Aflatoxins (AFs) are metabolites produced by some fungi such as *Aspergillus* spp., *penicillium* spp. and *Rhizopus* spp. They are considered to be among the most dangerous mycotoxins. Aflatoxicosis caused by aflatoxin (AF) B_1 and related toxins represent one of the most serious diseases of rabbits and other animal species. Rabbits are considered of the most sensitive animals to aflatoxicosis. Ingestion of AFs by rabbits showed many effects including reduction of feed intake, poor efficiency of feed conversion and feed efficiency, poor growth, malabsorption of various nutrients, decreased tissues integrity, increased susceptibility to infection, vaccine and drug failure and increased sensitivity to temperature extremes. Great pathological changes in most body organs are induced by AFs ingestion. Such changes are liver and kidney dysfunctions and genetic damage (carcinogenicity, teratogenicity and mutagenicity). Consequently, productive (feed utilization and growth traits) and reproductive (ovaries and testes functions, semen quality and fertility measurements) performances are extremely affected. Aflatoxicosis can be avoided through prevention of contamination. This can be attained by correct harvesting, drying and storage of field crops. Feedstuffs decontamination can be achieved by removal or inactivation of AFs using non-nutritive absorptive materials and physical, chemical and nutritional treatments, as well as, biodegradation.

Keywords: Aflatoxins, rabbit production, reproduction, hazards, control.

RESUMEN

Las aflatoxinas (AFs) son metabolitos producidos por algunos hongos como son; *Aspergillus* spp., *penicillium* spp. y Rhizopus spp. Son consideradas de las micotoxinas más peligrosas. La aflatoxicosis causada por AF B_1 y sus toxinas relacionadas representa una de las enfermedades más serias en los conejos y otras especies. Los conejos son considerados como una de las especies más sensible a la aflatoxicosis. La ingestión de AF por conejos tiene muchos efectos incluyendo reducción en el consumo, pobre eficiencia de conversión alimenticia, reducido crecimiento, mala absorción de nutrientes, daño en la integridad de tejidos, incremento en la susceptibilidad a infección, mayor sensibilidad a temperatura extrema. Grandes cambios patológicos son inducidos en muchos órganos por efecto de la ingestión de AF. Tales cambios incluyen disfunción de hígado y riñon, así como daño genético (carcinogénico, teratogénico y mutagénico). Consecuentemente, los comportamientos productivo y reproductivo son afectados en extremo. La aflatoxicosis puede ser evitada mediante la prevención de la contaminación. Esto puede ser logrado mediante la correcta cosecha, secado y almacenamiento de los granos. La descontaminación puede ser lograda por remoción o inactivación de AF's empleando materiales con capacidad de absorción, así como el empleo de tratamiento físicos, químicos y nutricionales, así como mediante la biodegradación de los mismos.

Palabras clave: Aflatoxinas, producción conejos, reproducción, riesgos, control.

INTRODUCTION

One of the most important problems in the field of human and animal nutrition is contamination of human foods and animal feeds with moulds and mycotoxins. It is estimated that more than 25% of the world cereals are contaminated with known mycotoxins, which are mainly produced by the fungal genera of *Aspergillus*, *Fusarium* and *Penicillum* during its growing on corps in the field, at harvest or during storage, as well as, during feeds processing (El-Darawany and Marai, 1994; Devegowda *et al.,* 1998).

Aflatoxins (AFs) are mycotoxins produced primarily by *Aspergillus flavus* and *Aspergillus parasiticus* fungi (Diekman and Green, 1992). Four AFs were isolated initially and identified as B_1, B_2, G_1 and G_2 based on their blue or green fluorescence properties and migration patterns during chromatography. The potency and carcinogenicity of these AFs are dependent on species, dose, duration of intake, age of animal and nutritional state, but it is generally agreed that B_1 is the most potent one (Pier, 1981). The problems with AFs do not end in feed refusal or reduction of animal performance, but it also can be transferred into meat or milk (Devegowda *et al.,* 1998). However, consumption of feedstuffs contaminated with AFs does not seem to impair the performance directly, but rather indirectly through other physiological systems (Diekman and Green, 1992), leading to serous economic problems relating to reproductive efficiency, which is the most important economic factor in animal production industry (Brekke *et al.,* 1977; James *et al.,* 1992; El-Darawany and Marai, 1994). Ingestion of AFs contaminated diet leads to toxicity which takes forms of carcinogenicity, hepatitis, nephritis, bile duct proliferation, fibrosis and cirrhosis of the liver and genacologic forms (Abd El-Hamid and Dorra, 1993). Acute aflatoxicosis (high dose) results in hemorrhage, fatty accumulation in liver and then death (Edds, 1973).

Rabbits are extremely sensitive to AFs (Clark *et al.,* 1982). The acute oral single dose LD_{50} for young rabbits is about 0.3 mg/kg of body weight, i.e. it is among the lowest of all species studied (Armbrecht *et al.,* 1970). Many of the clinical signs and clincopathologic changes of aflatoxicosis in rabbits are similar to those reported in swine, goats and cattle. Accordingly, rabbits may be a potential model for studying aflatoxicosis in these species (Carnaghan *et al.,* 1967).

However, relatively little is known about aflatoxicosis and AFs mechanisms in rabbits. This review will throw some lights on the effect of AFs on production and reproduction of rabbits. Other animals will be included, whenever needed. Description of AFs and aflatoxicosis, as well as, avoiding contamination and methods of avoiding contamination and decontamination, will be included.

AFLATOXINS AND AFLATOXICOSIS

Aflatoxins

Aflatoxin types

AFs are mainly produced by the strains of *Aspergillus flavus* Linkex and Fries and *A. parasiticus* Spear. AFs are also produced by other moulds, namely *A, niger*, *A. ochraceus*, *A. oryzae*, *A. ostianus* Whemer, *A. rubber* and *A. werttii* and *Penicillium citrinum*, *P. frequentams*, *P. puberulum* Bainer and *P. vaiable*, and *Rhizopus* spp. (Scott *et al.,* 1967). Importance of the AFs has tended to overshadow the steady increase in knowledge of mycotoxins produced by *Aspergillus* and other genera.

The derivatives and metabolites of AFs, which have been studied intensively, include B_1, B_2, G_1, G_2, M_1, M_2, $B_2\alpha$, $G_2\alpha$, R_o (Aflatoxicol), B_3 (Parasiticol), GM_1, P_1, Sterigmatocystins and the glucuronide of aflatoxicol (Mirocha *et al.,* 1971; Goldblatt and Stoloff, 1982). AFs M_1 and M_2 are animal metabolites of B_1 and B_2 and 4-hydroxy derivatives of B_1 and B_2, respectively. The major AFs are B_1, B_2, G_1 and G_2. The B_1 and B_2 show strong blue fluorescence, while G_1 and G_2 show green yellow fluorescence under UV light (Nesbitt *et al.,* 1962). AFs $B_2\alpha$ and $G_2\alpha$, which are 2-hydroxy derivatives of B_2 and G_2, respectively, have been isolated and characterized (Dutton and Heatheote, 1968), and they are relatively less toxic (Legator and Withrow, 1964; Lillehoj and Cieglar, 1969).

Concentrations of the different AFs vary greatly according to the fungus strain, substrate and conditions of growth. Generally, AF B_1 is found in greatest concentration, G_1 at intermediate concentration, while B_2 and G_2 have the least concentration. B_1 has the highest potency of the group as a toxin and as a carcinogen, and in most practical purposes, the term AF means AF B_1. Commonly, concentrations of B_1 or total AF are reported in analytical determinations (Diener and Davis, 1969).

Aflatoxins physical and chemical properties

Molecular formula, molecular weights and other physical properties of AFs are summarized in Table 1. The maximum absorption and the shape of spectrum of AFs have been reported to depend on conditions of the measurement (Chelkowski, 1974). The relative fluorescence intensities of AFs are different when measured in different solvents in the solid state. The alkaline pH of the solvent also causes changes in the UV spectra and fluorescence intensity (Itoh *et al.,* 1980).

AFs have closely similar structures and forms of highly oxygenated, naturally occurring heterocyclic compounds. AFs belong to mycotoxins (a group of compounds). These compounds contain a coumarin nucleus and a bifuran with either a cyclopentenone (AFs B_1 and B_2) or six-member lactone (AFs G_1 and G_2) attached to the coumarin moiety.

The word AFs initially refers to the four major compounds, AF B_1 (AFB_1), B_2 (AFB_2), G_1 (AFG_1) and G_2 (AFG_2). The letters refer to their fluorescent colour (blue and green), while the numbers refer to their position relative to the solvent front on a thin layer chromatography plate (Palmgren and Hayes, 1987).

Twelve structurally related compounds have been identified and grouped as AFs (Dvorkova, 1990) including AFs M_1 and M_2, which are 9α -hydroxy AFB_1 and AFB_2, respectively (Holzapfel *et al.,* 1966). These are milk toxins and have a blue fluorescence on the thin layer chromatography plates (Iongh *et al.,* 1964). These toxins were first isolated from milk of cows ingested AF-contaminated feed. However, AF M_1 and AFM_2 can also be found in urine, liver and kidneys, as well as, in contaminated grains and cultures of the mould. They are acutely toxic as B_1 and B_2. AF $B_2\alpha$ and $G_2\alpha$ are hydroxylated B_2 and G_2, as they are formed by the hydration of B_1 and G_1, and were isolated from cultures of *A. flavus* (Dutton and Heathcote, 1968; Heathcote and Dutton, 1969). Aflatoxicol is called AF R_0, and was isolated firstly as a reduced product of AF B_1 by various microorganisms (Detroy and Hesselline, 1970). Parasiticol, also known as AF B_3, was found to be as natural metabolite of *A. flavus* (Heathcote and Dutton, 1969), as well as, by *A. parasiticus*. AF GM_1 was first detected in cultures of *A. flavus* by Dutton and Heathcote (1968) who established its structure. Dalezios *et al.* (1971) found that AF P_1 was the major metabolite of AF B_1 in monkey urine.

