



Mycotoxins in Dairy Feed and its Harmful Impact on Animal Health: Diagnostic Aids and Treatment: A Big Animal Health Challenge

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Abstract

Monitoring the certain health conditions and properly identifying the diseases are the most important steps in getting the high productions from dairy cattle. Mycotoxins are chemicals produced by fungi (molds) under certain conditions, not essential for fungal itself growth or reproduction, having toxic affects to animals and humans. More than 250 mycotoxins have been detected. For many toxins, their toxicological characteristics have not been fully determined until now. There are many kinds of mycotoxins, causing different kinds of mycotoxicoses. Mycotoxins enter into the body, usually by consumption of contaminated feed, do acts on cells causing the mycotoxicoses. Mycotoxicoses are not contagious, nor is there significant stimulation of the immune system. Aflatoxin produced by *Aspergillus flavus* and *Aspergillus parasiticus*, commonly found in corn, milo, cottonseed and peanuts, while its concentrations in grains is very enough to cause acute aflatoxicosis. The five important aflatoxins are aflatoxin B₁, B₂, G₁, G₂, and M₁. Aflatoxin is a liver poison (hepatotoxin) in all species that consume it, however, ruminants tolerate it better than do monogastrics or poultry. It causes liver damage and liver cancer at high doses. Aflatoxin exposure leads to depress the immune system, causes liver damage, liver cancer and abortions. Depression, anorexia, reduced gain or milk production, subnormal body temperature and slow rumen motility are the clinical signs of aflatoxicosis. Ingestion of ergot alkaloids contain in the sclerotia of *Claviceps* spp, commonly found in cereal grains causing Ergot toxicosis, leads to causeagalactia in lactating females. Fumonisin are produced by *Fusarium moniliforme* and *F. proliferatum*, found primarily in white and yellow corn, having three kinds, fumonisins B₁, B₂, and B₃. Equine leukoencephalomalacia (ELE) is a fatal disease of horses and Porcine pulmonary syndrome in swine are caused by fumonisins, through inhibition of enzymes involved in the production of sphingosine (important component of cell membranes for neurons) from sphinganine. Vomitoxin or Deoxynivalenol is produced by *Fusarium roseum* (*F. graminearum*) and *F. moniliforme*. It is commonly found in corn, wheat, barley, milo and rarely found in oats, hay or forages. Vomitoxin is not very toxic, associated with feed refusal and decreased feed consumption leads to affect the animal performance by inhibiting the protein and nucleic acid synthesis. Zearalenone is produced by *Fusarium roseum* (*F. graminearum*) and *F. moniliforme*, found in corn, wheat, barley, milo and occasionally in oats. Zearalenone is a chemical that can act similarly to the female sex hormone estrogen, leads to disrupt the estrus cycle in females, causes infertility and feminization in males, and precocious puberty in sexually immature females. Zearalenone content typically found in grains. Its production become increase due to unusual environmental conditions during the growing season and insufficiently stored dried grain usually having enough adversely effect on animals. Mycotoxins present in the feed/ration can be treated by adopting Modern agricultural practices, giving usually supportive therapy and Antidotes, giving activated charcoal to decrease the ingested

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mycotoxins absorption, using feed additives as mycotoxins binders, removing, stopping and preventing further exposure of contamination to animal feed.

Keywords: Mycotoxins; Aflatoxin; Fumonisin; Deoxynivalenol; Zearalenone; Dairy Feed; Animal Health Challenge

1. Introduction

Mycotoxins are secondary metabolites produced by a wide variety of fungal species that cause nutritional losses and represent a significant hazard to the food chain. Mycotoxins are capable of causing disease and death in both humans and other animals. The term 'mycotoxin' is usually reserved for the toxic chemical products produced by fungi that readily colonize crops. The exposure risk of mycotoxins to human is either directly through foods of plant origin (cereal grains) or indirectly through foods of animal origin (kidney, liver, milk and eggs). Mycotoxins causes a number of illnesses in human and animal such as decrease in food consumption (anorexia), depression or inhibition on immune system function and haematotoxicity [1; 2; 5]. *Aflatoxins* are naturally occurring poisonous carcinogens and mutagens metabolites derived from polyketides produced by different species of toxigenic fungi, which grow in soil, decaying vegetation, hay, and grains, abundantly found in warm and humid regions of the world [4]. *Fusarium* species are probably the most prevalent toxin producing fungi of the northern temperate regions and are commonly found on cereals grown in the temperate regions of America, Europe and Asia. These are common mycotoxins throughout the world, mainly associated with cereal crops, in particular corn, wheat, barley, rye, rice and oats [19]. *Vomitoxin* is called as *vomitoxin* due to its strong emetic effects after consumption, because it is transported into the brain. Its belongs to the trichothecene group of mycotoxins, a strong inhibitors of protein synthesis and is formed by fungi of the genus *Fusarium*. *Vomitoxin* often occurs in many plant products, particularly in cereal crops such as wheat, corn, barley, oats and rice [23]. Zearalenone is a potent estrogenic metabolite produced by some *Fusarium* and *Gibberella* species. The human and livestock exposure to Zearalenone through the diet poses health concern due to the onset of several sexual disorders and alterations in the development of sexual apparatus [5].

