W o r l d
R a b b i t
S c i e n c e

MYCOTOXINS IN RABBIT FEED: A REVIEW[1]

Mézes M.[*] and Balogh K.[*,†]

[*]Szent István University, Faculty of Agricultural and Environmental Sciences, Department of Nutrition, POB. 303, H-2103 Gödöllő, Hungary.
[†]Research Group of Animal Breeding and Hygiene, Faculty of Animal Science, University of Kaposvár, POB. 16, H-7401 Kaposvár, Hungary.

ABSTRACT: Rabbit meat constitutes a measurable portion of the human diet. Thus, the ingredients used in rabbit feed and their contamination with undesirable substances are fundamentally important both in terms of the quality of the meat and the potential human health impacts associated with the animal-based food-production chain. The inclusion of feed ingredients which are contaminated with toxic substances may have a range of biological or toxicological effects on animal production. Rabbit feed ingredients that constitute complete feed products are derived from different raw materials and the contamination of feed materials would represent an important potential hazard. This review summarizes some of the toxic effects of mycotoxins, such as aflatoxins, ochratoxin, citritin, patulin, trichothecenes (deoxynivalenol, diacetoxyscirpenol, T-2 toxin), zearalenone, fumonisins, moniliformin and fusaric acid.

Key Words: feed, mycotoxins, toxicology, rabbit.

INTRODUCTION

Mycotoxins are invisible secondary metabolites of moulds which may persist in feed even when the moulds that produced them are no longer present (Scott, 1990). Rabbit production is important in tropical and subtropical agricultural systems (Cheeke, 1986), and some low-cost rabbit feed constituents, such as maize-milling waste, may be infected with moulds (mainly *Aspergillus* and *Penicillium spp*.), and consequently may contain mycotoxins. The occurence of mycotoxin in rabbit feed is high in some countries. For example, 77% of rabbit feed samples analysed in India were contaminated with aflatoxins (Mohanamba *et al*., 2007), and 78% of the samples analysed in Argentina were contaminated with ochratoxin A (Dalcero *et al*., 2002). Nearly all mycotoxins are cytotoxic, disrupting various cellular structures such as membranes and interfering with cellular processes such as protein, RNA and DNA synthesis (Guerre *et al*., 2000). Mycotoxins destroy the tissues by oxidizing proteins and most of them have immunosuppressive effects (Kumar *et al.*, 2008). Some of them cause acute toxicity, evidenced by digestive disorders or dermatitis. Some of them are carcinogenic, resulting in genetic mutations or causing deformities in developing embryos. Mycotoxins can have very pervasive yet sub-clinical effects on the health of rabbits which very often remain unnoticed. When the clinical symptoms of mycotoxin poisoning can be observed, significant damage has already occurred. Improper harvesting, packaging and

storage, or the prolonged shipping of feed ingredients may enhance the potential for mould growth and mycotoxin production. Dirty harvesting, manufacturing and pelleting equipment, and storage bins may also contribute to mycotoxin contamination (Houssein and Brasel, 2001).

The symptoms of mycotoxicosis are sometimes similar to those of better-known ailments. Mycotoxins may cause fever (Cannon *et al*., 1982), gastrointestinal problems, internal bleeding, haemorrhages or bruising, stomach ulcers (Aziz *et al*., 1995), mouth sores, kidney or liver damage (Szilágyi *et al*., 1994), central nervous system problems (Gabal *et al*., 1986), immune-suppression (Richard *et al*., 1991; Kumar *et al*., 2008), tumour-genesis, eye and lung problems, hypertrophy of the adrenal cortex, reproductive organ problems (Szilágyi *et al*., 1994), damage to the heart muscle, tachycardia, skin problems (Fairhurst *et al*., 1987), bone marrow and spleen problems (Niyo *et al*., 1988), blood abnormalities (Mizutani *et al*., 1997), rectal prolapses and increased vascular fragility.

Poisoning may give rise to chronic or acute incidences depending on the amount of mycotoxin-contaminated feed ingested and the damage to organs is cumulative over a period of time. A high incidence of gastrointestinal upsets and diseases associated with depressed immune function (e.g. *Pasteurella*) may indicate that a mycotoxin problem exists (Richard *et al*., 1991). There are some clinical signs which may appear in rabbits, such as severe pain in the abdomen, while radiograph series may reveal gut shutdown but no physical blockage, and sometimes severe bloating as an effect of deoxynivalenol (Fioramonti *et al*., 1993). Aflatoxicosis causes hypothermia and several blood abnormalities, e.g. high urea and creatinine levels, calcium-phosphorus imbalance, abnormal levels of liver enzymes (AST, ALT, GGT) (Sahoo *et al*., 1993) and impaired activity of the enzymes of the xenobiotic transforming system (Guerre *et al*., 2000). In the case of T-2 toxicosis, low hematocrit and red blood cell levels, ulcers in the mouth, stomach and oesophagus, feed refusal, weight loss, and some ovarian dysfunction were found (Fekete *et al*., 1992).

The European Commission has made recommendations (2006/576/EC) regarding the maximum level of several mycotoxins in complete diets (European Commission, 2006) and introduced regulations (2003/100/EC) regarding aflatoxins (European Commission, 2003). However, these only apply to certain cases, particularly with regard to rabbit feed (Table 1). There is only limited data on the occurrence of important mycotoxins in rabbit feed and this is therefore an important area for future research and surveys. However, the recommended maximum amount of mycotoxins in complete feed can be extrapolated to rabbit feed.

AFLATOXINS

Rabbits are highly susceptible to aflatoxins which are produced by *Aspergillus* moulds. The median lethal dose (LD_{50}) of aflatoxin B_1 (AFB_1) in rabbits was determined as a single oral dose of 300 mg/kg body weight (BW) (Cardona *et al*., 1991). However AFB_1 as low as 15 mg/kg feed caused high levels of morbidity and mortality (Makkar and Singh, 1991). Haemolytic anaemia and strong cytotoxic effects were also observed by Verma and Mehta (1998). Feeding rabbits a diet naturally contaminated with 50 mg/kg

Table 1: Recommended maximum amount of mycotoxins in complete feed.