AF Q_1 was found to be the major product *in vitro* conversion of AF B_1 by monkey liver tissue and accounted for up to 55% of the AF B_1 converted. Also, Aflatoxicol H_1 was noticed to be another major conversion product *in vitro* of AF B_1 in human and monkey liver tissues (Masri *et al.,* 1973).

Cucullu *et al.* (1976) reported that AF D_1 was a major product obtained when AF B_1 was detoxified with ammonia. AF B_1 is the most acutely toxic compared to the other AFs. It is a stable compound and can only be destroyed by strong alkali. However, in dilute solution, it is very sensitive to light and very insoluble in water. Accordingly, great care must be taken if experiments are set up, in which AF is administrated to animals in their drinking water. The insolubility of AF presents some problems in studies involving the use of single doses around the LD_{50} or adding the toxin to cells in culture. Dimethyl formamide is a useful solvent for many purposes. The intense and characteristic fluorescence of the AF has provided the basis for methods of estimation (Fishbein and Falk, 1970).

LD_{50} values

The acute medium lethal dose (LD_{50}) of AF B_1 [mg/kg body weight (BW)] in different animal species is presented in Table 2. Smith (1982) reported that the LD_{50} (mg/kg BW) values for AF B_1 were 0.30 in rabbits, 0.36 in ducklings, 0.55 in cats, 0.62 in pigs, 1.40 in guinea pigs, 1.86 in turkeys, 2.00 in sheep, 5.50 in rats and 6.50 in chicken. The relative toxicity of AFs B_1, G_1, B_2 and G_2 were 100, 50, 25 and 12.5%, respectively (Buntenkotter, 1973). Rats LD_{50} is smaller than in mice, i.e. rats are more susceptible to the carcinogenic effects of AF B_1 than mice (Wogan *et al.*, 1974). However, although mice are relatively more resistant to the acute toxic effects of AF B_1 than are rats, the neonatal mouse has a very low LD_{50} value and also is susceptible to AF B_1 induced cancers (Vesselinovitch *et al.*, 1972). Male rats have lower LD_{50} values and are more susceptible than females for inducing hepatic tumors by AF B (Wogan and Newberne, 1967). Further, within species, the LD_{50} value may vary according to strains, sex, administration methods and animal age. Additionally, the nutritional status of the animal or the concurrent composition of the diet may affect the acute toxicity. Regarding the strain, Wogan *et al.* (1974) found that the Fischer (F-344) rats strain is more susceptible to the acute toxicity of AF B_1 and also to its carcinogenicity than the Sprague-Dawley strain.

Generally, AFs causes clinical illness and death when consumed in high quantity, but they suppress immunity of young animals at lesser levels (Clark *et al.*, 1980, Huff *et al.*, 1986; Harvey *et al.*, 1989; Abd El-Hamid *et al.*, 1992; Shehata, 2002).

Clinical signs of aflatoxicosis were characterized by 49.3 % mortality (Hamilton, 1971) in laying hens. Also, ingestion of a mixture of AFs B_1+G_1 caused an increase in the number of stillbirths and total litter mortality in female rats (EI-Darawany, 1985). Coppock *et al.* (1989) found that aflatoxicosis was diagnosed in 600 pigs (2500-3500 μg AF/kg of feed) of which 400 died and 200 were markedly affected.

Residues of aflatoxins

Toxic residues of AFs in animal products were harmful to public health. In one-day Hubbard chicken, residues of AFs were 100, 250, 500 and 750 ppb in liver, heart, breast muscle and kidney, respectively, as detected after 2 weeks of feeding the contaminated diet. AF residue was decreased with increasing age of birds. In breast muscle, AF residue was related to concentration of AF in the diet (Teleb and Fakhry, 1988). Similarly, residues of AF B_1 were obtained only in liver, kidneys and longissimus dorsi muscle of white male pigs fed diets containing 500, 650 or 800 ppb AFs B_1+G_1. Values were directly related to the level of contamination (Bonomi *et al.,* 1994)

Recoveries of AF B_1, AF M_1 and aflatoxicol from artificially contaminated meat tissues were 74-95 % for AF B_1, 60-80 % for AF M_1 and 80-95% for aflatoxicol (Sabino *et al.,* 1996). The minimum effective dose (MED) of AF determined according to epidemiological studies coupled with laboratory experiments and mathematical corrections, was found to be less than 10 ppb. It may be assumed that no level of AF is free of risk (Hamilton, 1986).

Table 1. Physical and chemical properties of aflatoxins*.

Items	Molecular Formula	Molecular Weight	Melting point (°C)	Ultraviolet absorption	Fluorescence emission
B_1	$C_{17} H_{12} O_6$	312	268-269	21.8	425
B_2	$C_{17} H_{14} O_6$	314	286-289	23.4	425
G_1	$C_{17} H_{12} O_7$	328	244-246	16.1	450
G_2	$C_{17} H_{14} O_7$	330	237-240	21.0	450
M_1	$C_{17} H_{12} O_7$	328	299	19.000 (357 nm)	425
M_2	$C_{17} H_{14} O_7$	330	293	20.4	-
$B_2\alpha$	$C_{17}H_{14} O_7$	330	240	18.0	-
$G_2\alpha$	$C_{17} H_{14} O_8$	346	190	14.1	425
R_0	$C_{17} H_{16} O_6$	314	230-234	9.7 (358 nm)	-
B_3	$C_{16} H_{14} O_6$	302	233-234	12.000	-
P_1	$C_{16} H_{10} O_6$	298	>320	14.9	-

* Adapted from Patterson (1977).

Table 2. LD_{50} of AF B_1* in different animal species.

Species	Age or weight	Sex	LD_{50} (mg/kg BW)
Rabbit (Dutch Belted)	3 months	M/F	0.30
Duck (White Pekin Khaki Campbell)	1 day	M/F	0.33-0.36
Pig (Poland – China)	Weanling	M	0.62
Trout (Rainbow)	9 months	M/F	0.81
Guinea pig	250 g	M	1.40
Sheep (Cross breed)	2 years	M	2.00
Monkey (Cynomolgus)	2 years	M	2.20
Monkey (Macaque)	38-44 months	F	7.80
Rat (Fisher)	0-4 days	M/F	1.10-1.36
	12 days	M/F	12.00-15.00
	21 days	M/F	8.00
	42 days	M/F	4.00-5.00
	70 days	M/F	0.75-1.30
	30 days	M	>150.00
	58 days	M	40.00
	100 days	M	12.00
Chicken	-	-	6.30

*Adapted from Ciegler (1975) and Busby and Wogan (1979).
BW= Body weight, M= Male, F= Female.

Factors influencing aflatoxin production

The growth of *A. flavus* group of fungi on agricultural commodities and its production of AFs is influenced by physical, chemical and biological factors. These factors are fungi strain, substrate nature, moisture and relative humidity, temperature and time of incubation, aeration, damage, growth and maturity of the host and irradiation (Hesseltine, 1983; Frisvad, 1995).

Fungi strain. Various strains isolated of fungi can produce AFs such as *A. flavus, A. parasiticus, A. oryzae, A. tamari,* A. flavus *Var. columnaris* and *A. parasiticus Var. globosus* (Raper and Fennell, 1965). Other species also produce one or more of AFs e.g. *A. niger, A. wentii, A. ruber,Penicillium puberulum*, *P. variable* and *P. frequentans* (Kulik and Holaday, 1967). These fungi produce more than 1500 secondary metabolites (Halama, 1982). Moreover, some isolates of actinomycetes were found to be AF producers (Dewedar *et al.,* 1985). The AFs produced by approximately 30 % of the strains of *A. flavus* and by *P. puberulum* are frequent contaminates of harvested feed and food (rice, corn, sorghum and other grains, peanuts, pecans, cassava, bread, milk products and some fermented products) stored under conditions of humidity and temperature (Edds, 1973).

A. flavus is a constituent of microflora of soil and air. It is classified as saprophyte and primarily occurs in damages and relatively inactive tissue (Hyde, 1974). Under favourable conditions of fungi growth in the storage, fungi get established and cause deterioration in stored foods and feedstuffs. It has been established that *A. flavus* can take place during growth of the plant and infect crops. Some strains of *A. flavus* do not produce AFs and are called as non-toxigenic strains (Lillehoj *et al.,* 1975).

Substrate nature. Generally, *A. flavus* produces AFs on numerous foods such as eggs, cheese, condensed and powder milk, vegetables and fruits. However, all materials do not support AFs production equally (Stubblefield and Shannor, 1974) and the varieties of the same feedstuff may differ in its susceptibility to *A. flavus* infection and AFs production (Rao and Tulpule, 1967).

Cereal grains, such as wheat and rice, in general, appear to be a good substrate for toxin production than the oilseeds such as cottonseed, soybean and peanuts (Diener and Davis, 1968). This may be due to the high proportion of carbohydrates in cereals, which may be metabolized by the fungus more easily than the fats. A comparative study with the three potent AFs producing isolates of *A. flavus* showed that corn, wheat and rice with or without added methionine supported production of higher yield of AFs than sorghum, peanuts and soybeans in standing and shake cultures (Hesseltine *et al.,* 1966).

Zinc plays an important role in the biosynthesis of AFs. Therefore, soybean as a poor substrate in this element can become an adequate medium if supplemented with Zinc (Gupta and Venkitasubramanian, 1975).