1.1. Aflatoxin

It is a kind of typical mold mycotoxin, produced by *Aspergillus flavus* which is related to *Aspergillus oryzae*. This was discovered first time from the mass poisoning of turkeys leads to mass death accident in UK in 1960, having strong carcinogenic and mutagenic characteristics. This mold (producer) is widely distributed in the tropical and subtropical areas, such as Southeast Asia, the US, and Brazil among others, and grows in feed, especially in peanut and cottonseed, causing aflatoxin contamination. Aflatoxins have been reported in many countries and on many spoiled feeds, especially harvested peanuts, peanuts-in-shells on hay, cottonseed meal, sorghum grain, corn, moldy bread, green chop sorghum, and rarely on ears of sweet corn. Currently the Ten-odd isomers of aflatoxin have also been discovered. However, most of these detected isomers in feed contaminated with molds are B1, B2, G1 and G2. M1 is a substance that is detected in the milk of cows which have taken feed contaminated with B1. Codex designates M1 allowance in milk as 0.5 ppb. As far as the physicochemical properties is concern, aflatoxin is a highly fluorescent substance, and B1,B2, M1 and M2 emit blue fluorescence, while G1 and G2 emit green fluorescence [24].

1.1.1. Symptoms of aflatoxicosis for livestock

In acute aflatoxicosis, hepatic jaundice and cirrhosis are clearly detected. Hepatic disorders manifest also in secondary signs such as loss of appetite, reduced growth rate, and many cases also reported with hemorrhagic diarrhea. Reduced lactation is also observed in lactating cows. In pathologic histology studies, fibrosis around the portal vein, proliferation of bile ductless is characteristic signs. Though permissible concentration in combined feed products is 20 ppb; in lactating cows and more sensitive young and weak animals, the permissible concentration in combined feed products (for suckling calves, suckling pigs and first stage broiler chicks) is 10 ppb [1].

1.1.2. Mechanism

Aflatoxins binds to DNA and/or proteins after epoxidation by cytochrome P450, leads to impair their functions. Aflatoxins are reported as having negative impact on the rumen micro flora, but no impact on digestive rate. Aflatoxicosis has severe immunosuppressant characteristics along with disorders of peripheral lymphocyte functions in cattle [12].

1.1.3. Measures for prevention of feed contamination

For the degradation of aflatoxins, several treatment strategies are reported. Among these treatment methods, the use of ultraviolet radiation, heat, oxidizing agents such as hydrogen peroxide, sodium hypochloride, or exposure to alkaline

substances like ammonia, sodium bisulfate and sulfur dioxide gas are the common examples to apply. Among these agents, the use of ammonia is commercially applied in detoxifying cotton seed and corn in the US. However, toxic residues and objectionable changes in the sensory and nutritional quality of decontaminated materials have been occurred. The effects of aflatoxin degradation techniques are still investigated and there is further need for new toxicological figures on the substances that are formed as a result of the degradation treatment [6].

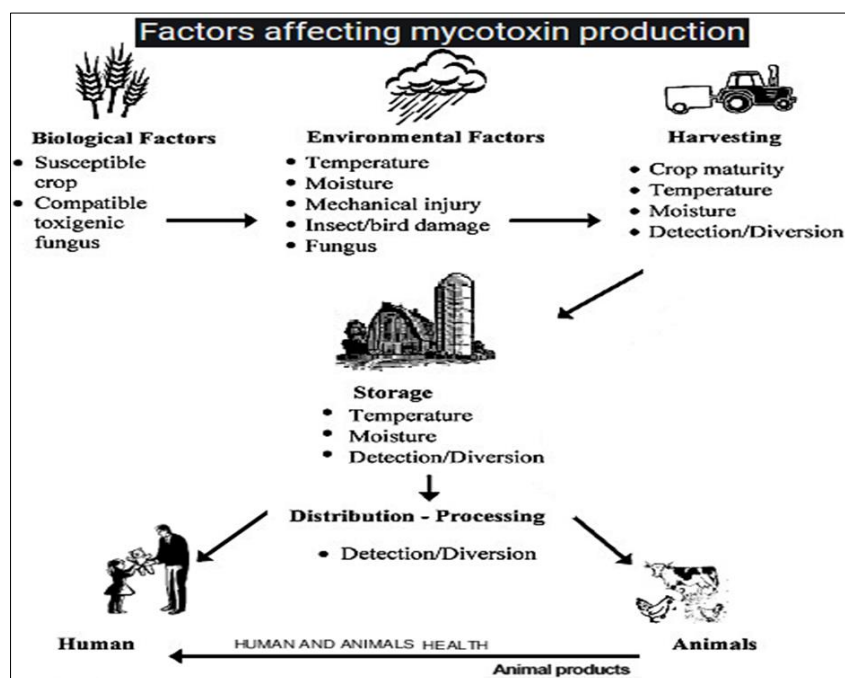


Figure 1 Illustrating the mycotoxins hazard on animal and human body via different animal product