Mycotoxin	Maximum content in mg/kg for feed with a moisture content of 12 %
Aflatoxin B_1	0.02
Ochratoxin A	5.00
Deoxynivalenol	5.00
Zearalenone	0.50
Fumonisin B1+B2	5.00

AFB_1 caused lesions in the liver (Abdelhamid *et al*., 2002). An exponential dose-dependent increase in plasma bilirubin concentration was also observed, which is more likely to be related to increased heme catabolism than to altered bile duct permeability (Guerre *et al*., 1997). AFB_1 toxicity also caused damage to other tissues, such as the kidney, testicles, brain and thyroids (Lakkawar *et al*., 2004). The teratogenic effects of AFB_1 on rabbits were described as enlarged eye sockets and enlarged fetal livers (Wangikar *et al*., 2005a) and the dose of 0.1 mg/kg BW was considered to be the minimum oral teratogenic dose (Wangikar *et al*., 2005b).

In addition to feed as the primary route of AFB_1 intake, the inhalation of contaminated dust particles may result in high local exposure of the nasal mucosa. Larsson and Tjälve (2000) assessed the bio-activation and toxicity of AFB_1 in the nasal mucosa after intranasal administration of AFB_1, (0.1, 1 or 2 mg) in rats and also examined whether translocation of the mycotoxin occurs from the nasal mucosa to the brain along olfactory neurons. The data indicated that materials transported in the olfactory nerves represented AFB_1 and/or some of its non-reactive metabolites. It was concluded that applying AFB_1 to the nasal mucosa resulted in high local bio-activation of the mycotoxin and translocation of AFB_1 and/or its metabolites to the olfactory bulb if administered as a purified mycotoxin. However, the inhalation of contaminated feed dust may have a different metabolism and/or response.

As mentioned previously, AFB_1 is a potent hepatotoxic and hepato-carcinogenic mycotoxin which requires bio-activation to an active AFB_1-8,9-epoxide (Essigmann *et al*., 1982) which binds to DNA. Both endo- and exo-stereoisomers of AFB_1-8,9-epoxide exist, and although they are both produced in a variety of tissues, only exo-AFB_1-8,9-epoxide binds efficiently to DNA (Eaton and Gallagher, 1994). In addition to epoxidation, microsomal monooxygenases transform AFB_1 to the less toxic metabolites aflatoxin M_1 (AFM_1) and aflatoxin Q_1 (AFQ_1). The rate of bio-transformation of AFB_1 depends on the tissues. For instance, values for AFM_1 formation in liver microsomes were greater than in the lung, but the rate of AFQ_1 formation was the same in the above-mentioned tissues (Daniels *et al*., 1990). Bio-activation-related toxicity of AFB_1 has also been observed in tracheal mucosa following intra-tracheal instillation of AFB_1 in rabbits (Coulombe *et al*., 1986). These results indicate that besides the liver, the lung and trachea are also capable of activating AFB_1 and that rabbit lung and tracheal microsomes show high activity for this reaction (Daniels *et al*., 1990). Different rabbit lung cell types have different abilities to bio-activate AFB_1. Daniels *et al*. (1993) found that it was highest in the microsomes of non-ciliated bronchiolar epithelial (Clara) cell-rich fractions.

Epoxide hydrolase and glutathione-S-transferase (GST) are both involved in hepatic detoxification of activated AFB_1, but the GST-catalyzed conjugation of glutathione to AFB_1-8,9-epoxides is thought to play the most important role in preventing epoxide binding to target macromolecules (Eaton and Gallagher, 1994). The glutathione-aflatoxin conjugate is transported from the cells with an ATP-dependent multidrug-resistance protein (Loe *et al*., 1997). Despite a preference for conjugating the more mutagenic AFB_1 exo-epoxide isomer, the relatively low capacity for GST-catalyzed detoxification of bio-activated AFB_1 in the lung may be an important factor in the susceptibility of the lung to AFB_1 toxicity (Stewart *et al*., 1996).

OCHRATOXIN

Ochratoxin A (OTA) is produced by several *Aspergillus* and *Penicillium* moulds. In a study by Dwiwedi *et al*. (2004), OTA from *A. ochraceus* was given via gastric intubation to rabbit does from 6 to 18 d of gestation at levels of 0.025, 0.05 and 0.1 mg/kg BW, respectively. Teratogenic effects were found among the 0.1 mg/kg dose group in the form of a significant increase in the incidence of gross anomalies (wrist drop, rudimentary tail, knuckling of fetlock and agenesis of tail), skeletal anomalies (agenesis of caudal vertebrae, incomplete ossification of skull bones and wavy ribs), and soft tissue anomalies (internal hydrocephalus, microphthalmia and kidney agenesis). The same embryo development abnormalities

were observed by Wangikar *et al*. (2005a). The number of live foetuses in the 0.1 mg/kg dose group was significantly lower than those of the 0.025 mg/kg dose group. The mean foetal weights and mean foetal crown to rump lengths of the 0.1 mg/kg OTA group were significantly lower than the 0.025 mg/kg dose group (Dwiwedi *et al*., 2004).

OTA is effectively transferred from the blood to the milk of lactating rabbit does and subsequently it is also possible for their kits to be exposed if the lactating rabbit does are fed a naturally-contaminated diet throughout the lactation period. Approximately 99% of absorbed OTA is bound to plasma proteins (Chu, 1974). However, the highest concentrations of OTA accumulated in rabbit does were found in the kidney followed by the liver, mammary gland and muscle. A linear relationship was found between the OTA concentrations in milk and in the plasma of the suckling kits with a ratio of 1 mg/L plasma/0.015 mg/L milk (*P<0.05*), indicating an effective transfer of the toxin (Ferrufino-Guardia *et al*., 2000). OTA is also extremely cytotoxic and may cause red blood cell haemolysis in rabbits (Zofair *et al*., 1996). In OTA-induced nephrotoxicity, the proximal tubuli of the kidney is the primary site targeted (Suzuki *et al*., 1975). The basolateral membrane organic anion transport pathway is involved in OTA accumulation in the proximal tubular cells, as was found *in vitro* (Groves *et al*., 1998). The excretion of OTA represents a substantial avenue for the removal of this mycotoxin from systemic circulation (Groves *et al*., 1999).