Moisture and relative humidity. The fungi, which produce AFs, can be grouped into three classes according to their moisture requirements. The first class contains the field fungi, which need 22-25% moisture. The second includes storage fungi, which need 13-18% moisture and the third, which is the advanced decay fungi, require over 18% moisture (Christensen, 1965).

Muold fungi like *Aspergillus* species or *Penicillium* species have lower water requirements in comparison with bacteria or yeast. They are capable of thriving even at water activity (a_w) values 0.8-0.9. Several *Xerophilic* species can also thrive even at values between 0.65 and 0.7 and the water content of the substrate is between 13 and 14%, which are conditions frequently prevail in stored cereals (Krogh, 1987).

Suitable relative humidity for growth is approximately 10 % lower for *A. glucus* than for *A. flavus* (Diekman and Green, 1992). Species of *Aspergillus* are capable to grow rapidly on grains, peanuts and other commodities at high moisture content (Christensen and Kaufman, 1969). *A. flavus* is generally classified as mesophyte due to that its minimum moisture requirement for the growth is between 80 and 90% RH (Panassenko, 1944). For growth the minimum RH is 80%, but it is higher for sporulation i.e. 85% (Panassenko, 1941).

The critical moisture content of foods or feedstuffs is, generally, established at substrate moisture in equilibrium with 56 or 70% RH, at which very few fungi grow. However, the critical moisture content differs according to the commodity. It is about 14.5% for sorghum (Christensen, 1970), 12.5 to 13.5% for wheat and maize (Christensen, 1973) and 8% for groundnut (McDonald, 1968). However, although AF contamination may not occur at this moisture content, but storage of the commodities at such borderline moisture may be risky (Austwick and Ayrest, 1963; McDonald and Harkness, 1964). The safe length of storage of grains depends upon the initial moisture content.

Temperature and incubation time. Growth temperatures for *A. flavus* classified as a mesophilic fungus are: minimum 6-8, optimum 36-38 and maximum 44-46 °C. The minimum and maximum temperatures for growth are affected by moisture, oxygen concentration, availability of nutrients and other factors (Semenuik, 1954; Tuite and Christensen, 1957). However, Mehan and Chohan (1974) indicated that AF was not produced below 20^0C and above 35^0C and Rabie and Smalley (1965) reported that the optimum temperature was 24 °C for producing AF B_1 and 30 °C for AF G_1. Schindler *et al.* (1967) mentioned that optimum temperatures for producing AF B_1 and G_1 are 24°C and 23°C, respectively.

Incubation time had a great effect on the proportion of AF B_1 and AF G_1 (Schindlcr and Eisenberg, 1968). The maximum toxin yield was attained after 5 to 12 days of muold development, followed by a decline in the AF level (Davis *et al.,* 1966). Schroeder (1966) reported that accumulation of AF in corn reached a peak following 4 days of incubation followed by a decrease to approximately 50 % of the maximum yield by the eighth day.

Aeration. Fungi are highly aerobic organisms, however, their oxygen (O_2) requirements for vegetative growth, sporulation and spore germination are highly variable (Littlefield *et al.,* 1966). Similarly, fungi are variable in their tolerance for high concentrations of carbon dioxide (Diener and Davis, 1969). Most of muolds cannot grow without at least 1 to 2 % oxygen (Halama, 1982).

Generally, reduced O_2 concentration decreases AF production, although the most sizeable decrease occurs when O_2 is reduced to 1% with the increase in CO_2 from 0 to 80 % (Halama, 1982). Similarly, AF production by *A. flavus* is reduced progressively with O_2 concentration reduction from 5 to 1% and CO_2 concentration increase from 0.03 to 100% (Hesseltine *et al.,* 1966, Landers *et al.,* 1967). AF B_1 production can be increased by 3 to 100 fold with shake culture versus stationary cultures of maize, groundnut, rice, sorghum, soybeans and wheat (Hesseltine *et al.,* 1966; Landers *et al.,* 1967).

Damage. *A. flavus* invasion and AF formation in kernels have been widely associated with pod mechanically damage in the groundnut in South Africa (Sellschop *et al.,* 1965). Mechanical damage to grains or groundnuts during harvest, handling or storage or cracking during heat drying or during decorticating of groundnuts can increase their vulnerability to fungi and consequently, increase in toxin development in kernels (Bampton, 1963; Schroeder and Ashworth, 1965). Intact shell serves as a barrier to fungus invasion, damage to kernel also increases nutrient availability to the fungus.

Insects play an important role in damage of the grains or kernels. They also act as vectors for fungal transmission. *A. flavus* was isolated from 10 species of insects commonly infected food grains (Srinath *et al.,* 1973).

Growth and maturity of the host. AFs accumulates in most crops after harvest (Schroeder, 1969), although AF contamination of maize may take place during pre-harvest stage (Lillehoj *et al.,* 1975). It is thought that the fungal spores settle on the maize silk, germinate and grow down in a non-injurious fashion. *A. flavus* has been shown to be present on mature pods of groundnut, but the major contamination occurs after the groundnuts are dug and before they are dried (Griffin and Garren, 1974). Both pods and kernels of one year old peanuts were more rapidly invaded by *A. flavus* than freshly immature and mature pods and kernels (McDonald and Harkness, 1964). In other words, higher percentage of *A. flavus* invasion occurred in over mature kernels and pods.

In cotton, low temperature during boll opening may limit AF development (Gardner *et al.,* 1974). The manner in which balls open may also influence the infection (Ashworth *et al.* 1969).

Irradiation. Using irradiation mean for increasing storage life of agricultural commodities increases its susceptibility to fungal attack and toxin production. Significantly higher values of AF production were obtained in irradiated than in non-irradiated wheat, maize, sorghum and pearl millet at 75 Krads and in root vegetables (potato and onion) irradiated at 10 Krads (Priyadarshini and Tulpule, 1976). Similar observations on AF B_1 and AF M_1 production by *A. flavus* were reported by Schindler *et al.* (1980). However, Ogbadu (1979) claimed that AF and AF B_1 production decreased in rice and red pepper, respectively, as the irradiation dose increased..

Interactions between the factors may be important in the biosynthetic pathways. For example, temperature effects, oxygen tension and small changes in oxygen tension are known to have potent biological effects (Halama, 1982).

Aflatoxicosis causes a variety of manifestations due to the ability of AFs to impair protein synthesis, react with macromolecules and cellular organelles and interfere with normal production of cellular regulators. Acute aflatoxicosis causes hepatic necrosis, derangement of hepatic functions, coagulopathy and extensive hemorrhagic lesions, resulting in death of the animal. Sub acute or chronic aflatoxicosis causes fatty changes in liver, enlargement of the gall bladder, periprotal fibrosis with proliferative changes in bile duct epithelium, icterus and also reduced rate of growth production. In addition to the liver, the thymus gland is also a primary target organ of AFs.

Consumption of AFs causes a marked suppression of cell mediated immune responses, as well as, macrophages, T cell population of the peripheral blood and antibody titers. Immunosuppressive effects are thought to arise from effects on antigen presentation and lymphokine production (Pier, 1986). Pier (1992) added other signs of clinical aflatoxicosis of the acute hepatic injury such as increasing the capillary fragility and hemorrhage and prolonged clotting times, as well as, blood pigments may appear in the urine and mucous membranes congestion and hemorrhage and death of the animal may occur within hours or a few days. Another information showed further clinical signs of aflatoxicosis. Butler and Barnes (1966) and Wogan and Newberne (1967) mentioned that in addition to hepatomas, AF implicates in the induction of neoplasm in the glandular stomach, kidney, lung, salivary gland, lachrymal gland, colon, and skin. Todd *et al.* (1968) clarified that clinical signs of aflatoxicosis (hemorrhage, ascites and edema) are similar to those of vitamin K deficiency. The clinical signs prior to death are central nervous system depression, muscle weakness, and edema of ventral abdominal wall and paleness of the eyes, ears and skin. At necropsy the most characteristic changes are enlargement, nodularity and light subcutaneous edema and dark colored material resembling blood in stomach and intestines.

Generally, AFs have many effects including malabsorption of various nutrients, decreased tissues integrity, poor growth, poor efficiency of feed conversion, enhanced susceptibility to infection, vaccine failure, drug failure, reproductive problems in males and females and increased sensitivity to temperature extremes, in farm animals (Hamilton, 1986).

Aflatoxicosis

Major economic losses in animals are associated with the sub acute or chronic forms of aflatoxicosis. However, there is a little doubt that AF itself is the toxic molecule and it is not like many compounds that change by enzymes in animal to produce the toxic metabolite.

Physiological effects of aflatoxicosis

Physiological effects of aflatoxicosis were reported by Edds (1973) and Hegazi (1984). The physiological consequences of continual AF dosing have been related to a rapid reduction of feed intake (Lynch *et al.,* 1971; Tawfik, 1975; Randall and Brid, 1979; Nowar *et al.,* 1981a; Shehata, 2002). Similarly, feed conversion efficiency (Schell *et al.,* 1993), feed efficiency and growth rate (Clark *et al.,* 1980; EI-Darawany, 1985; Huff *et al.*, 1986; Panangala *et al.*, 1986; Harvey *et al.,* 1989; Abd El-Hamid *et al.,* 1992; Schell *et al.,* 1993) were found to decrease when AF is consumed at lesser level. However, Randall and Brid (1979) found that feed efficiency was not affected by feeding AF B_1 to chicken. Particularly, Panangala *et al.* (1986) found that the feed containing 300 ppb AF affected growth rate when feeding process was prolonged for a long time in weaned swine.