1.1.4. Influences of aflatoxin on food, livestock and on human

The aflatoxicosis disease has a public health importance, because of the toxin is excreted in cow's milk. On the basis of damage to the human health concern about through milk and dairy products, the prevention of the healthy damage is planned by regulation for M1 in the aflatoxin and milk of feed. Aflatoxin is now an important consideration in the etiology of human hepatocellular carcinoma. Aflatoxin M1, a metabolite of aflatoxin B1, is found in the milk of dairy cattle fed on moldy feed. If a mammal such as a dairy cow consumes aflatoxin B1 in the diet, about 1-3% amount of B1 that is consumed will appear in milk as aflatoxin M1. Aflatoxin M1 is stable in raw milk and in processed milk products and is unaffected by pasteurization or processing into cheese and yogurt. This toxin have the ability to induce tumors in experimental animals and the relatively large consumption of milk by children has made in a food contaminant of worldwide of priority concern. On the other hand, meat from animals that have consumed aflatoxin-contaminated feed is of lesser significance, though an outbreak of acute toxicosis in human and dog caused by an intake of the aflatoxin-contaminated corn has been reported in Kenya and India. The ratio of aflatoxin B1 in the dairy to aflatoxin M1 found in milk is reported to be approximately 75:1. The ratio of aflatoxin concentration in feed to that in eggs and the livers of certain animals are determinate to be higher [13; 25].

1.2. Fumonisin

These are phytotoxic mycotoxins which are synthesized by various species of the fungal genus *Fusarium* such as *Fusarium verticillioides* and *Fusarium proliferatum*. *Fusarium* species are probably the most prevalent toxin producing fungi of the northern temperate regions and are commonly found on cereals grown in the temperate regions of America, Europe and Asia. The most important *Fusarium* mycotoxins are fumonisins, TCs such as T-2, HT-2, DON, DAS, FUS-X, NIV, diacetylvalenol, neosolaniol and Zearalenone (ZEA). They are common mycotoxins throughout the world, mainly associated with cereal crops, in particular corn, wheat, barley, rye, rice and oats [21].

Recently, twenty-eight fumonisins have been isolated and they can be divided in four series known as A, B, C and P. The fumonisin toxin as (FB1, FB2 and FB3) are the principal fumonisins analyzed as natural contaminants of cereals. *F. verticillioides* produce several mycotoxins, the most prominent of which is called fumonisin B1 (FB1). The carcinogenic mycotoxin fumonisin B2 was discovered for the first time in *Aspergillus niger*, an industrially important species. FB1 is

the diester of propane-1,2,3-tricarboxylic acid and a pentahydroxyeicosane in which the C14 and C15 hydroxy groups are esterified with the terminal carboxy group of propane-1,2,3-tricarboxylic acid (TCA). FB2 is the C-10-deoxy analogue of FB1 and FB3 is the C-5-deoxy analogue of FB1 [7].

Fumonisin toxins found in food are produced mainly in the field, although some toxin synthesis may occur during storage. Temperature and moisture conditions are crucial factors affecting fungal infection and toxin synthesis. Infection of cereal grains with *Fusarium* species can trigger serious human and animal diseases. *F. verticillioides* was the predominant fungus isolated from moldy corn associated with a field outbreak of equine leukoencephalomalacia (ELEM) in South Africa during 1970 characterized by liquefaction's necrosis in the white matter of the cerebral hemispheres of horses [17]. Fumonisin toxicosis in swine was mentioned porcine pulmonary edema (PPE) after outbreaks of a fatal disease in pigs fed with *F. verticillioides* contaminated corn screenings from the 1989 corn crop in Iowa, Illinois, and Georgia [10]. In addition to corn or corn-based foods and feeds, the occurrence of fumonisins has also been reported in some products such as beans, rice, sorghum, corn, wheat noodles, curry, chili pickle, beer and corn-based brewing adjuncts [11].