CITRININ

Citrinin was originally isolated from *Penicillium citrinum*, but has been found to be produced by a variety of other moulds, such as other *Penicillium* and *Aspergillus* species. Citrinin acts as a nephrotoxin in all farm animal species, including rabbits, but its acute toxicity varies (Bennett and Klich, 2003). The 72 h LD_{50} of citrinin was 50 mg/kg BW by intraperitoneal administration and 134 mg/kg BW by the oral route (Hanika *et al*., 1983). Citrinin induces mitochondrial permeability pore opening (Da Lozzo *et al*., 1998) and inhibits respiration by interfering with complex I of the respiratory chain (Chagas *et al*., 1995). In the experiment carried out by Hanika *et al*. (1984), a single oral dose of citrinin was given by oesophageal tube at dose levels of 20, 80 or 100 mg/kg BW. The highest dose caused azotaemia and metabolic acidosis with haemo-concentration and hypokalaemia within one day, whereas the effect of the two lower doses caused blood urea nitrogen and serum-creatinine levels to increase and creatinine clearance to decrease, indicating renal failure. Urine analysis indicated tubular dysfunction and necrosis with glucosuria, isosthenuria and cylindruria. Another possible consequence of a low dose of citrinin toxicosis is the impairment of rabbits' reproductive performance in both genders as discovered by Ajayi *et al*. (2005).

PATULIN

Patulin is produced by a variety of moulds, particularly *Aspergillus* and *Penicillium spp*. It is commonly found in mouldy high moisture corn (Tapia *et al*., 2005). The effects of sublethal doses of patulin on the immune system were investigated in rabbits (Escuola *et al*., 1988). They found significant suppression of peritoneal leucocytes and mitogenic response as induced by phorbol myristyl acetate, concanavalin A and, in particular, pokeweed mitogen. These effects were parallel to decreasing serum immunoglobulin levels.

FUSARIUM MYCOTOXINS

Fusarium fungi are commonly found and their mycotoxins are probably the most economically significant grain mycotoxins on a global basis (Wood, 1992). *Fusarium* mycotoxins are a group of chemically diverse mycotoxins which include trichothecenes such as T-2 toxin, HT-2 toxin, diacetoxyscirpenol (DAS), monoacetoxy-scirpenol (MAS) and deoxynivalenol (DON), in addition to fumonisins, moniliformin, zearalenone (ZEN), fusaric acid, and verrucarin A (De Nus *et al*., 1996). The effects of *Fusarium* mycotoxins are varied and include the inhibition of protein synthesis (trichotecenes), sphingolipid

biosynthesis (fumonisins) and estrogenic effects (zearalenone). Clinical signs of *Fusarium* mycotoxicosis often remain unclear because of their immune-suppressive effect, particularly trichothecenes, which may cause decreased resistance to infectious diseases (Ueno, 1973).

Trichothecenes

Trichothecene mycotoxins are mainly produced by *Fusarium* moulds in fields and cause intoxication through consuming contaminated cereal crops in the compound feed (Placinta *et al*., 1999). Over 150 different, but structurally related, trichothecenes have been chemically identified. However, most of the toxicological data is derived from a few trichothecenes, primarily T-2 toxin and DON. Most of the trichothecenes cause severe toxicosis in rabbits, with relatively low LD_{50} values, as shown in Table 2 (Wannemacher and Wiener, 1997).

Most of the trichothecenes are partially metabolised by the microsomal xenobiotic transforming enzyme system. For instance, microsomal non-specific carboxyesterase produces C-4 acetyl residues of DAS, T-2 toxin, fusarenon-X and diacetylnivalenol (Ohta *et al*., 1978). As a result of the metabolism of trichothecenes mainly in the liver, their accumulation in rabbit meat is moderate or negligible. The rate of metabolism of trichothecenes, e.g. T-2 toxin, depends on the duration of exposure and decreases over a long period of time (Ványi *et al*., 1989). T-2 toxin causes lipid peroxidation in liver microsomes (Guerre *et al*., 2000), which also impairs the extent and/or activity of xenobiotic transformation (Mézes *et al*., 1996). Guerre *et al*. (2000) found that a daily dose of 0.25 mg/kg BW of T-2 toxin resulted in decreased monooxygenase activity in rabbit livers. At a lower daily dose of T-2 toxin (0.1 mg/kg BW), no significant effects on drug metabolizing enzymes or any microsomal oxidative damage were observed. Some nutritional effects such as a deficiency or excess of some fat-soluble vitamins, namely vitamins A and E (Tutelyan and Kravchenko, 1988), increased the toxic effects of trichothecenes by impairing the activity of the xenobiotic transforming enzyme system.

Trichothecenes inhibit cellular protein synthesis, a property which is probably the cause of many of the symptoms associated with trichothecene toxicosis. For instance, T-2 toxicosis results in hyper-aminoacidemia (Wannemacher and Dinterman, 1983) due to the inhibition of hepatic protein synthesis (Meloche and Smith, 1995). Subsequent elevations in blood tryptophan levels can result in increased concentrations of tryptophan in the brain. Tryptophan is the precursor of the neurotransmitter serotonin and the serotoninergic neurons are thought to be important mediators of behaviour such as appetite, muscle coordination and sleep. Serotonin synthesis in the brain is poorly regulated and can be promoted by increased concentrations of tryptophan (Leathwood, 1987). An increased amount of brain serotonin is thought to cause loss of appetite and sleepiness.