Serum gluxamic oxalacetic transaminase (GOT), gluxamic pyrovic transaminase (GPT), alkaline phosphatase (ALP), 5-nucleotidase, gamma glutamyl transferase and plasma bilirubin and urea were found to increase in calves, rats, broilers and rabbits as a function of aflatoxicosis (Edds, 1973; Hegazi, 1984; EI-Darawany, 1985; Kubena *et al.,* 1990a; Nowar *et al.,* 1992; EI-Zahar *et al.*, 1996). However, no change was found in 5-nucleotidase and GPT in female rats (EI-Darawany, 1985) and plasma protein decreased significantly in mature NZW buck rabbits (EI-Zahar *et al.*, 1996). But, all these parameters were improved during the recovery period. Similar to that obtained in growing NZW rabbits fed 65.72-91.23 ppb AF contaminated diet for 7 weeks (Fayed, 1999) or fed 125 ppb AF B_1 contaminated diet (Shehata, 2002).

Both serum GOT and GPT enzymes are indicators of hepatocellular damage. Serum gamma glutamyl transferase activity is a sensitive indicator of liver dysfunction (Kubena *et al.,* 1990a).

Regarding kidney function, serum creatinine level increased significantly by ingestion a mixture of AFs B_1+G_1, which indicated lower glomerular filtration rate in both male and female rats (EI-Darawany, 1985).

Blood clotting time prolonged by ingestion AFs mixture (B_1+G_1) in rats (EI-Darawany, 1985). The coagulation defect caused by aflatoxicosis is primarily due to diminished hepatic synthesis of coagulation factors (Baker and Green, 1987). These findings were previously reported by Doerr *et al.* (1975, 1976) who provided some evidence that factors I (fibrinogen), 11 (prothrombin), V (labile factor), VII (stable factor) and X (Stuart-power) factors were impaired during aflatoxicosis in chicken. The sensitivity of fibrinogen to AF is perhaps due to liver dysfunction caused by aflatoxicosis.

Haemorrhagic anemia syndrome caused in poultry by AF is characterized by haemorrhages into the muscular and internal organs, particularly in subcutaneous tissue (Muller *et al.*, 1970). The anemic response to AF administration in lactating goats was evident from observed decrease in erythrocyte count, haemoglobin percentage, mean corpuscular haemoglobin and mean corpuscular hemoglobin concentration percentage together with increases in packed cell volume (PCV) and mean corpuscular volume (MCV) (Hassan *et al.,* 1983). Similar results were observed in blood picture measurements in mature NZW rabbits orally treated by AF B_1 (15 or 30 Ng/kg body weight every other day) (Ibrahim, 2000)

Chicken ingesting AFs suffered from depletion of oxycarotenoid pigments, since AFs induce a pale bird syndrome (Tyczkowski and Hamilton, 1987). Pale bird syndrome in chicken is a result to interference with the accumulation of pigment rather than the increase of pigment depletion (Jonathan *et al.,* 1988).

The absolute values of total body water (TBW) and total body solids (TBS) and percentages of TBW and TBS relatively to the live body weight of rats decreased ($P<0.01$) as a result of ingesting a mixture of AF B_1+G_1 (Nowar *et al.,* 1992).

Hepatic toxicity signs

Hepatic toxicity signs were observed in different species of animals in different organs, as well as, in different forms by different investigators.

Liver tissue examination in calves showed bile duct proliferation, perivascular edema, fibroblastic infiltration, dilated lymphatic ducts and loss of glycogen, resulting of daily AF doses as low as 0.04 mg/kg body weight over an experimental period of 6 weeks (Lynch *et al.,* 1971). Similar episodes of hepatic toxicity in ducklings, pigs and calves, were described in Uganda and Kenya (Allcroft, 1969).

Morphological changes in the lymphatic system were found to be clearly correlated with that in the liver and the histological examinations of the injured livers of AF treated animals which showed a peripheral necrosis and bile duct proliferation (Slowik *et al.,* 1985). Occurrence of periportal necrosis in the liver after oral dosing indicates that the toxic substance reached the liver in the portal bloodstream (Zuckerman *et al.,* 1967).

Lipids in the liver increased in broiler chicken fed contaminated diet by AF (Smith and Hamilton, 1970; Tung *et al.,* 1972). The steatorrhoea caused by AF, apparently reflects a lipid malabsorption syndrome caused by an impaired ability to digest lipids (Osborne and Hamilton, 1981).

Some liver fibrosis but no tumors were observed at 3 years after reducing AF intake in monkeys (Cuthbertson *et al.,*1967). Similarly, the studies of the National Cancer Institute found that no tumors in survived newborn monkeys even when repeated dosing with AF, although some of the animals developed a nodular fibrosis (Burnside *et al.* 1957)

Severe and fatal functional derangement of liver may be developed in Guinea pigs and monkeys submitted to a continual exposure of AF at a lower level. In other species such as the rat, general liver function remains satisfactory, but transformation of some cells to malignant carcinoma readily takes place. A more detailed analysis of liver function changes in rats and guinea pigs exposed to AF, is needed to explain these differences in response to AF.

The factors that influence the toxic effects of AF are sex, nutrition, environmental stresses and exposure to other chemicals (duration and dose) including other mycotoxins (Delvi, 1986).

Genetic damage

It is known that AFs produce three forms of genetic damage: carcinogenicity, teratogenicity and mutagenicity. The hepatic carcinogenicity has received the most intense scientific attention.

Carcinogensis is an important aspect of aflatoxicosis in animals, since the carcinogenic effect of AF B_1 has been demonstrated many times for several animal species. Several evidences indicated that the acute toxicity of the AFs may be an important determinant in cancer development, since the acute toxicity of AF B_1 correlates with the susceptibility to hepatic cancer (Vesselinovitch *et al.*, 1972). However, Roebuck and Maxuitenko (1994) reported that the relationship between acute toxicity and cancer is not direct, but only species that are sensitive to the acute effect of AF B_1 are more susceptible to hepatic cancers by some regime of AF B_1 exposure. Cova *et al.* (1990) found that hepatocellular carcinomas occurred by exposing ducks to AFs. Similarly, Halver (1969) reported that hepatic cancer occurred in hatchery-raised trout in the United States. Meanwhile, no hepatic cancer from AFs has been reported in chicken, i.e. they are apparently highly resistant. Adenocarcinoma of the glandular stomach was developed, probably reflecting a direct carcinogenic action of AF on the stomach mucosa in rats fed a batch of groundnut meal containing 10 ppm of AF (Butler and Barnes, 1966). A high incidence of liver tumors was also found in survived rats after more than two years of LD_{5o} dose (Butler and Barnes, 1968). This indicates that AFs are the most active liver carcinogen in rats. AF B_1 affected the liver and other organs particularly the digestive tract, urogenital system and the central and peripheral nervous systems (Goerttler *et al.*, 1970; Biedermann, 1972; Mennel and Ivankovic, 1975).

Teratogenic effects were observed in chicks. Mortality occurred when embryos were injected with high doses of a mixture of AFs B_1+G_1 into air sac of the egg at the eighth day from the beginning of hatching. Hatched chicks suffered from malformation of limbs, particularly the absence of some phalanges (EI-Darawany, 1985).

Aflatoxin B_1 is a potent mutagenic and carcinogenic mycotoxin and the Epidemiological studies have established that it is one of the important risk factors for hepatocellular carcinoma. Upon appropriate metabolism in cytochrome P 450-dependant reaction, the resulting epoxide binds to DNA and induces point mutations. Salmonella microsuspension assay was used to study the mutagenic activity of aflatoxin B_1 at the presence of S9 fraction in TA 98 and TA 100 tester strains. TA 98 strain showed higher sensitivity than TA 100 in mutagenic action of AFB_1 (Pierzynowska and Grzesiuk, 1998).

With regard to the mode of action of AF at a biochemical level, much attention has been paid to its capacity to react with DNA (Clifford and Ress, 1967), but there is nothing unique to AF in this respect. Several workers agreed that earliest changes in the liver cells after a single dose of AF were seen in the molecules, which would be consistent with some effect on nucleic acid metabolism. It appears to inhibit RNA synthesis and the induction of microsome enzymes. In albino rats, liver DNA, RNA and glycogen decreased and total lipids increased with daily ingestion of a mixture of AFs B_1+G_2 for 15 weeks (EI-Darawany, 1985). Additionally, Mashaly *et al.* (1986) found that treatment of chicks for 5 weeks with 50 and 100 mg AF B_1/kg feed caused significant decrease in RNA synthesis and slight decrease in muscle protein synthesis. Preliminary studies by Butler and Barnes (1968) and Lijinsky (1968), using electron microscopic radio-autography on AF treatment, suggested that after a single hepatotoxic dose, AF is bound and persists in liver cell cytoplasm more than it does in the nucleus.

RABBIT PRODUCTION AND EPRODUCTION AS AFFECTED BY AFs

Rabbit production

AFs affect animal performance via reducing feed intake and growth and can cause serious economic problems for animal production industry (Brekke *et al.,* 1977).

Feed utilization

Feed and water intake in several species were reduced by exposure of rabbits to AFs. In Baladi rabbits, Abd EI-Hamid *et al.* (1986) and Abd El-Hamid (1990) found that AF-contaminated diet (100 ppb each of crystalline AFs B_1, B_2, G_1 and G_2) given for 21 days induced significant decreases in daily consumption of feed and drinking water. Similar results were obtained by Hafez *et al.* (1983), Abd EI-Hamid *et al.* (1985), Abd El-Mageed (1987), Maru *et al.* (1987), Fayed (1999) and Shehata (2002). In addition to feed consumption, it was found that feed efficiency decreased in male rabbits given orally (210 µg AFs B_1+G_1 /kg body weight) for 5 weeks (Abd El-Mageed, 1987).