1.2.1. Mechanism

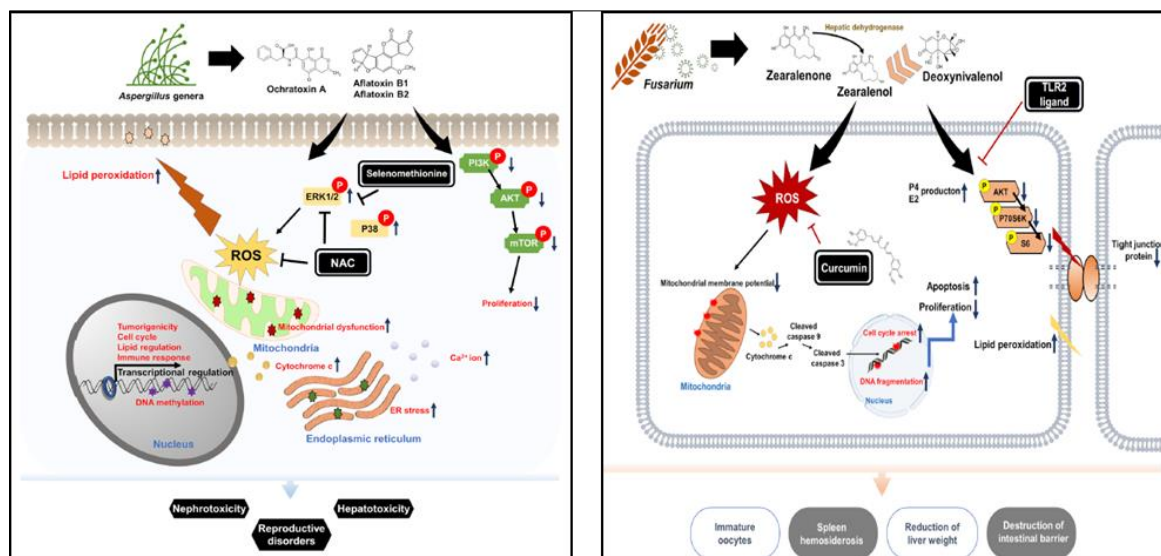
Fumonisin structurally resemble sphingoid bases such as sphingosine. The structural similarity between sphinganine and FB1 suggests that the mechanism of action of this mycotoxin is mainly via disruption of sphingolipid metabolism. This mechanism is reflected in effects on protein kinase activity, on cell growth and differentiation, in cell death (apoptosis), carcinogenicity and involvement of lipid peroxidation. Inhibition of biosynthesis of sphingolipids has been seen at different levels and is reflected in changes of the ratio sphinganine/sphingosine. This ratio may be used as indicators of FB1 exposure, mechanism of action of sphingolipids and their metabolites in the toxicity of FB1. Structurally, fumonisins resemble sphingolipids and can alter sphingolipid biosynthesis suggesting that sphingolipid alterations play an important role in disease and carcinogenesis in DNA damage for FB1 [5; 20].

1.2.2. Toxicity of fumonisins

Fumonisin is known to be the cause of leuko-encephalomalacia in equines and in rabbits, pulmonary edema and hydrothorax in swine, cardiac failure in baboons, atherogenic effects in vervet monkeys, brain haemorrhage in rabbits, renal cancer and hepatocarcinogenic in rats and some birth defects (especially neural tube defects). Fumonisin additionally produce mild to fatal toxicity in liver, kidney and heart in horses, pigs, cattle, sheep, chickens, ducks, rabbits, rats and mice. The effects of cytotoxicity of FB were observed in turkey and in broiler chicks lymphocytes, chick macrophages, in rabbit kidney RK13 cells. Epidemiological evidence indicates a link between human esophageal cancer and ingestion of *Fusarium verticillioides* contaminated corn. FB1, in cereals was associated with the incidence of a high rate of human esophageal cancer in Africa, in northern Italy, in Iran, the Southeastern of the United States and with promotion of primary liver cancer in certain endemic areas of the People's Republic of China. The International Agency for Research on Cancer (IARC) has evaluated the cancer risk of fumonisins to humans and grouped them as group 2B (probably carcinogenic). They are toxic to animals and at least one analogue, FB1, is carcinogenic to rodents. Their effect on human health is unclear. The mechanisms of FB1-induced carcinogenesis are uncertain and the information on FB1 mutagenic properties is limited and controversial. Some reports show that fumonisins have been described some genotoxic effect in mammalian cells *in vitro*, including clastogenic effects, chromosomal aberrations and sister chromatid exchange, or DNA synthesis. In some animal species such as horse, mouse, pig and rat; NOAELs expressed as mg FB1/kg body weight. The recommended maximum levels for fumonisins in corn and corn products intended for human consumption are based on available information on the occurrence of fumonisins, FDA accepted that typical fumonisin levels found in corn and corn products intended for human consumption are much lower than the recommended levels [14].

1.3. Vomitoxin

It is called as Deoxynivalenol (DON) due to its strong emetic effects and its action as a feed refusal factor and it was first characterized and named following its isolation from *Fusarium*-infected barley in Japan. DON is produced by *F. graminearum* and *F. culmorum* among other *Fusarium* species. Both species have different optimum temperatures for growth (25 and 21°C, respectively) and this probably affects geographical distribution. In developed countries where grains are dried to ≤13% moisture content to prevent mold growth, DON is the most important pre-harvest problem. However, it can also be produced during storage in the world where moisture content of stored grains is less rigorously controlled. Concurrent fungal infections with DON production in the field are mainly dependent on weather conditions and are favored by low temperatures and high humidity [22].