At a single oral dose of 4 mg/kg BW, T-2 toxin was lethal for rabbits within 48 hours and this dose was proposed as the LD_{50} value for rabbits (Glávits *et al*., 1989). Faecal, caecotroph and urine toxin concentrations were related to toxin consumption (Fekete *et al*., 1989a). It has been suggested that the high toxin level of the caecotroph may play a role in the high sensitivity of rabbits, and that animals consume the toxin-containing caecotroph (Fekete *et al*., 1989b) because of coprophagy.

Table 2: Relative acute toxicity of the most abundant trichothecene mycotoxins in rabbits.

Trichothecene mycotoxin	Route of administration	LD_{50} (mg/kg BW)
T-2 toxin	Intramuscular	1.1
T-2 toxin	Dermal (in dimethylsulfoxide)	10.0
4,15-diacetoxyscirpenol	Intravenous	1.0
Verrucarin A	Intravenous	0.54

The main toxic effect of T-2 toxin is the inhibition of protein synthesis which was proven by Ueno *et al*. (1973) when rabbit reticulocytes were treated with low concentrations of T-2 toxin and marked degradation of polyribosomes was observed. Feed containing sublethal amounts of T-2 toxin (12.5 and 25 mg/kg feed) caused emaciation, subacute catarrhal gastritis, necrosis of the lymphoid cells of the intestinal mucosa, depletion and necrosis in the lymphoid follicles of the ampulla ilei, spleen and lymph nodes (Fekete *et al*., 1989a). Niyo *et al*. (1988) described leukopenia, marginal anaemia, and an increased number of morphologic changes in nucleated erythrocytes followed by a regenerative haematological response, centrilobular hepatocellular swelling portal and periportal fibrosis as effects of T-2 toxicosis. Necrosis of lymphocytes, cells of the mononuclear phagocyte system, and myeloid haemocytogenesis were characteristic among most rabbits treated with T-2 toxin (Niyo *et al*., 1988; Glávits *et al*., 1989). T-2 toxin and its metabolites also decrease the spermiogenesis and libido in bucks, possibly because the conversion of pregnenolone to testosterone (Fenske and Fink-Gremmels, 1990) is inhibited.

The effects of dermal exposure to T-2 mycotoxin showed moderate oedema and erythema at the site of exposition in two hours. Cutaneous injury may be due to ischemia caused by microcirculatory failure (Yarom *et al*., 1987). DAS, T-2 toxin, HT-2 toxin and fusarenon-X were tested for dermatotoxicity in rabbits, as manifested by the induction of allopecia. The greatest toxicity was shown by DAS and T-2 toxin (Leonov *et al*., 1990).

The toxic effects of deoxynivalenol (DON) or vomitoxin are rarely observed in rabbits. However, rabbit producers have usually been concerned with higher than normal deaths due to diarrhoea in rabbits. The DON levels of commercial diets, particularly those that contain more than 1 mg/kg DON have been blamed by some rabbit producers for this problem. The effects of DON on gastric emptying, intestinal propulsion and bloating in mice and rats and gastrointestinal myoelectrical activity in rats have been described by Fioramonti *et al*. (1993). Gastric emptying and intestinal transit were evaluated after force feeding DON (0.05 to 1 mg/kg BW). DON was found to inhibit gastric emptying according to the dose, and intestinal propulsion was reduced only at the highest dose (1 mg/kg).

Pregnant does fed a DON-contaminated diet (0.3 and 0.6 mg/kg) showed marked weight loss, but no teratogenic effect was found (Khera *et al*., 1986). In an *in vitro* erythrocyte model system, extremely high doses of DON (130 mg/mL) caused haemolysis (Rizzo *et al*., 1992), but that effect was not proven *in vivo* at naturally occurring contamination levels (0.5 to 3.0 mg/kg feed).

Zearalenone

Like the trichothecenes, zearalenone (ZEN) is produced by *Fusarium* fungi, but it is chemically unrelated (Koch, 1981) and it has estrogenic properties in monogastrics (Sundlof and Strickland, 1986) and ruminants (Roine *et al*., 1971). ZEN toxicity is more readily recognized than trichothecenes, because the symptoms are more specific. Even though there is limited data regarding the estogen-like effect of ZEN on rabbits, symptoms of ZEN toxicosis in ruminants such as heifers, cows and ewes are low conception rates, poor fertility, vaginitis and vaginal secretions (Coppock *et al*., 1990, Smith *et al*., 1995).

The effects of low (10 mg/kg BW) and high (100 mg/kg BW) oral doses of purified ZEN were studied by Čonková *et al*. (2001) in rabbits. Low ZEN doses resulted in a significant increase in ALP activity, while high ZEN doses showed significant increases of AST, ALT, AP, GGT, and LDH activity, indicating possible liver toxicity due to the chronic effects of the toxin.

In rabbit bucks, ZEN impairs spermatogenesis and decreases libido, although only at high doses (117.3 mg/kg feed) (Fenske and Fink-Gremmels, 1990).

Pompa *et al*. (1986) found that in the presence of NADH, ZEN at dose levels of 0.1, 1 and 2 mg/kg BW enhanced the reducing activity of the microsomal fraction of the liver. Furthermore, it was observed that hepatocytes mainly produced α-zearalenol, the more uterotrophic metabolite.

Fumonisins

Fumonisins are a family of mycotoxins that were first isolated from cultures of *Fusarium verticillioides* (Gelderblom *et al*., 1988), followed shortly thereafter by elucidation of the structures of the prevalent isoforms fumonisin B_1 (FB_1) and B_2 (FB_2) (Bezuidenhout *et al*., 1988). It has been shown that the biochemical mode of action of the fumonisins is due to their chemical structure, which is related to sphingosine. They act as inhibitors of sphingolipid biosynthesis by inhibiting the enzyme sphingosine N-acetyltransferase (Wang *et al*., 1991) in most livestock species, including rabbits.