Similarly, significant decrease occurred in digestibility of dry matter and nitrogen free extract due to the low level of AF treatment, while organic matter and crude protein decreased significantly with the high level of treatment, in mature NZW rabbits treated orally by AF B_1 15 or 30 µg/kg BW every other day (Ibrahim, 2000). Marked decrease was also found to occur in digestion coefficients of dry matter, crude protein, crude fibre, nitrogen free extract and a lesser decrease occurred in ethyl ether, in male rabbits given orally (210 µg AF B_1+G_1 /kg body weight) for 5 weeks (Abd El-Mageed, 1987). Reduction values in digestion of total digestible nutrients (TDN) intake, digestible crude protein intake, nitrogen balance and digestible energy intake were about 65.96, 78.82, 106.25 and 79.42, respectively, in growing NZW rabbits fed 65.72-91.23 ppb AF contaminated diet for 7 weeks (Fayed, 1999).

Cellulose digestion, volatile fatty acid formation, proteolysis and motility of the gastrointestinal tract decreased as a function AFs digestion (Diekman and Green, 1992). Reduction in feed conversion due to AF B_1 treatment may be due to aflatoxicosis or to its effect on the hypothalamic center controlling feed intake, as well as, the hazardous effect of AF B_1 on the digestion and absorption of different nutrients (Sharma and Salumkhe, 1991). Additionally, the toxic effects on the nephrons that lead to excretion of vital blood components in the urine and the effect on neuroendocrine system controlling metabolic pathways, may not be excluded.

Growth

Body weight and weight gain decreased in different breeds of growing or mature rabbits treated with AFs (Clark *et al.,* 1980, 1982; Morisse *et al.,* 1981; Sahoo *et al.,* 1993; EI-Zahar *et al.,* 1996; Fayed 1999; Ibrahim, 2000; Lotfy, 2000; Nowar *et al.,* 2000; Shehata, 2002). Particularly, Hafez *et al.* (1983) announced that AF B and AF G decreased body weight in male and female Bouscat rabbits. Similar conclusion was reported by Abd El-Hamid *et al.* (1985, 1986) and Abd El-Hamid (1990) in Baladi rabbits treated with AFs B_1, B_2, G_1 and G_2 in the diet, and by Lal-Krishna and Dawra (1991) in Angora rabbits treated with 90-540 µg/kg levels of AF B_1.

Linear ($P<0.01$) reduction of the live body weight represented 11.9 % after 4 days and reached 36 % on day 16 of the experiment, when feeding rabbits a contaminated diet (860 ppb AFs B_1+G_1) (Nowar *et al.,* 1996). Body weight also decreased gradually due to AF treatment and the decrease level was higher with the high dose of AF than with the lower one, when mature NZW rabbits ingested orally AF B_1 , 15 or 30 µg/kg BW every other day (Ibrahim, 2000). The decrease values in body weight were 5.23, 11.54 and 1.16% in three treated groups, while that of the control increased by 3.44 % in mature NZW rabbit bucks given orally 50 µg AF / kg live weight daily for 10 or 17 days, 5 µg AF per head and 0 AF (control), respectively, for 30 days (EI-Zahar *et al.*, 1996). Growth rate also retarded markedly in male rabbits given orally 210 µg AFs B_1+G_1 /kg body weight for 5 weeks (Abd EI-Mageed, 1987).

The reduction in body weight of animals treated with AF is not only due to the AF-induced depression of feed intake, but may also be due to the reduction in RNA and DNA and protein syntheses. The mechanisms for this effect include inhibition of ribonucleic acid, RNA (Clifford and Ress, 1966) and deoxyribonucleic acid (DNA) synthesis (Rogers and Newbeme, 1967), as well as, decreased RNA polymerase activity (Gelboin *et al.,* 1966). In addition, AF can bind with DNA and RNA and prevents the protein synthesis in the body (Pier,1992). Growth depression is the consequence to protein synthesis reduction. Mashaly *et al.* (1986) found that treatment of chicks for 5 weeks with 50 and 100 mg AF B_1/kg feed caused a significant decrease in RNA synthesis and slight decrease in muscle protein synthesis. From another point of view, Cheeke and Shull (1985) reported that AF caused an interference with lipid metabolism, since an accumulation of lipid in the liver is associated with AF ingestion, resulting in a condition known as fatty liver. The effect is believed to be due to impaired transport of lipids out of the liver after their synthesis rather than increasing in their synthesis. Also, AFs cause an inhibition of fatty acid and cholesterol biosynthesis.

The changes in the hormonal balance in AF-treated animals may contribute at least partially in impairment of body weight and other performance parameters. The reduction in testosterone level may result in impairment of growth, since it has an anabolic effect on protein synthesis and a reduction in testosterone concentration as that was observed in males of different species when treated with AFs (Clarke *et al.,* 1986, 1987). Also, the catabolic effect of cortisol may play an important role in body weight loss, since it decreased with aflatoxicosis (Hassan *et al.,* 1983).

Mortality

Very little is known about AFs effect on rabbits (Abd El-Hamid *et al.,* 1985). However, it was reported that rabbits are more sensitive to AFs than most of the other animals (Ueno, 1987). The acute oral single dose LD_{50} for young rabbits is about 0.3 mg/kg of body weight, i.e. among the lowest of any species studied.

Moderate to severe death losses can occur when the feed contains small concentrations of AFs (Newbeme and Butler, 1969). In India, a loss of 4 000 of 7.000 Angora rabbits had been reported, when AF was found in the feed (Mehrotra and Khanna, 1973). Similarly, presence of AFs B_1, B_2, G_1 and G_2 in a low concentration (100 ppm of each AF) in the diet of Baladi rabbits decreased survival rate (Abd El-Hamid, 1990). Mortality in NZW, California and V line rabbits treated with more than 100 µg AFs B_1+G_1 / kg diet, differed according to sex and age. With the acute dose of B_1+G_1, aflatoxicosis induced death within 6-16 days. Mortality resulting from acute aflatoxicosis ranged between 55.04 and 61.74 %, i.e. higher than 50 % for all breed stocks (Nowar *et al.,* 1994). Similar findings were recently reported by different investigators in different breeds of growing or mature rabbits treated with AFs (EI-Zahar *et al.,* 1996; Ibrahim, 2000; Lotfy, 2000; Nowar *et al.,* 2000; Shehata, 2002).

Aflatoxicosis adverse effects were shown on post-weaning, as well as, on pre-weaning rabbits through the suckled milk, since mammary glands have shown to take part in excretion of AFs or its metabolic products (Longh *et al.,* 1964).

Rabbit reproduction

Males

Reviewed results of semen characteristics as affected by AFs are presented in Table 3. Semen quantity and quality traits (ejaculate volume, wave motion, sperm motility, sperm concentration, total sperm output, dead and abnormal spermatozoa and semen initial fructose) were adversely affected due to aflatoxicosis effects in mature rabbit bucks (Hafez *et al.,* 1983; Picha *et al.*, 1986; EI-Zahar *et al.,* 1996; Ibrahim, 2000; Lotfy, 2000; Nowar *et al.,* 2000; Shehata, 2002). However, Briggs *et al.* (1974) reported that ejaculate volume did not change in broiler breeder males fed a diet containing 20 ppm AF for 4 weeks. Egbunike (1979) also found that treatment of rats with 50 µg AF B_1/kg body weight for eleven days, failed to exert any change in daily sperm production rate and efficiency of spermatogenesis. Similarly, Choudhary *et al.* (1994) found that administration of 10 µg AF B_1/day/animal had no effect on spermatogenesis, in male albino rats.

The decrease in ejaculate volume induced by aflatoxicosis may be a result of the decrease in testosterone production which controls the function of the male accessory glands. This explanation is supported by the finding of Picha *et al.* (1986) who noted significant correlations between concentrations of testosterone and estradiol 17β with semen volume in boars. The latter trait was influenced by the season of the year and that AF content of the feed was the highest in April (11.6 µg /kg) and the lowest in summer (<1 µg /kg). The hazardous effects of AF on sperm density may be attributed to the direct effects of AF on the testicular tissues, whereas the reduction in sperm motility and sperm cell concentration may be due to damage of seminiferous tubules of the testes and absence of spermatogenesis (EI-Zahar *et al.,* 1996; Ibrahim, 2000; Lotfy, 2000). The degenerative effects of AF on seminiferous tubules were attributed to the decrease of gonadotrophic hormones of the anterior pituitary gland, which led to the decrease of testosterone secreted from interstitial cells of the testes (Clarke *et al.,* 1986). The decrease in seminal fructose content may be related to the reduction induced by AF in gonadotrophic hormones and/or testosterone, which control accessory gland function and activity (EI-Zahar *et al.,* 1996).

Testes. Mild degenerative changes in tunica vaginalis accompanied with testicular atrophy of the seminiferous tubules and complete absence of spermatozoa were reported in mature NZW male rabbits treated with 50µg AF/kg live weight daily for 10 or 17 days and with 5 µg AF per head daily for 30 days (EI-Zahar *et al.,* 1996). Significant gross changes were also reported in the right testis which appeared shrunken, partly adhered to the abdominal cavity with a 50% reduction in weight as compared to the control (left testis), when injecting AF B_1 in the right testes of mature rats at a dose of 50 µg. At the same time, the weights of the testis were slightly affected at the 25 and 10 µg doses (Gopal *et al*., 1980). Relative testis weight was also significantly lower in mature NZW rabbits orally treated by AF B_1, 15 or 30 µg/kg BW, every other day (Ibrahim, 2000).