Source: Figures adopted from Changwon et al., 2020

Figure 2 A (left side) Physiological functions of aflatoxin B1, aflatoxin B2, and ochratoxin A in animal cells. Aflatoxins and ochratoxin A are mycotoxins produced primarily by fungi of the *Aspergillus* genera. In animal cells, these mycotoxins have mechanism of an increase in the activity of MAP kinases such as ERK1/2 and P38, and they promote oxidative stress. Transcriptomic analysis suggests that these mycotoxins are involve in modulating the various properties such as tumorigenicity, cell cycle control, and lipid regulation. These mycotoxins also inhibit cell proliferation through mitochondrial disruption, induction of ER stress, and inhibition of PI3K/AKT signaling pathways. N-acetyl-L-cysteine and selenomethionine alleviate mycotoxin- induced toxicity. The effects of aflatoxin B1, aflatoxin B2, and ochratoxin A result in nephrotoxicity, hepatotoxicity, and reproductive disorders in farm animals. **B (right side)** Physiological functions of zearalenone and deoxynivalenol in animal cells. Zearalenone and deoxynivalenol are mycotoxins produced by the *Fusarium* species. Zearalenone is metabolized in the liver to form zearalenol, which promotes ROS generation and induces mitochondria-dependent cell death. Deoxynivalenol augments the effects of zearalenol by inhibiting the PI3K/AKT signaling pathway. In intestinal cells, deoxynivalenol induces epithelial barrier destruction by inhibiting tight junction proteins. Curcumin and TLR2 ligands alleviate the toxicity of zearalenone and deoxynivalenol, respectively. Exposure to both zearalenone and deoxynivalenol causes ovarian, splenic, liver, and intestinal dysfunction in farm animals

1.3.1. Mechanism

Vomitoxin is a mycotoxin that commonly contaminates cereal-based foods worldwide. It is detected often at the ppm level. DON is generally found in various cereal crops such as wheat, barley, oats, rye, rice and corn and is produced mainly by two important cereal pathogens: *F. graminearum* Schwabe and *F. culmorum* Sacc., which cause ear rot in maize and head blight in wheat. Natural occurrence of vomitoxin in cereals is certainly prevalent from South America, Canada, China and many countries of Europe have showed contamination levels in excess of 50% in oats, barley, wheat and barley. vomitoxin and either of two mono-acetylated derivatives –3- and -15-acetyl vomitoxin are frequently found together in cereal-based products. Several chemical reagents such as ammonia, calcium hydroxide, chlorine, hydrochloric acid, ozone, sodium bisulfite and sodium hydroxide have the ability to degrade vomitoxin, however, none of them have been applied till now because these chemicals interfere with standard processing of grains and represent health hazards. Vomitoxin is stable under weakly acidic conditions but is unstable under alkaline conditions [16].

1.3.2. Toxicity of vomitoxin

The molecular mode of action of vomitoxin involves disruption of normal cell structure and function by inhibiting protein synthesis via binding to the ribosome and by activating critical cellular kinases involved in signal transduction related to proliferation, differentiation, and apoptosis. The mechanism of these effects has been noticed as an alteration in the serotonergic activity of both the peripherous and central nervous system. At the cellular level, the main toxic effects of vomitoxin are immunosuppressant or immunostimulation depending upon the dose and duration of exposure. Although these effects have been largely characterized in the mouse, several investigations with vomitoxin suggest that immunotoxic effects are also likely in domestic animals. The symptoms of acute toxicity studies in sensitive species include abdominal distress, increased salivation, malaise, diarrhea, emesis and anorexia. In addition to, the most common effects of chronic toxicity studies in experimental animals are decreased weight gain, anorexia, and altered

nutritional efficiency. The main effects of vomitoxin at low dietary doses appear to be decreased growth and anorexia, while higher doses induce vomiting (emesis), immunotoxic effects and changes in brain neurochemicals [9].

In animals, at low dosages of vomitoxin, hematological, clinical and immunological alterations are temporary and decrease as compensatory/adaptation mechanisms are founded. According to the sensitivity between the species, pigs are more sensitive to vomitoxin than mice, poultry, and ruminants, in part because of differences in metabolism of vomitoxin, with males being more sensitive than females. Animal species differ with regard to the absorption, distribution, metabolism, and elimination of vomitoxin. From acute toxicity studies in animals it seems that DON might produce similar effects in humans. *In vivo* vomitoxin suppresses normal immune response to pathogens and concurrently induces autoimmune-like effects which are similar to human immunoglobulin A (IgA) nephropathy. In Asia the sign of illness in humans, such as vomiting, nausea, dizziness and headaches, associated with the consumption of cereals contaminate with vomitoxin. Furthermore, the IARC placed vomitoxin in Group 3, not classifiable as to its carcinogenicity to humans [26].