FB_1 was found to be nephrotoxic and hepatotoxic in rabbits (Gumprecht *et al*., 1995), and it has also been shown to exert deleterious effects on the haematopoietic organs (Mariscal-Quintanar *et al*., 1997). Histological examinations of the liver showed centrolobular lipid infiltration and discrete cell necrosis, while nephrosis of the proximal tubuli was observed in the kidney. The effect of FB_1 on rabbit kidney cells was investigated *in vitro* and found to be cytotoxic and genotoxic (Rumora *et al*., 2002). Lung oedema was found only in a small number of rabbits fed a FB_1-contaminated diet (Orova, 2003). The teratogenic effect of FB_1 was also described using an oral dose of 300 mg/d for 14 d (Kovács *et al*., 2003) but a lack of embryotoxicity was found at lower (0.1, 0.5 or 1.00 mg/d) oral doses (LaBorde *et al*., 1997). In addition, changes of water distribution in the brain and lung of embryos in pregnant rabbit does fed the FB_1-contaminated diet were investigated using magnetic resonance spectroscopy by Orova (2003) and significant changes were found in both tissues as a consequence of FB_1 toxicosis even during intrauterine development.

In rabbit bucks, FB_1 (24.6 mg/kg feed) had no significant effect on testicular histometry. However, the weight distribution in the epididymides of the experimental animals demonstrated that the caput and caudal segments were significantly depressed in rabbits which were fed the highly contaminated diet. Results suggest that FB_1 may provide some degenerations in the caput and caudal segments of the epididymides (Ogunlade *et al*., 2006).

Moniliformin

Moniliformin is mainly produced by *Fusarium moniliforme*. It acts as an inhibitor of the tricarboxylic acid cycle in intermediary metabolism. No data has been reported on moniliformin toxicosis in rabbits, which might be due to its rare occurrence and low concentrations in feed (Thiel *et al*., 1986).

Fusaric acid

Fusaric acid is produced by several *Fusarium* species and may act synergistically with the trichothecenes to reduce feed intake and cause lethargy in sensitive species (Smith, 1992), but there is no data available on rabbits. *In vitro* studies support the concept of a toxicological synergism between fusaric acid and the trichothecenes (Dowd, 1988), and Bacon *et al*. (1995) reported an interaction between fusaric acid and fumonisin B1. In contrast, an *in vivo* trial with rats did not prove the synergism between fusaric acid and fumonisin B1 (Voss *et al*., 1999).

REFERENCES

Abdelhamid A.M., Ragab M.A., El-Shaieb A.F. 2002. The use of tafla or aluminosilicate for alleviating toxic effects of aflatoxin-contaminated diets of growing rabbits. *In Proc.: 1st Conf. Animal & Fish Production, Mansoura, Egypt, July, pp. 389-413.*

Ajayi F.O., Balogun O.O., Ovuru S.S., Mgbere O.O. 2005. Reproductive performance of rabbits fed maize-milling waste based diets. *Afr. J. Biotechnol., 4: 439-443.*

Aziz N.H., El-Aziz A.M.A., Omran R.M.A. 1995. Effects of T-2 mycotoxin on histopathological changes in rabbits. *Biomed. Lett., 51: 271- 281.*

Bacon C.W., Porter J. K., Norred W.P. 1995. Toxic interaction of fumonisin B1 and fusaric acid measured by injection into fertile chicken egg. *Mycopathologia, 129: 29-34.*

Bennett J.W., Klich M. 2003. Mycotoxins. *Clin. Microbiol. Rev., 16: 497-516.*

Bezuidenhout S.C., Gelderblom W.C.A., Gorst-Allman C.P., Horak R.M., Marasas W.F.O., Spiteller G. Vleggaar R. 1988. Structure elucidation of the fumonisins, mycotoxins from *Fusarium moniliforme. J. Chem. Soc. Chem. Commun., 1988: 743-745.*

Cannon M., Cranston W.I., Hellon R.F., Townsend Y. 1982. Inhibition, by trichothecene antibiotics, of brain protein synthesis and fever in rabbits. *J. Physiol., 322: 447-455.*

Cardona T.D., LLangantileke S.G., Noomhorm A. 1991. Aflatoxin research on grain in Asia: its problems and possible solutions. *In: Semple, R.L., Frio, A.S., Hicks, P.A., Lozare, J.V. (ed.) Mycotoxin prevention and control in foodgrains. FAO, Bangkok, pp. 309-322.*

Chagas G.M., Oliveira M.B., Campello A.P., Klüppel M.L. 1995. Mechanism of citrinin-induced dysfunction of mitochondria. III. Effects on renal cortical and liver mitochondrial swelling. *J. Appl. Toxicol., 15: 91-95.*

Cheeke P.R. 1986. Potentials of rabbit production in tropical and subtropical agricultural systems. *J. Anim. Sci., 63: 1581-1586.*

Chu F.S. 1974. A comparative study of the interaction of ochratoxins with bovine serum albumin. *Biochem. Pharmacol., 23: 1105-1113.*

Coppock R.W., Mostrom M.S., Sparling C.G., Jacobsen B., Ross S.C. 1990. Apparent zearalenone intoxication in a dairy herd from feeding spoiled acid-treated corn. *Vet. Hum. Toxicol., 32: 246-251.*

Coulombe R.A.Jr., Wilson D.W., Hsieh D.P.H., Plopper C.G., Serabjit-Singh C.J. 1986. Metabolism of aflatoxin B$_1$ in the upper airways of the rabbit: role of the nonciliated tracheal epithelial cell. *Cancer Res., 46: 4091-4096.*

Čonková E., Laciaková A., Pástorová B., Seidel H., Kováč G. 2001. The effect of zearalenone on some enzymatic parameters in rabbits. *Toxicol. Lett., 121: 145-149.*

Dalcero A., Magnoli C., Hallak C., Chiacchiera S.M., Palacio G., Rosa C.A.R. 2002. Detection of ochratoxin A in animal feeds and capacity to produce this mycotoxin by *Aspergillus* section Nigri in Argentina. *Food Addit. Contam., 19: 1065-1072.*

