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Synergistic Effects of Fumonisins B1 and B2 in Pigs: A Review

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Abstract: The productivity of swine farming depends on the large amount of nutrients that may contain mycotoxins. This review addresses the main smoke functions in food, its physical-chemical characteristics, metabolization, immunological factors and preventive measures. Fungal contamination can occur during virtually all stages of the development of the plant organism. The clinical results in animals are dependent on the amount of mycotoxins in their organism associated with the mycotoxin type, leading to pulmonary edema, decreased food intake and weight gain, and reduced ability to move. Pulmonary edema caused by fumonisin (FUMO) is the cause of the disease, but the definitive diagnosis is based on the observation of the lesions and the presence of FUMO in the raw materials of the diet. Prevention can be by use of additives as an adsorbent that can decrease or control existing toxins in the identified diet. It is necessary to have a careful assessment of the benefits of the more stringent prevention standards on the contamination of fumes, as well as their economic losses in the food chain.

Key words: Mycotoxins, intoxication, immunosuppressant, swine breeding.

1. Introduction

The presence of mycotoxins in food is described as secondary metabolites produced by fungi during the production process and storage of grains, with the possibility of being toxic to humans, animals and plants [1]. Several species of fungi such as *Aspergillus*, *Fusarium*, *Penicillium*, *Streptomyces* can be found in grains and forage used in food [2].

Several species of fungi may produce the same type of mycotoxin, but a single species of fungus can produce more than one type of toxin [3]. However, the *Fusarium* species are able to synthesize several mycotoxins [4], and to the trichothecene class, zearalenone (ZON) and fumonisins (FUMO) are the ones that most affect health and productivity in animal husbandry. This genus of pathogenic fungi is economically important, causing damage to maize and sorghum crops every year [5].

More than 500 different mycotoxins are known to exhibit large structural differences with different chemical and physico-chemical properties [6]. Among the toxins considered to be at greatest risk to human and animal health are aflatoxins (AFLA), ochratoxin (OTA), ZON, deoxynivalenol (DON) and FUMO according to Iamanaka *et al*. [7].

The literature cites that mycotoxins can not be classified only by their mechanism of action given their diversity of chemical structures [8]. The *in vitro* study may provide the basis for predicting interactions between mycotoxins [9]. Initially, Kubena *et al.* [10] demonstrated *in vivo* the additive effects between FUMO B1 and OTA by studies in young turkeys, but it is emphasized that the synergistic interactions between FUMO B1 and OTA depend on the doses used [11].

2. Metabolic Fungi and Their Characteristics

FUMO are mycotoxins, secondary metabolites of fungi, especially of the genus *Fusarium*, being structurally related with: A (A1-A4), B (B1-B4), C

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(C1-C4) and P [12]. However, in greater abundance is FUMO B1 followed by FUMO B2 and in the sequence to FUMO B3 [13] which is considered to be the most toxic.

There are several kinds of FUMOB identified, however the FUMO B1 and FUMO B2 constitute up to 70% of the FUMOB found in naturally contaminated foods [14]. Fungal species of the genus *Fusarium*, especially by *Fusarium verticillioides* is the main producers of these toxins [15].

The fungal growth is sensitive to the minimum temperature for the growth of this, so not necessarily in the minimum and maximum temperature there will be toxin production. The ideal temperature for FUMO production was calculated by means of regression analysis, being 24.5 °C and 24.3 °C (± 2 °C) for FUMO B1 and FUMO B2, respectively [16].

Mycotoxins are known to maintain toxicity after exposure to elevated processing temperatures. FUMO are thermally stable at temperatures above 150 °C, but can be effectively removed in food samples [17]. However, these thermal processes result in the conversion of intact FUMO into hydrolyzed FUMO which are more cytotoxic than FUMO B1 [18].

The temperature and humidity conditions during the plant development period as well as during the storage period are often the causes of pathogen infection and mycotoxin production [19]. The optimal temperature range for the growth of *F. verticillioides* is between 22.5 °C and 27.5 °C and minimum water activity of 0.98 [20].