1.4. Zearalenone

It has been discovered accidentally as the cause of a reproductive disorder in pigs known as vulvovaginitis. It is one of the most common *Fusarium* mycotoxins in the temperate regions of America, Europe and Asia. It is most frequently encountered on corn, but also contaminates other cereals and plant products. Zearalenone (previously known as F-2 toxin) may occur in the form of four hydroxyl derivatives. Zearalenone is a non-steroidal, estrogenic mycotoxin produced by *Fusarium* species. Zearalenone are produced by the fungi *Fusarium* spp. Mycotoxins produced by *Fusarium* spp. are of two general types: 1) the nonestrogenic TCs, including DON, NIV, T-2, and DAS; 2) the mycoestrogens, including ZEA and zearalenol. Zearalenone and some of its metabolites have been shown to competitively bind to estrogen receptors. The relative binding affinities to the rat uterine cytoplasmic receptor for Zearalenone and derivatives are α -zearalenol and β -zearalenol, respectively. The most important characteristic of *Fusarium* species is their ability to synthesize Zearalenone, and its co-occurrence with certain TCs raises important point regarding additive and/or synergism in the etiology of mycotoxicoses in animals [15].

Zearalenone is found, especially, as a contaminant in corn. It may possibly also be occur in oats, barley, wheat and sorghum. However, Zearalenone production is favored by high humidity and low temperatures conditions. It may cooccur with vomitoxin in grains such as wheat, barley, oats and corn and fumonisins in corn. Sometimes Zearalenone may occur as a contaminant co-exist DON. Generally, vomitoxin is found in higher doses than Zearalenone when this occurs [26].

1.4.1. Mechanism

The action way of Zearalenone and its derivatives involves displacement of estradiol from its uterine binding protein, elucidating an estrogenic response.

1.4.2. Toxicity of Zearalenone

It is associated with reproductive problems in specific animals and possibly in humans. *In vivo* studies have shown that Zearalenone is rapidly metabolized in animals and humans. Free and conjugated forms of Zearalenone have been found in the milk of cows under experimental conditions. That high concentrations of the toxin are required to elicit such a response indicates that consumption of contaminated feed by dairy cows would not result in a risk to public health. Zearalenone and some of its metabolites have been shown to competitively bind to estrogen receptors in a number of *in vitro* systems. Bindings to specific receptors have been displayed in uterus, mammary gland, liver and hypothalamus in different species. The contamination of corn with Zearalenone is a threat to animal and public health and seriously reduces the quality of corn products. Fertility problems have been observed in swine and sheep. Any compound with hormonal activity may be genotoxic and/or carcinogenic and there is few case that Zearalenone show both types of activity in some animal species. Zearalenone are transmitted to piglets in sows' milk, causing estrogenism in pigs. The most important effects of Zearalenone primarily include the urogenital system. Swine are the most commonly affected animals. Also, cattle, poultry and laboratory rodents affected. Zearalenone causes changes in the reproductive system of laboratory animals such as mice, rats, guinea-pigs, hamsters, rabbits and domestic animals. Zearalenone may be an important etiologic agent of intoxication in young children or fetuses exposed to this mycotoxin, which results in premature thelarche, pubarche, and breast enlargement. Zearalenone has been evaluated by the International Agency or Research on Cancer in 1993, based on inadequate data and limited evidence Zearalenone has been allocated, together with other *Fusarium* toxins, in group 3 (not classifiable as to their carcinogenicity to humans). Hepatocellular adenomas and pituitary tumors were observed in carcinogenicity in mice. Its use for increasing meat production in cattle is allowed in some countries, such as the USA, and forbidden in others, such as the countries of the European Community. Such

differences in legislation in different parts of the world cause to difficulties in trade between such countries. FDA recommends that animals implanted with this agent must be kept from slaughter for at least 60 days and post implantation were not monitored [18].