In mature White Leghorn males, testes weights also decreased when fed a diet containing 20 µg AF/g diet (Sharlin *et al.,* 1980). Similar changes were reported in endocrine, testicular weight and absolute and relative combined testes weights after treatment with 10 or 20 ppm AF at 3 different stages of development, in male chicken (Clarke *et al.,* 1987).

Reproductive hormones. The hormones involved in regulating reproduction were found to be affected by the ingestion of AFs. Serum testosterone concentration decreased significantly in mature NZW rabbits orally treated by AF B_1, 15 or 30 µg/kg BW every other day (Ibrahim, 2000). Similarly, a decline in plasma testosterone (Cottier *et al.,* 1969; Clarke *et al.,* 1986, 1987) and a rise in luteininzing hormone level (Cottier *et al.,* 1969; Clarke *et al.,* 1986) were shown in mature White Leghom chicken by dietary AFs.

Table 3. Libido and semen traits of buck rabbit as affected by aflatoxicosis.

Treatments	Control group	Treated group		Authors
	Libido (sec.)			
B_1G_1 (100+100 ppb, orally)	13.3	12.8	ns	Lotfy (2000)
	Ejaculate density			
AFs mixture (5 µg/head/daily, orally)	2.0	1.7		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 10 d.	2.0	2.0		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 17 d.	2.0	1.6		El-Zahar *et al.* (1996)
	Hydrogen-ion (pH)			
AFs mixture (5 µg/head/daily, orally)	8.15	8.21		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 10 d.	8.15	8.24		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 17 d.	8.15	8.21		El-Zahar *et al.* (1996)
B_1+G_1 (100+100 ppb, orally)	6.95	7.17	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	7.01	6.90		Shehata (2002)
	Ejaculate volume (ml)			
AFs mixture (5 µg/head/daily, orally)	1.12	0.49		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 10 d.	1.12	0.39		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 17 d.	1.12	0.22		El-Zahar *et al.* (1996)
B_1 (15 µg/kg BW every other day, orally)	0.71	0.67	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	0.71	0.62	*	Ibrahim (2000)
B_1+G_1 (100+100 ppb, orally)	0.65	0.33	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	0.49	0.54		Shehata (2002)
B_1 (500 ppb/kg diet)	52.92	46.46		Shehata (2002)

Table 3 (Continued).

Treatments	Control group	Treated group		Authors
	Mass motility (%)			
AFs mixture (5 µg/head/daily, orally)	4.1	2.7		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 10 d.	4.1	3.0		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 17 d.	4.1	2.4		El-Zahar *et al.* (1996)
B_1 (15 µg/kg BW every other day, orally)	3.2	2.74	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	3.2	2.49	*	Ibrahim (2000)
B_1+G_1 (100+100 ppb, orally)	50.97	29.93	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	3.46	2.79		Shehata (2002)
	Progressive motility (%)			
AFs mixture (5 µg/head/daily, orally)	43.0	26.0	*	El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 10 d.	43.0	29.0	*	El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 17 d.	43.0	27.0	*	El-Zahar *et al.* (1996)
B_1 (15 µg/kg BW every other day, orally)	74.1	63.8	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	74.1	57.8	*	Ibrahim (2000)
B_1+G_1 (100+100 ppb, orally)	50.97	29.93	*	Lotfy (2000)
	Sperm concentration ($x10^6$/ml)			
AFs mixture (5 µg/head/daily, orally)	278.0	290.0		El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 10 d.	278.0	170.0	*	El-Zahar *et al.* (1996)
AFs mixture (50 µg/head/daily, orally), 17 d.	278.0	248.0	*	El-Zahar *et al.* (1996)
B_1 (15 µg/kg BW every other day, orally)	318.3	301.5	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	318.3	297.1	*	Ibrahim (2000)
B_1+G_1 (100+100 ppb, orally)	272.0	189.3	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	283.0	247.9		Shehata (2002)
	Sperm concentration ($x10^6$/ejaculate)			
B_1 (15 µg/kg BW every other day, orally)	227.5	202.2	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	227.5	187.0	*	Ibrahim (2000)
B_1+G_1 (100+100 ppb, orally)	176.8	62.47	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	152.6	138.3		Shehata (2002)
	Dead sperm (%)			
B_1 (15 µg/kg BW every other day, orally)	9.17	10.30	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	9.17	12.46	*	Ibrahim (2000)
B_1+G_1 (100+100 ppb, orally)	29.7	41.97	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	28.0	43.25	*	Shehata (2002)
	Abnormal sperm (%)			
B_1+G_1 (100+100 ppb, orally)	23.8	31.2	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	21.8	31.21	*	Shehata (2002)
	Acrosomal integrity (%)			
B_1+G_1 (100+100 ppb, orally)	13.1	22.1	*	Lotfy (2000)
B_1 (500 ppb/kg diet)	14.8	21.46	*	Shehata (2002)
	Initial fructose concentration			
B_1 (15 µg/kg BW every other day, orally)	212.5	208.6	*	Ibrahim (2000)
B_1 (30 µg/kg BW every other day, orally)	212.5	189.3	*	Ibrahim (2000)

* = P, 0.05, ns = Not significant, Sec. = Seconds and d =Day.

Drop in testosterone is a resultant to impairment of the Leydig cell function caused by the disruption of spermatogenesis by chronic AFs treatment (Egbunike, 1979). The suppression of plasma testosterone and testicular weight, as well as, the delay in peak levels of LH, indicated that a delay in the onset of sexual maturation may be associated with aflatoxicosis (Clarke *et al.,* 1987).

Females

In the literature, information reviewed for aflatoxicosis effects on the reproductive performance of doe rabbits, were scanty. Reproductive performance was found to be adversely affected in female and male rabbits treated with 7.8 ppm AF B and 4.92 ppm AF G daily for 7 days (Hafez *et al.,* 1983). Further, ingestion of AFs influenced the subsequent reproductive performance of the female (EI-Darawany, 1985) and supported the genotoxic potential of AF in animals (Leonard *et al.,* 1975).

Microscopic examination of the ovaries of female rabbits treated with 0.15mg AF B_1/kg BW showed some pathological alterations in the form of coagulative necrosis which appeared mainly in the growing and mature follicles, and decrease in number of Graffian and growing follicles with increased number of atretic follicles and small areas of degenerative changes. Uterine structure of the treated females did not show any pathological changes in the endometrial or myometrial layers, except in one animal (treated with the high level of AF) which showed the ulceration of mucosa with degenerative changes in the uterine gland (Abd El–Wahhab, 1996).

Lower fertility measurements were recorded in female rats subcutaneously injected by 7.0, 3.5, 1.4 or 0.7 mg/kg BW of AFs, showing 4.0, 5.9, 6.8 and 6.4 implants/female, respectively, compared with 7.8 implants/female in the control. The dead implants were 3.2, 3.8, 2.8 and 2.0, respectively. The pre- and post-implantation loss was significant in all the treated groups (Leonard *et al.,* 1975). Two unrelated toxic actions have been suggested to explain the AF effects on females fertility: 1. An indirect effect on the dam mediated by AF induced hypovitaminosis A, and 2. A direct antagonistic interaction with steroid hormones receptors, due to structural similarity of AF and steroid hormones (Cheeke and Shull, 1985).

Teratogenic effects, following daily ingestion of a mixture of AFs B_1 + AF G_1 by pregnant white rats from the eighth to the twelfth day of gestation caused a reduction in the number of implantation sites and fetal weight and increase in reabsorption of fetuses. Vertebral column changes, mainly the absence of one or more coccygeal vertebrae and in some cases compaction of the vertebral column, were observed. Limb defects included the absence of some metacarpal and metatarsal bones and some phalanges. Percentages of malformation in the vertebral column and limbs were estimated to be 18.10 and 41.69, respectively (EI-Darawany, 1985; Nowar *et al.,* 1986).

Regarding milk production, histopathological and histochemical examination of mammary glands revealed increased fibrosis and collagen deposition with thick-walled blood vessels in animals received AF B_1 (50 μg/kg of body weight) daily for 10 days during the first, second and third trimester of the gestation period, with an additional untreated control group;. These pathological changes may be the cause of the decrease in secretion of milk inside the alveoli (Amin *et al.,* 1991).

Clinical signs

Clinicopathologic changes of experimental aflatoxicosis in rabbits are similar to those reported in swine, goats and cattle (Abrams, 1965; Sisk *et al.,* 1968; Newbeme, 1973; Samarajeewa *et al.,* 1975; Osuna *et al.,* 1977). Accordingly, rabbits may be a potential model for studying of aflatoxicosis.

Before death, aflatoxicosis in rabbits exhibited loss in appetite, diarrhea and emaciation, when fed natural contaminated diet contained 860-ppb of AF B_1+G_1 (Nowar *et al.,* 1994, 1996). Clark *et al.* (1980) mentioned that NZW male rabbits given orally AF levels of 0.05 and 0.062 showed anorexia, decreased weight gain, lethargy, emaciation, dehydration, icterus and death, but levels of 0.25, 0.03 mg / kg BW) did not produce clinical aflatoxicosis or blood change. Pier (1981) and EI-Zahar *et al.* (1996) reported that the major clinical and pathologic effects include anorexia, reduction of body weight gain, subnormal body temperature and dry nuzzle. Lesions of liver damage are characterized by fatty infiltration, vacuolated hepatocytes, hepatocellular necrosis, bile duct proliferation and diffuse fibrosis.

Death of rabbits occurred within 6 to 16 days after feeding the contaminated diet (acute aflatoxicosis) (Nowar *et al.,* 1994, 1996). Similarly, Shehata (2002) reported that growing and mature NZW rabbits that fed 125 or 500 ppb AF B_1 contaminated diet died after 13 and 43 days, respectively, from the start of the experiment.