Da Lozzo E.J., Oliveira M.B., Carnieri E.G. 1998. Citrinin-induced mitochondrial permeability transition. *J. Biochem. Mol. Toxicol., 12: 291-297.*

Daniels J.M., Liu L., Stewart R.K., Massey T.E. 1990. Biotransformation of aflatoxin B$_1$ in rabbit lung and liver microsomes. *Carcinogenesis, 11: 823-827.*

Daniels J.M., Matula T.I., Massey T.E. 1993. DNA binding and mutagenicity of aflatoxin B$_1$ catalyzed by isolated rabbit lung cells. *Carcinogenesis, 14: 1429-1434.*

De Nus M., Rombouts F., Notermans S. 1996. *Fusarium* molds and their mycotoxins. *J. Food Safety, 16: 15-58.*

Dowd P.F. 1988. Toxicological and biochemical interactions of the fungal metabolites fusaric acid and kojic acid with xenobiotics in Heliothis zea and Spodoptera frugiperda. *Pestic. Biochem. Physiol., 32: 123-131.*

Dwivedi P., Wangikar P.B., Sinha N. 2004. Teratogenic effects of ochratoxin A in rabbits. *World Rabbit Sci., 12: 159-171.*

Eaton D.L., Gallagher E.P. 1994. Mechanisms of aflatoxin carcinogenesis. *Annu. Rev. Pharmacol. Toxicol., 34: 135-172.*

Escuola L., Thomsen M., Bourdiol D., Pipy B., Peuriere S., Roubinet F. 1988. Patulin immunotoxicology: Effect on phagocyte activation

and the cellular and humoral immune system of mice and rabbits. *Int. J. Immunopharmacol., 10: 983-989.*

Essigmann J.M., Croy R.G., Bennett R.A., Wogan G.N. 1982. Metabolic activation of aflatoxin B$_1$: Patterns of DNA adduct formation, removal and excretion in relation to carcinogenesis. *Drug Metab. Rev., 13: 581-602.*

Europena Commission. 2003. Commission directive 2003/100/EC of 31 October 2003 amending Annex I to Directive 2002/32/EC of the European Parliament and of the Council on undesirable substances in animal feed. *No. 2003/100/EC, 31 October 2003. Off. J. Eur. Comm., 1 November 2003, L 285, 33-37.*

European Commission. 2006. Commission Recommendation of 17 August 2006 on the presence of deoxynivalenol, zearalenone, ochratoxin A, T-2 and HT-2 and fumonisins in products intended for animal feeding. *No. 2006/576/EC, 17 August 2006. Off. J. Eur. Comm., 23 August 2006, L 229, 7-9.*

Fairhurst S., Maxwell S.A., Seawin J.W., Swanston D.W. 1987. Skin effects of trichothecenes and their amelioration by decontamination. *Toxicology, 46: 307-319.*

Fekete S., Tamás J., Ványi A., Glávits R., Bata A. 1989a. Effect of T-2 toxin on feed intake, digestion and pathology of rabbits. *Lab. Anim. Sci., 39: 603-606.*

Fekete S., Tamás J., Ványi A., Glávits R., Bata A. 1989b. Effect of T-2 toxin fed in sublethal quantity on digestion in the rabbit. *Magy. Allatorv. Lapja., 44: 739-740.*

Fekete S., Huszenica G., Szilágyi M., Albert M., Szilágyi A.1992. Effect of long-term feeding of sublethal quantities of T-2 toxin upon the ovarian activity of the rabbit. *J. Appl. Rabbit Res., 15: 583-593.*

Fenske M., Fink-Gremmels J. 1990. Effects of fungal metabolites on testosterone secretion *in vitro. Arch. Toxicol., 64: 72-75.*

Ferrufino-Guardia E.V., Tangni E.K., Larondelle Y., Ponchaut S. 2000. Transfer of ochratoxin A during lactation: exposure of suckling via the milk of rabbit does fed a naturally-contaminated feed. *Food Addit. Contam., 17: 167-175.*

Fioramonti J., Dupuy C., Dupuy J., Bueno L. 1993. The mycotoxin, deoxynivalenol, delays gastric emptying through serotonin-3 receptors in rodents. *J. Pharmacol. Exp. Ther., 266 : 1255-1260.*

Gabal M.A., Awad Y.L., Morcos M.B., Barakat A.M., Malik G. 1986. Fusariotoxicoses of farm animals and mycotoxic leucoencephalomalacia of the equine associated with the finding of trichothecenes in feedstuffs. *Vet. Hum. Toxicol., 28: 207-212.*

Gelderblom W.C.A., Jaskiewicz K., Marasas W.F.O., Thiel P.G., Horak M.J., Vleggaar R., Kriek N.P.J. 1988. Fumonisins - novel mycotoxins with cancer promoting activity produced by *Fusarium moniliforme. Appl. Environ. Microbiol., 54: 1806-1811.*

Glávits R., Ványi A., Fekete S., Tamás J. 1989. Acute toxicological experiment of T-2 toxin in rabbits. *Acta Vet. Hung., 37: 75-79.*

Groves C.E., Morales M.N., Wright S.H. 1998. Peritubular transport of ochratoxin A in rabbit renal proximal tubules. *J. Pharmacol. Exp. Ther., 284: 943 -948.*

Groves C.E., Nowak G., Morales M. 1999. Ochratoxin A secretion in primary cultures of rabbit renal proximal tubule cells. *Am. Soc. Nephrol., 10: 13-20.*

Guerre P., Burgat V., Galtier P. 1997. Dose-related increase in liver heme catabolism during rabbit aflatoxicosis. *Toxicol. Lett., 92: 101-108.*

Guerre P., Eeckhoutte C., Burgat V., Galtier P. 2000. The effects of T-2 toxin exposure on liver drug metabolizing enzymes in rabbit. *Food Addit. Contam., 17: 1019 – 1026.*

Gumprecht L.A., Marcucci A., Weigel R.M., Vesonder R.F., Riley R.T., Showker J.L., Beasley V.R., Haschek W.M. 1995. Effects of intravenous fumonisin B1 in rabbits: Nephrotoxicity and sphingolipid alterations. *Nat. Toxins, 3: 395-403.*