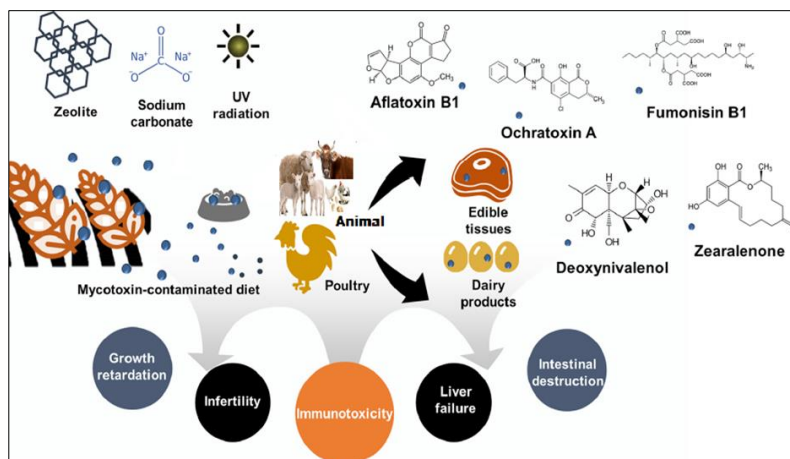


Figure 3 Adopted from Changwon et al., 2020 [4]. Major mycotoxins exerting toxicity in exposed cells derived from farm animals. Aflatoxin B1, ochratoxin A, fumonisin B1, zearalenone, and deoxynivalenol are the most frequently found mycotoxins in the feed of farm animals. Mycotoxins induce either increased apoptosis or decreased proliferation, or both in animal cells. There are various physiological changes that underlie mycotoxin-induced cytotoxicity, including oxidative stress, autophagy, ER stress, and signaling pathways.

1.5. Exposure of Mycotoxin and Monitoring methods to minimize the risk of mycotoxins

Table 1 Summary of different mycotoxins and their physiological functions

Mycotoxin	High Risk Food	EU	Primary Absorption sites	Producing Organism	Chemical Structure	Effects on Mammalian Cells
Aflatoxin (B1, B2, G1, G2, M2)	Grains (Wheat etc)	Total 4 to 15ug/kg AFB1 2 to 12 ug/kg	Duodenum/ Jejunum	Aspergillus	Difurano- coumarin derivatives	Carcinogenic
Aflatoxin M1	Milk	0.05 ug/kg	Duodenum/ Jejunum	Aspergillus	Difuranocoumarin derivatives	Carcinogenic
Fumonisin	Maize & maize-products	1.0 ug/kg	Duodenum/ Jejunum	Fusarium alternaria	Isoflavonoid compounds	Carcinogenic Hepatotoxic
Vomitoxin	Grain (Wheat etc)	500 to 1750 ug/kg	Duodenum/ Jejunum	Fusarium graminearum	type B trichothecene- sesquiterpenes	Emetic & Nephrotoxic
Zearalenone	Grains	20 to 400 ug/kg	Small & large intestine	Fusarium	Phenol resorcylic acid Lactones	Estrogenic activity Potential carcinogenic & teratogenic

Source: Adopted from EU legislation concerning mycotoxins in food and feed

It is important to note that fungi producing mycotoxins have a large possibility to grow on a variety of different crops and foodstuff and can penetrate deep into food and do not just grow on the surface. Exposure to mycotoxins leads to cause immunotoxicity and impair reproductive function in farm animals. In addition, exposure of tissues, such as the

kidneys, liver, and intestines, to mycotoxins can exert histopathological changes that can interfere with animal growth and survival. Mycotoxins have adverse effects in biological activity interfering into regulate signaling pathways, induces the oxidative stress, endoplasmic reticulum stress, apoptosis, and proliferation in porcine and bovine cells. Fungi usually does not grow in properly dried and stored foods, so efficient drying of commodities and maintenance of the dry state, or proper storage, is an effective measure against fungi growth and the production of mycotoxins [15: 19].

2. Conclusion

Mycotoxins are poisonous chemical compounds produced by certain fungi. The fungi that produce mycotoxins in food fall broadly into two groups: those that invade before harvest, commonly called field fungi, and those that occur only after harvest, called storage fungi. The favourable conditions for mycotoxins production are instigated with poor hygienic conditions at the time of transportation and storage, high temperature and moisture content and heavy rains. Mycotoxins are distributed in different items such as animal feeds, cereal crops, leguminous plants and animal products. Aflatoxin, fumonisin, Zearalenone, and vomoxin are thought to be the most threatening to farm animals, are naturally occurring in farm animal feed and frequently identified during monitoring. Moreover, mycotoxins, which accumulate in animal tissues and are present in the blood and milk of livestock, can be a threat to people who consume meat or dairy products. Concentrated animal feed stuffs have chances of highest level of mycotoxins and sorghum assumes as the main source of aflatoxin. Health effects occur in companion animals, livestock, poultry and humans because aflatoxins are potent hepatotoxins, immunosuppressant, and mutagens and carcinogens. Recently, Various chemical and biological methods has been used to minimize the mycotoxin toxicity, however recently the new biological and advanced scientific methods are introducing for mitigation of the mycotoxin toxicity, and through continues research, it is hope to reduce the economic losses experienced by farmers and also resolve the risks to human health.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