After death, hemorrhage was shown in the abdominal cavity, the liver was pale in appearance and friable and the gall bladder was enlarged and distended with urine. Macroscopically lesions were hepatic-renal degenerative changes, focal coagulative necrosis, beside congestion of the blood vessels and lymphocytic infiltration, in addition to hepatic portal edema and hyperplasia of bile ducts. In the heart, congestion, edema and replacement of the red pulp by lymphocytem, were observed. Relative weights of liver, kidneys, heart and adrenal gland were significantly higher in rabbits suffered from aflatoxicosis than in the control (Abel EI-Hamid, 1990; Nowar *et al.,* 1996; Shehata, 2002). Meanwhile, absolute weights of lungs were lower in AF treated animals than in those fed the control diet (Nowar *et al.,* 1996). Ibrahim (2000) found that the relative weights of spleen, brain, liver and kidneys were insignificantly affected and the bladder relative weight increased significantly in mature NZW rabbits orally treated by AF B1 (15 or 30 μg/kg of body weight every other day).

CONTROL OF AFLATOXINS TOXIC EFFECTS

Three general decontamination strategies are available; these are: a. Physical removal of the contaminated portion of the feedstuffs, b. Chemical, heat or radiation treatment of the commodity in order to destroy the toxic sources and c. Addition to animal feed, materials that bind the toxins and make the toxic sources unavailable during digestion or that enable the animal to counteract their deleterious effects (Beaver, 1991; Ayyat and Marai, 1997). However, decontamination strategy must be economically feasible (i.e. the cost of decontamination should be less than the value of the contaminated commodity). To meet such criteria, the following should be considered: 1. Mycotoxin must be destroyed, removed or inactivated, 2. The procedure must be safe and do not produce any toxic or carcinogenic compounds, 3. The feedstuff should retain its nutritive value and remains palatable, 4. The physical properties of feedstuff should not be significantly altered and 5. Fungal spores and mycelia should be destroyed without formation of new toxins.

The use of microbial inactivation, irradiation, ammoniation, ozone degradation and sequestering agents have been reported by several authors for the decontamination and remediation of the highly contaminated feedstuffs. Most of these methods are costly, time-consuming and only partially effective. Researches indicate that a number of adsorbents are capable of binding toxins and reducing or preventing its toxic effects (Ayyat and Marai, 1997). The major advantages of adsorbents include low cost, safety and easy inclusion in animal feeds. However, not all adsorbents are equally effective in protecting livestock against the toxic effects of AFs. The ability of adsorbents for binding with AFs depends on: toxins and adsorbents concentration, temperatures, pH and treatment time (Ramos and Hernandez, 1996; Ayyat and Marai, 1997; Grant and Phillips, 1998; Lemke *et al.*, 1998; Shehata, 2002).

Detoxification of Aflatoxins

Adsorbents

One practical approach has been to use non-nutritive adsorptive materials in the diet to reduce AFs absorption from the gastrointestinal tract. Dietary additions of zeolite (Smith, 1980; Ayyat and Marai, 1997), bentonite (Carson, 1982; Ayyat and Marai, 1997), spent bleaching-clay from canola oil refining (Smith, 1984) and charcoal (Dalvi and Ademoyero, 1984; Dalvi and McGowan, 1984), have been used.

Clay minerals. Addition of tafla clay (it is a desert clay (Marai *et al.,* 1996)) to AFs (862 ppb AF B_1 + AF G_1) naturally contaminated diet in rabbits, improved ($P<0.05$) growth performance, digestibility of all nutrients compared to those fed AFs diet alone, and also maintained the level of blood serum metabolites to that recorded in rabbits fed the uncontaminated diet. The magnitude of improvement was greater with 1 % tafla and lower with 3 % tafla. Fecal AF (as % of intake) in rabbits fed AF diet with 1, 2 and 3 % tafla recorded 72.7, 58.1 and 50 %, respectively (Nowar *et al.*, 1996). Similar results were obtained by Shehata (2002).

Transmission of 107 ppb AF from feed to milk in dairy cattle was reduced significantly by dietary additions of three clay products at 1.25 % of diet dry matter. Dietary addition of clay resulted in an average reduction of 61% transmission of AF from feed to milk and 58 % in milk AF concentration. Meanwhile, none of the studied clay products affected the dry matter intake or milk yield. The effectiveness of the three clay products was similar in reducing concentrations of AFs in milk (Diaz *et al.,* 1997). A beneficial effect of addition of 5 % soil in the diet on detoxification of AFs (300 ppb AF B_1 + AF G_1 orally/kg BW), was also reported in rats (Abd El-Mageed, 1987). The number of 2 of 4 species of zeolite (0.5 %) reduced the toxicity of (AF 3.5 mg/kg feed) by 41 and 29 %, and the other 2 species insignificantly diminished the toxicity of the same AF level in growing broiler chicken of 1 day to 3 weeks of age (Harvey *et al.*, 1993). Addition of 0.25, 0.5 and 0.75 % bentonite reduced the effect of 800 ppb AF and significantly improved average daily body gain, but without any benefits for more than 0.5 % bentonite (Lindemann *et al.*, 1993) in pigs. Feeding a diet containing > 500 ppb AF diet + natural sodium bentonite showed an increase in live weight gain and feed intake than with an AF diet alone in poult turkey (Santurio *et al.*, 1998). Natural sodium bentonite treatment at 5 g/kg feed for prevention of toxic effect of AF (3 mg/kg feed) improved body weights by 31.3%, feed intake by 23.8% and production efficiency by 40.1% in Ross male broiler chicken at day 42 of age. However, weights of liver, heart, pancreas, crop and biochemical variables were not affected by dietary natural sodium bentonite. (Santurio *et al.*, 1999).

In vitro, adsorption of 1 montmorillonite silicate was 1000, 425-450, 230 and 200 µg for the naturally occurring AF B_1, AF G_1, AF G_2 and AF B_2, respectively (Ramos and Hernandez, 1996).

Hydrated sodium calcium aluminosilicate (HSCA). The use of HSCAS can diminish many of the adverse effects of dietary AFs in chicken, as indicated by the increase in serum gamma glutamyl transferase activity and the decrease in triglycerides and albumin in the blood (Kubena *et al.,* 1990a). HSCA (0.5%) can protect against the effects of: AF (5 and 7.5 mg AF /kg diet) in chicken, (0.5 and 1 mg AF /kg diet) in male turkey poults and (2.5 mg AF / kg diet) in growing broilers (Kubena *et al.*, 1990a, 1991, 1993). The value of 2 % HSCA may be of a high–affinity effect for 2.6 mg or 400 µg AF / kg of diet in male ducklings (Yeonghsiang *et al.*, 1995). Addition of HSCA to AF contaminated diets protects pigs from some toxic changes, in addition to that immunological measurements in the AF + HSCA groups were significantly different than those of AF alone group, but the values were still not equivalent to those of the control (Harvey *et al.*, 1994).

Maternal mortality during gestation at days 6-13 was 9% when using AF B_1 (2 mg/kg body weight) with 0.5 % clinopitiolite and 64% with AF alone. The AF alone or AF + clinopitiolite reduced feed intake. The animals did not recover after stopping the dosing regimen, whereas feed intake of animals treated with HSCA + AF was comparable to that of the control group at day 16 of gestation. Liver of the animals treated with HSCA + AF B_1 was normal comparable to that of the control. More severe toxicity symptoms were observed in liver of the animal treated with clinopitiolite + AF B_1 than in the animal treated with AF B_1 alone (Abd El-Wahhab, 1996). Contrarily, HSCA did not protect from AF B_1 toxicity in turkey poults orally dosed by 0.75 mg AF B_1 /kg diet (Edrington *et al.*, 1996).

The proposed mechanism of AF chemisorptions by HSCA is the formation of a complex by the β-carbonyl system of the AF with uncoordinated edge site of aluminum ions in HSCA (Phillips *et al.*, 1990, 1995). Computer modeling was used to provide additional information. The preliminary evidence indicated that AF B_1 may react at surfaces and within the inter layers of HSCA particles (Phillips *et al.*, 1995). The protective effects of HSCA also appear to involve sequestration of AFs so that they become not available for gastrointestinal tract absorption by chicks. The mechanism is probably either chemisorptions (i.e. strong bond formation) between HSCA and AFs (Phillips *et al.,* 1988) or an interaction between HSCA and other food management practices (Kubena *et al.,* 1990b), thereby reducing the bioavailabilty of AFs (Davidson *et al.,* 1987).

Modified yeast cell wall. Modified yeast cell wall mannanoligosaccharide (MOS), which is based on an esterified glucomannan derived from cell wall of a selected strain of *Saccharomyces cerevisiae*, causes stimulation of the specific immune system in turkey, increases antibody titer values against infection with burysal and Newcastle diseases of broilers fed AF and adsorbed mycotoxins. The adsorption was higher for AF, zearalenone, fumonisin, deoxynivalenol and ochratoxin by 1% of MOS. The adsorption was higher at pH 6.8 in comparison with pH 4.5 (Devegowda *et al.,* 1998). Supplementation of mycosorb (natural product containing 10% mannanoligosaccharide compound extracted from *Saccharomyces cerevisiae*) at 0.1 and 0.2 % to diets containing up to 200 ppb AF, resulted in improvement of body weight, feed efficiency and total serum proteins. Supplementation of mycosorb to graded levels of AF (100, 200 or 400 ppb) did not show significant alterations in gamma glutamyl transferase activity and weight of liver, bursa of Fabricius, gizzard and spleen in commercial broilers (Swamy and Devegowda, 1998).