Contamination with mycotoxins is also affected by climatic factors such as temperature and relative humidity available in pre- and post-harvest [21]. In a study conducted in the state of Paraná, ONO *et al.* [22] found that the combination of high relative humidity and temperature are key to fungus growth and subsequent contamination with mycotoxins.

As a consequence of the continental dimensions of the country, there is a possibility that the presence and content of mycotoxins in foods produced and consumed are unequal among the different regions [23].

In Brazil, the highest incidence of FUMO contamination occurs in cereals, mainly in the south of the country [24]. FUMO are found mainly in corn and corn products [25].

3. FUMO in Animal Diet

Corn meal, an ingredient of high concentration in feed, is generally more attacked by FUMO in many countries, with concentrations of 330 μg/g FUMO B1 already present in pork diets [26]. The species *F. verticilioides* is responsible for the root rot, stem and deterioration of stored maize grains, that is, causing disease in all stages of maize development, whose predominance is asymptomatic plant infection [27].

Animals like humans are exposed to mycotoxins through food. As contamination of food by mycotoxins is difficult to avoid, prevention should occur through strict monitoring of food of animal and plant origin [28]. Estimates indicate that about 25% of the world's food is affected by mycotoxin-producing fungi [25], where the main food contaminants are cereals (corn, rice and wheat) and legumes (beans, peanuts, peas and soybeans), besides rations and processed products [7].

The toxic effects induced by fungal toxins are dependent on the level of intake, duration of exposure, the toxin species, the mechanisms of action and metabolism. When consumed at high levels they trigger acute organic disorders known as mycotoxicoses, many of them can be teratogenic, cancerinogenic, estrogenic, neurotoxic and immunosuppressive [6].

3.1 Metabolizable and Immunosuppressive Agents

In the ration when ingested the FUMO have low bioavailability and are rapidly metabolized and excreted. Its mode of action is related to its toxicity in the interference of sphingolipids biosynthesis, which is of great importance for the maintenance of cell

membrane integrity, regulation of cell surface receptors, ion pumps, regulation of growth factors and other systems vital for the functioning and survival of the cell.

The main mechanism of toxic action of FUMO B1 is related to the inhibition of the biosynthesis of cell membrane sphingolipids, according to Souto *et al.* [29]. Sphingolipids are present in cell membranes, playing a key role in cell regulation and membrane protein control, mediating cell growth, cell differentiation and death [30].

According to Haschek *et al*. [31], the FUMO cause immunosuppression and increase the susceptibility of animals to infectious diseases, being immunotoxic generates effects on cellular responses, humoral factors and cytokine mediators of the immune system. The effects on immunity and resistance are often difficult to recognize in the field because the signs of the disease are associated with the infection and not with the toxin [32]. Furthermore, in animal models, the immunosuppressive effects of toxins occur at lower levels of ingestion than the effects of the toxin on othertoxicity parameters, such as feed intake and growth rate.

Pigs are potentially exposed to high FUMO B1 levels in the short-term diet, with swine pulmonary edema (EPS) being the main pathology. FUMO interfere with the metabolism of sphingosine-sphinganine [33], impairing the metabolism of sphingolipids [30].

3.2 Synergistic Effects of FUMO in Finished Piglets and Pigs

In the production of animal it was found that the liver and kidney retain most of the absorbed FUMO [34]. Swine is susceptible to poisoning, in which FUMOB contaminated diets cause inappetence and depression, inducing cardiovascular toxicity, pulmonary edema and liver degeneration, and, at high concentrations, can lead to pancreatic, hepatic and renal damage [35]. The heart and the pancreas may also be affected by diets containing FUMOB [32]. Flaccidity and dilation of the cardiac walls were observed in piglets poisoned with FUMO, and liver, lung and kidney involvement may occur [32].

The disease causes pulmonary edema in pigs [36], this edema was first documented in pigs in 1981 in the USA, after exposure to corn contaminated with *F. verticillioides*.