References

- [1] Altug T. Introduction toxicology and food, CRC press. 2003.
- [2] Bennett JW, Klich M. Mycotoxins. Clin. Microbiol. Rev. 2003; 16: 497-516.
- [3] Broggi LE, Resnik SL, Pacin AM, González HH, Cano G, Taglieri D. Distribution of fumonisins in dry-milled corn fractions in Argentina. Food Addit. Contam. 2002; 19: 465-469.
- [4] Changwon Yang, Gwonhwa Song, Whasun Lim. Effects of mycotoxin-contaminated feed on farm animals. Journal of Hazardous Materials. 2020; 389: 122087, 1-10.
- [5] Cheng L, Qin Y, Hu X, Ren L, Zhang C, Wang X, Wang W, Zhang Z, Hao J, Guo M, Wu Z, Tian J, An L. Melatonin protects in vitro matured porcine oocytes from toxicity of Aflatoxin B1. J. Pineal Res. 2019; 66: e12543.
- [6] FAO. FAO Food and Nutrition Paper 81. Worldwide Regulations for Mycotoxins in food and feed in 2004. <http://www.fao.org/docrep/007/y5499e/y5499e00.htm>
- [7] FDA. Fumonisin levels in human foods and animal feeds. 2001.
- [8] FDA. Background paper in support of fumonisin levels in corn and corn products intended for human consumption, Available at: <http://www.micotoxinas.com.br/boletim36.pdf>, accessed 9 November 2001.
- [9] Ghareeb K, Awad WA, Zebeli Q, Bohm J. Deoxynivalenol in chicken feed alters the vaccinal immune response and clinical biochemical serum parameters but not the intestinal and carcass characteristics. J. Anim. Physiol. Anim. Nutr. (Berl). 2016; 100: 53–60.
- [10] Haschek WM, Gumprecht LA, Smith G, Tumbleson ME, Constable PD. Fumonisin toxicosis in swine: An overview of porcine pulmonary edema and current perspectives. Environ. Health Perspect. 2001; 109: 251-257.

- [11] Ho JA, Durst RA. Detection of fumonisin B1: Comparison of flow-injection liposome immunoanalysis with high-performance liquid chromatography. *Anal. Biochem.* 2003; 312: 7-13.
- [12] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Human. 1993; 56: 245-395.
- [13] JECFA. Safety evaluation of certain food additives and contaminants. WHO Food Additiv Series. 2001; 40: 1-102.
- [14] Jackson LS, Bullerman LB. Effect of processing on Fusarium mycotoxins. *Adv. Exp. Med. Biol.* 1999; 459: 243-261.
- [15] Lee HJ, Ryu D. Worldwide occurrence of mycotoxins in cereals and cereal-derived food products: public health perspectives of their co-occurrence. *J. Agric. Food Chem.* 2017; 65: 7034–7051.
- [16] Lucke A, Doupovec B, Paulsen P, Zebeli Q, Bohm J. Effects of low to moderate levels of deoxynivalenol on feed and water intake, weight gain, and slaughtering traits of broiler chickens. *Mycotoxin Res.* 2017; 33: 261–271.
- [17] Marasas WFO. Discovery and occurrence of the fumonisins: A historical perspective. *Environ. Health Perspect.* 2001; 109: 239–243.
- [18] Ma R, Zhang L, Liu M, Su YT, Xie WM, Zhang NY, Dai JF, Wang Y, Rajput SA, Qi DS, Karrow NA, Sun LH. Individual and combined occurrence of mycotoxins in feed ingredients and complete feeds in China. *Toxins (Basel)*. 2018; 10.
- [19] Magan N, Aldred D. Post-harvest control strategies: Minimizing mycotoxins in the food chain. *Int. J. Food Microbiol.* 2007; 119: 131–139.
- [20] Omurtag GZ, Yazıcıoglu D, Beyoglu D, Tozan A, Atak G. A review on fumonisin and trichothecene mycotoxins in foods consumed in Turkey. *ARI, ITU-Bulletin.* 2006; 54: 39-45.
- [21] Pestka JJ, Smolinski AT. Deoxynivalenol: Toxicology and potential effects on humans. *J. Environ. Sci. Health B.* 2005; 8: 39-69.
- [22] Pestka JJ, Smolinski AT. Deoxynivalenol: Toxicology and potential effects on humans. *J. Environ. Sci. Health B.* 2005; 8: 39-69.
- [23] Vincelli P, G Parker. Fumonisin, vomitoxin, and other mycotoxins in corn produced by Fusarium fungi. Univ. of Kentucky CES publication ID-121. 2002.
- [24] Williams JH, Phillips TD, Jolly PE, Stiles JK, Jolly CM, Aggarwal D. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. *Am. J. Clin. Nutr.* 2004; 80(5): 1106–22.
- [25] Yin YN, Yan LY, Jiang JH, Ma ZH. Biological control of aflatoxin contamination of crops". *J Zhejiang Univ Sci B.* 2008; 9(10): 787–92.
- [26] Yunus AW, Ghareeb K, Twaruzek M, Grajewski J, Bohm J. Deoxynivalenol as a contaminant of broiler feed: effects on bird performance and response to common vaccines. *Poultry Sci.* 2012; 91: 844–851.