Hanika C, Carlton W.W., Tuite J. 1983. Citrinin mycotoxicosis in the rabbit. *Food Chem Toxicol., 21: 487- 493.*

Hanika C., Carlton W.W., Boon G.D., Tuite J. 1984. Citrinin mycotoxicosis in the rabbit: Clinicopathological alterations. *Food Chem. Toxicol., 22: 999-1008.*

Houssein H.S., Brasel J.M. 2001. Toxicity, metabolism and impact of

mycotoxins in humans and animals. *Toxicology, 167: 101-134.*

Khera K.S., Whalen C., Angers G. 1986. A teratology study on vomitoxin (4-deoxynivalenol) in rabbits. *Food Chem. Toxicol., 24: 421-424.*

Koch H. 1981. Leitfaden der Medizinischen Mykologie. *3. Auflage. VEB Gustav Fischer Verlag, Jena, pp. 150.*

Kovács M., Romvári R., Orova Z., Kovács F., Horn P. 2003. Investigations on the foetotoxic effect of fumonisin B₁ in pig and rabbit. *Acta Agr. Kaposváriensis, 7: 9-17.*

Kumar M., Dwivedi P., Sharma A.K., Telang A.G., Patil R.D., Singh N.D. 2008. Immunotoxicity of ochratoxin and citrinin in New Zealand White rabbits. *World Rabbit Sci., 16: 7-12.*

LaBorde J.B., Terry K.K., Howard P.C., Chen J.J., Collins T.F.X., Shackeford, M.E., Hansen, D.K. 1997. Lack of embryotoxicity of fuminisin B1 in New Zealand white rabbits. *Fundam. Appl. Toxicol., 40: 120-128.*

Lakkawar A.W., Chattopadhyay S.K., Johri T.S. 2004. Experimental aflatoxin B1 toxicosis in young rabbits – A clinical and patho-anatomical study. *Slov. Vet. Res., 41: 73-81.*

Larsson P., Tjälve H. 2000. Intranasal instillation of aflatoxin B₁ in rats: Bioactivation in the nasal mucosa and neuronal transport to the olfactory bulb. *Toxicol. Sci., 55: 383-391.*

Leathwood P.D. 1987. Tryptophan availability and serotonin synthesis. *Proc. Nutr. Soc., 46: 143-146.*

Leonov A.N., Zotova E.V., Soboleva N.A., Kononenko G.P. 1990. Dermatotoxic activity of structurally related trichothecenes from *Fusarium* fungi. *Dokl. Vsesoyuznoi Ordena Lenina i Ordena Trudovogo Krasnogo Znameni Akademii Sel'skokhozyaistvennykh Nauk imeni V.I. Lenina, No.2: 52-55.*

Loe D.W., Stewart R.K., Massey T.E., Deeley R.G., Cole S.P. 1997. ATP-dependent transport of aflatoxin B1 and its glutathione conjugates by the product of the multidrug resistance protein (MRP) gene. *Mol. Pharmacol., 51: 1034-1041.*

Makkar H.P.S., Singh B. 1991. Aflatoxicosis in rabbits. *J. Appl. Rabbit Res., 14: 218-221.*

Mariscal-Quintanar M.G., Garcia-Escamilla R.M., Garcia-Escamilla N., Torres-Lopez J., Bautista-Ordonez J.A., Rosiles-Martinez R. 1997. Effect of ingesting *Aspergillus* flavus and *Fusarium moniliforme* on the cytology of bone marrow and blood and on serum albumin and globulin concentrations. *Veterinaria Mexico, 28: 75–81.*

Meloche J.L., Smith T.K. 1995. Altered tissue amino acid metabolism in acute T-2 toxicosis. *Proc. Soc. Exper. Biol. Med., 210: 260-266.*

Mézes M., Virág Gy., Barta M, Abouzeid A.D. 1996. Effect of lipid peroxide loading on lipid peroxidation and on the glutathione and cytochrome systems in rabbits. *Acta Vet. Hung., 44: 443-450.*

Mizutani Y., Ito Y., Ohtsubo K. 1997. Inhibition of platelet aggregation *in vitro* by trichothecene mycotoxins. *Mycotoxins, 44: 41-44.*

Mohanamba T., Rao M.R., Habibi S.M.M. 2007. Aflatoxin contamination in animal feeds. *Ind. Vet. J., 84: 416.*

Niyo K. A., Richard J.L., Niyo Y., Tiffany L.H. 1988. Pathologic, hematologic, and serologic changes in rabbits given T-2 mycotoxin orally and exposed to aerosols of *Aspergillus* fumigatus conidia. *Am. J. Vet. Res., 49: 2151-2160.*

Ogunlade J.T., Ewuola E.O., Gbore F.A., Bandyopadhyay R., Niezen J., Egbunike G.N. 2006. Testicular and epididymal sperm reserves of rabbits fed fumonisin contaminated diets. *World Appl. Sci. J., 1: 35-38.*

Ohta M., Matsumoto H., Ishii K., Ueno Y. 1978. Metabolism of trichothecene mycotoxins. II. Substrate specificity of microsomal deacetylation of trichothecenes. *J. Biochem. (Tokyo), 84: 697-706.*

Orova Z. 2003. Investigations on the teratogenic effects of fumonisin B1 in swine and rabbit. *Thesis, University of Kaposvár, Kaposvár, pp. 23.*

Placinta C.M., D'Mello J.P.F., Macdonald A.M.C. 1999. A review of worldwide contamination of cereal grains and animal feed with *Fusarium* mycotoxins. *Anim. Feed Sci. Technol., 78: 21-37.*

Pompa G., Montesissa C., Di Lauro F.M., Fadini L. 1986. The metabolism of zearalenone in subcellular fractions from rabbit and hen hepatocytes and its estrogenic activity in rabbits. *Toxicology, 42: 69-75.*