Saccharomyces cerevisiae at 0.5 % is more effective than 0.75 % zeolite and sodium bisulfate against the deleterious effects of AF B_1 (1 mg/kg feed), on broiler performance (Khosravi and Modirsanei, 1999).

Activated charcoal. Gain weight and feed consumption of one-day-old chicks were reduced profoundly with the use of 10-ppm AF B_1 with or without activated charcoal for 8 weeks. The toxicity which developed severe liver damage in the experimental chicken was reduced considerably by addition either the activated charcoal that reduced glutathione, Cysteine, selenium, beta-carotene, or administration, or with Fisten administered orally (Dalvi and Ademoyero, 1984).

Activated charcoal at 600 ppm was highly effective in preventing chronic aflatoxicosis, while it was less effective at 300 ppm (Umesh *et al.,* 1991). Activated charcoal (200 ppm) reduced the inhibitory effect of AF B_1 (0.5 ppm/kg feed) on feed intake and body weight in broilers. There was also a significant improvement in serum enzymes (Jindal *et al.,* 1994). Contrarily, the activated charcoal did not affect adsorption of AF (5 and 20 ppm) *in vitro* (Maryamman *et al.,* 1991). Edrington *et al.* (1996) reported that activated charcoal did not reduce urinary excretion of AF M_1 in turkey poults orally dosed with 0.75 mg AF B_1/kg body weight, also it did not have any protective effects on AF toxicity.

Physical treatments

Physical separation techniques allow removal of contaminated material using manual, mechanical or electronic means before further processing. The physical removal of contaminated material involves separation of discoloured, damaged or obviously mouldy grains (Jemmali, 1983). Drying of crops in the field and before storage can prevent the production of AFs. In arid zone areas, this can easily be achieved without artificial drying. Simple low cost solar drier (Kato *et al.*, 1990) could be used in watery areas. Pre-harvest maize treated with chitosan reduced the growth of *A. flavus* and AFs production (Cuero *et al.,* 1991).

Loss of toxicity may occur by exposing groundnut oil stored in a glass bottle to bright sunlight for at least one hour. The effect of such exposure on the quality of the groundnut oil may need to be considered (Jemmali, 1983).

Chemical treatment

Treatment of grains with ammonia appears to be a viable approach to detoxification of AF. Ammoniation results in a significant reduction in the level of AF in contaminated peanut and cottonseed meals (Masri *et al.,* 1969). Ammoniation, either as aqueous or gaseous ammonia at a level of 1 %, can be used in corn that has moisture content of 15-22%. The process is a simple static one with a holding period of several weeks. However, the treated corn is discoloured and smells of ammonia, that restrict corn use as an animal feed. Feeding studies with rainbow trout showed that AF-contaminated corn treated with ammonia was not significantly different from untreated, uncontaminated corn (Jemmali, 1983). Park *et al.* (1983) used ammonia-detoxified cottonseed meal to feed cattle and laying chicken. Studying the detoxification rate for AFs B_1, B_2, G_1 and G_2 by NaOH, NH_4OH and $NaHCO_3$ showed that the detoxification rate for AF B_1 was higher than that of AF B_2 and the rates for AF G_1 and AF G_2 were similar. There are no differences in the detoxification rates using citric acid, acetic acid and lactic acid or the oxidizing compounds (NaO, H_2O_2 and HCHO) among the different AFs (Mashaly *et al.,* 1983). Detoxification was high in maize on autoclaving (0.073 kg/cm^2/2.5h) as also on autoclaving processed by 2% NaOH treatment. Autoclaving of toxic materials pretreated with Ca (OH) $_2$+HCHO caused the maximum detoxification (92-94%). However, the $Ca(OH)_2$+HCHO treatment severely depressed chick growth (Lakshmirajam *et al.,* 1984).

AF B_1 was decreased from 401 to 29.5 ppb in groundnut meal treated with 4% calcium hydroxide and 0.5% paraformaldehyde in an autoclave at 2 atm for 20 minutes. In 2 trials lasting 10 and 22 days, AF M_1 was less in milk of 2 dairy cows when they were given diets with detoxified meal than when they were given contaminated untreated meal (Piva *et al.,* 1985).

Feeding a control diet (group 1), AF contaminated diet (which had been sun dried) (group 2) or ammoniated with 15% ammonium hydroxide solution w/w at 15% moisture and sun dried (goup 3) to Yorkshire pigs, showed that group 3 had mild degenerative changes in hepatocytes but no other tissues, group 2 had moderately severe lesions and group 1 had no signs of toxification (Sriraman *el al.*, 1990). Treatment of maize with propionic acid also reduced *A. flavus* activity resulting in very low AF levels (Ilangantileke *et al.,* 1989).

AF can be removed from plant oils by the use of caustic soda and bleaching clays during the refining process. Any AF present in the crude oil is completely removed. The AF content of unrefined hydraulic-pressed oil can be reduced by filtration. In pilot plant studies in India, almost complete removal has been achieved with a special adsorption filter unit, which easily replaces the conventional cotton cloth filter (F.A.O., 1977). AFs have also been removed by extraction of oilseed cakes with a solvent mixture of hexane (50%), acetone (48%) and water (1.5%).

Decontamination of oilseed cake and peanut meal by a mono-methylamine and calcium hydroxide mixture has been used on an industrial scale. The process involves the simultaneous use of lime at 2% and mono-methylamine (prepared as an aqueous solution) at 0.5% by weight of feed. The mechanism of destruction of AF B_1 is probably similar to that in ammoniation, i.e. opening of the lactone ring and decarboxylation (Jemmali, 1983; Park *et al.*, 1983).

Prevention of aflatoxicosis of growing rabbits fed AF-contaminated diet (833 µg of aflatoxins/kg) using 5% hydrogen peroxide (H_2O_2) and γ-radiation at a dose level of 500 krad (5 kGy), indicated that the use of H_2O_2 and γ-radiation for the destruction of aflatoxins in contaminated diets induces adverse effects in the animals (Soliman et al., 2001).

In a contaminated feed, no reduction was observed in AF level (5 and 20 ppm) when treated with urea, *in vitro* (Maryamman *et al.*, 1991).

Nutritional treatment

Addition of vitamin A, E and K to the ration increased the body weight gain, but did not prevent the development of clinical signs, mortality or histological changes of aflatoxicosis in rats (Todd *et al.,* 1968).

Experiments have been conducted to decrease the toxic effects of AFs in rats by using vitamin C, soil and honey. The best results were obtained with vitamin C or soil. These effects were related to the biological role in digestive enzymes biosynthesis and activation with vitamin C, and the possible adsorption of AFs by the silica content of the soil (Abd El-Mageed, 1987). Salem et al (2001) also found beneficial influences of ascorbic acid in reducing the negative effects of AFB_1 on production and reproduction of mature male rabbits in their studies on two sublethal doses (15 or 30 µg/kg of body weight; every other day) of AFB_1.

The studies on Rhesus monkeys showed that there is synergism between protein/calorie malnutrition and AF induced hepatocarcinogenesis and that may explain the higher incidence of hepatocellular carcinoma in certain areas of the world where contamination of foods with AFs and malnutrition are prevalent (Meera *et al.,* 1989). The dietary modifications, i.e., raising of crude protein by 3% and supplementation of additional levels of riboflavin, pyridoxine, folic acid and choline in AFs contaminated diets, protected laying quails from the performance depressing effects of 0.75 ppm AF (Johri *et al.,* 1990).

The effect of dietary AF B_1 (420 and 840 ppb) with or without 2 ppm folic acid and 0.3 ppm selenium in growing swine, showed decrease in average daily gain with the increase in dietary AF level. Megalla and Mohran (1984) reported that the consumption of fermented dairy products reduced the chance of toxicity of AFs. Essential oil from the leaves of *Cinnamomum tamala* can be used to decontaminate *A. flavus* and *A. parasiticus* toxins (Misra *et al.*, 1987).

Contrarily, Edrington *et al.* (1994) reported that no benefits can be obtained in lamb performance when fishmeal was substituted with soybean meal, either with or without 2.5 mg AF/kg of feed. Similarly, it was found that vitamin E may not have a sparing effect on aflatoxicosis in growing swine and pigs and that AF exposure might exacerbate vitamin A and E deficiencies in pigs (Harvey *et al.,* 1994). Further, low levels of AFs may depress certain aspects of cellular immunity in weanling pigs, as well as,. supplementation of methionine did not improve immune function in pigs given AFs (Heugten *et al.,* 1994).

Biodegradation

Destruction of AF by biological inactivation can be achieved by utilizing the ability of microorganisms to attack or transform the toxic compounds. *Flavobacterium aurantiacum* was found to remove remarkably AF from a liquid medium, without the production of toxic by-product (Ciegler *et al.,* 1966). *Flavobacterium aurantiacum* also removed AF B_1 from peanut milk. This bacterium grew in both defected and partially defected peanut milk and was not inhibited by the presence of AF (Hao *et al.,* 1987). Fermentation of contaminated grains has been shown to be degrade AF (Lindenfelser and Ciegler, 1970). The best ability of biodegradation AF B_1 and ochratoxin A is in medium MRS that possesses *Lactobacillus acidophilus* strains. Moreover, lactic acid bacteria from bakery starter decreased the content of ochratoxin A with about 94% in flour after 24 hrs of fermentation by mixed starter population of lactic acid bacteria for traditional production of bread (Piotrowska and Zakowska, 1998).

CONCLUSIONS

Ingestion of AFs by rabbits induces great pathological changes, organs dysfunction, and genetic damage and decreases the productive and reproductive performance. Contamination can be avoided by correct harvesting, drying and storage of feed crops. Removal or inactivation of AFs can be achieved by the use of special methods such as non-nutritive adsorbents and physical, chemical and nutritional treatments or by biodegradation.

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