Acute intoxication of pigs by FUMO is clinically easy to detect and is characterized by signs of pulmonary edema. The most characteristic changes in affected animals include anorexia, lethargy, open mouth, increased respiratory rate, jaundice and cyanosis on the skin is more evident in the ears, snout, sclera and mucous membranes. There are also excessive salivation, hepatic encephalopathy syndrome, moist rust on the lungs, and watery diarrhea [37].

The piglets preferentially remained in lateral decubitus position and presented reduced water and feed consumption [32].

In this way, they can be easily confused with malnutrition, genetic deficiency and inadequate management. The lot usually presents significant developmental unevenness of the animals with decreased food intake and weight gain with significant worsening of feed conversion. They have bristles with less brightness, bristles and animals circulate more frequently in the bay without feeding [37].

In male pigs, contamination with 1-10 ppm per FUMO B1 resulted in increased blood cholesterol in the animals, as well as changes in the weight of the pancreas and adrenal glands [38]. The main FUMO B1 lesions in pigs are associated with pulmonary edema, hydrothorax, hepatic nodular degeneration, hyperplasia and esophageal lesions, mainly occurring in chronic intoxications [32].

Haschek *et al.* [31] describe that FUMO toxins in finished pigs are characterized by lung, liver, cardiovascular and immune system injury and effects on growth rate and carcass composition. The pigs

develop edema within 4-7 d when fed FUMO B1, containing food or culture material at concentrations of 16 mg/kg. Likewise, pulmonary edema can be fatal within 7 d.

In weaned piglets, cases of pulmonary edema with concentrations of 10-40 ppm with periods of ingestion of four weeks have been detected [31].

In 3-week-old hybrid male piglets consuming FUMO B1 doses of 0.5 mg per kilogram per live weight for day equivalent to 7 ppm of FUMO B1 for 6 d, there was a significant increase in oral *Escherichia coli* spread, however, there were no deaths, only variation in weight gain [39].

3.3 Control and Methods of Decontamination by FUMO

As a precautionary measure to avoid the effects of FUMO in animal husbandry, the United States and the European Union recommend the tolerance limits of 20.0 mg/kg (millet for pigs) and 5.0 mg/kg (pork rations), according to Souto *et al.* [29]. However, there are no tolerance limits for FUMO in animal feed ingredients or in Brazil [29].

The physical decontamination method involves the use of such as activated charcoal, cholestyramine [17], hydrated sodium and calcium aluminosilicate and Egyptian montmorillonite [40] demonstrated effectively that decontaminations methods binds mycotoxins in the gastrointestinal tract of animals, reducing the bioavailability of the toxin in the diet.

Chemical treatment with ammonium hydroxide can reduce FUMO B1 levels in contaminated maize by 79%, since the treatment of maize with $Ca(OH)_2$ can reduce the concentration of FUMO by about 50% [17].

One way to biologically control *F. verticillioides* is to use an endophyte bacterium, *Bacillus subtilis*, which reduces the accumulation of FUMO B1 during the life cycle phase of the fungus in which no infection is observed, although this is present [41]. In addition, the fungus competes with the fungus for the same ecological niche in the plant [41].

The use of yeast *Exophiala spinifera* is able to promote the hydrolysis of FUMO B1 in aminopentol and tricarballylic acid, as well as the decontamination of aminopentol with the release of CO_2 [17].

Among field strategies there is the management of insect infestation and previous crop residues, crop rotation, harvest time management and ideal grain storage conditions, soil fertilization, use of biocontrol, application of fungicides, among others [42].

4. Considerations

The observation of the synergistic effects *in vivo* together with the control of FUMO in pig feed is useful epidemiological investigation and public health monitoring of the population. The great demand of food for the breeding of pigs and other animals, increases the difficulty in controlling the contamination by FUMO that can happen during the time of harvest and processing of the animal feed. However, the discovery of the FUMO concentration limits allowed in laboratory analyses for each animal species generates possibilities for better controls of the raw materials supplied in the diets. The following goals are to identify those nations that would have a greater impact of contamination, establish stricter global legislation, assess health benefits as well as economic losses.

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