Richard J.L, Bray G.A., Ryan D.H. 1991. Mycotoxins as immunomodulators in animal systems. Mycotoxins, cancer and health. *Pennington Centre Nutrition Series, Volume 1, pp. 196-22.*

Rizzo A.F., Atroshi F., Hirvi T., Saloniemi H. 1992. The hemolytic activity of deoxynivalenol and T-2 toxin. *Nat. Toxins., 1: 106-110.*

Roine K., Korpinen E.L., Kallela K. 1971. Mycotoxicosis as a probable cause of infertility in dairy cows. *Nord. Vet. Med., 23: 628-632.*

Rumora L., Kovacic S., Rozgaj R., Cepelak I., Pepeljnjak S., Grubisic T.Z. 2002. Cytotoxic and genotoxic effects of fumonisin B₁ on rabbit kidney RK13 cell line. *Arch. Toxicol., 76: 55-61.*

Sahoo P.K., Chattopadhyay S.K., Charan K. 1993. Biochemical alterations in experimentally induced chronic aflatoxicosis in rabbits. *Ind. Vet. J., 70: 909-913.*

Scott P.M. 1990. Trichothecenes in grains. *Cereal Foods World, 35: 661-666.*

Smith T.K. 1992. Recent advances in the understanding of *Fusarium* trichothecene mycotoxicoses. *J. Anim. Sci., 70: 3989-3993.*

Smith J., Wesselink C., Parr J., Sprosen J.M., Fowke E.A., Towers N.R., Laboyrie D. 1995. Effect of zearalenone on ewe pregnancy rates. *In: Toxicology and Food Safety. Toxicology and Food Safety Research Group, Ruakura Research Centre, Hamilton, pp. 123.*

Sundlof S.F., Strickland C. 1986. Zearalenone and zeranol: potential residue problems in livestock. *Vet Hum Toxicol., 28: 242-250.*

Stewart R.K., Serabjit-Singh C.J., Massey T.E. 1996. Glutathione S-transferase-catalyzed conjugation of bioactivated aflatoxin B₁ in rabbit lung and liver. *Toxicol. Appl. Pharmacol., 140: 499-507.*

Suzuki S., Kozuka Y., Satoh T., Yamazaki M. 1975. Studies on the nephrotoxicity of ochratoxin A in rats. *Toxicol. Appl. Pharmacol., 34: 479-490.*

Szilágyi M., Fekete S., Huszenicza Gy., Albert M. 1994. Biochemical and physiological effects of long-term sublethal T-2 toxin feeding in rabbits. *Acta Biol. Hung., 45: 69-76.*

Tapia M., Stern M., Soraci A., Meronuck R., Olson W., Gold S., Koski-Hulbert R., Murphy M. 2005. Patulin-producing molds in corn silage and high moisture corn and effects of patulin on fermentation by ruminal microbes in continuous culture. *Anim. Feed Sci. Technol., 119: 247-258.*

Thiel P.G., Gelderbloom W.C.A., Marasas W.F.O., Nelson P.E., Wilson T.M. 1986. Natural occurrence of moniliformin and fusarin C in corn screenings known to be hepatocarcinogenic in rats. *J. Agr. Food Chem., 34: 773-781.*

Tutelyan V.A., Kravchenko L.V. 1988. Nutrition effects on T-2 toxin toxicity. *Proc. Jpn. Assoc. Mycotoxicol., Suppl. 1: 107-108.*

Ueno Y., Nakajima M., Sakai K., Ishii K., Sato N., Shimada N. 1973. Comparative toxicology of trichothec mycotoxins: Inhibition of protein synthesis in animal cells. *J. Biochem., 74: 285-296.*

Ványi A., Glávits R., Bata A., Fekete S., Tamás J. 1989. The pathological effects, metabolism and excretion of T-2 toxin in rabbits. *J. Appl. Rabbit Res., 12: 194-200.*

Verma R.J., Mehta D.N. 1998. Occurrence of hemolytic anemia during aflatoxicosis. *Ind. J. Environ. Toxicol., 8: 5-7.*

Voss K.A., Porter J.K., Bacon C.W., Meredith F.I., Norred W.P. 1999. Fusaric acid and modification of the subchronic toxicity to rats of fumonisins in F. moniliforme culture material. *Food Chem. Toxicol.,37: 853-861.*

Wang E., Norred W.P., Bacon C.W., Riley R.T., Merrill A.H. 1991. Inhibition of sphingolipid biosynthesis by fumonisins: implications for diseases associated with *Fusarium moniliforme*. *J. Biol. Chem., 266: 14486-14492.*

Wangikar, P.B., Dwivedi, P., Sinha, N., Sharma, A.K., Telang A.G. 2005a. Teratogenic effects in rabbits of simultaneous exposure to ochratoxin A and aflatoxin B₁ with special reference to microscopic effects. *Toxicology, 215: 37-47.*

Wangikar P.B., Dwivedi P., Sinha N., Sharma A.K., Telang A.G. 2005b. Effects of aflatoxin B1 on embryo fetal development in rabbits. *Food Chem Toxicol., 43: 607-615.*

Wannemacher R.W., Dinterman R.E. 1983. Plasma amino acid changes in guinea pigs injected with T-2 mycotoxin. *Fed. Proc., 42: 625.*

Wannemacher R.W., Wiener S.L. 1997. Trichothecene mycotoxins. *In: Medical Aspects of Chemical and Biological Wearforce. Textbook of Military Medicine, Burden Institute, Washington, D.C., pp. 721.*

Wood G.E. 1992. Mycotoxins in foods and feeds in the United States. *J. Anim. Sci., 70: 3941-3948.*

Yarom R., Bergmann F., Yagen B. 1987. Cutaneous injury by topical T-2 toxin: Involvement of microvessels and mast cells. *Toxicon, 25: 167-174.*

Zofair S.M., Mathew S., Verma R.J. 1996. Ochratoxin-induced hemolysis in rabbits. *Ind. J. Exp. Biol., 34: 592-593.*