THE WORLD OF MYCOTOXINS - A SYSTEMATIC REVIEW

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Abstract

Mycotoxins are secondary toxic metabolites produced by filamentous fungi, which are predominantly found in agricultural products worldwide. Mycotoxins appear in the food chain due to fungal contamination of crops both before and after harvest. Exposure to mycotoxins can occur by consuming contaminated food (a direct factor) or by consuming feed contaminated by animals, through milk (an indirect factor). Fungal proliferation and mycotoxin production have a higher input due to environmental factors. Chemically, most mycotoxins are stable and thus survive food processing. Among the most important mycotoxins are aflatoxins, ochratoxin A, zearalenone and trichothecenes. The species that synthesize these mycotoxins belong to the genera Aspergillus, Penicillium and Fusarium and, unfortunately, they can trigger mutagenic, nephrotoxic, carcinogenic, teratogenic, cytotoxic, neurotoxic and estrogenic effects. This paper provides an overview of the world of mycotoxins, from emergence to adverse effect on contamination of agricultural products, which is of major importance as it affects food and feed safety, food security and trade.

Key words: *contamination, fungi, mycotoxins.*

INTRODUCTION

The word "mycotoxin" is derived from the greek word *mykes*, which means fungus or mold, and the latin word toxicum, poison or toxin (Singh & Mehta, 2020). Mycotoxins are toxic secondary metabolites that are produced by fungi and not just any, but filamentous fungi. Analyzing the situation, speaking more strictly, they are defined as secondary metabolites of fungal origin. They show in vivo toxicity to vertebrates after natural introduction (i.e. ingestion, inhalation, etc.) (Streit et al., 2013). Mycotoxins are toxic and harmful to humans and animals to varying degrees and can contaminate grain grains in the field as well as in storage. These result in negative effects on human and animal health. Mycotoxins are present in agricultural products such as cereals and oilseeds. If ingested in high enough concentrations, they exert severe toxic effects on humans and animals (Liang et al., 2016). While it is difficult to infer any long-term trends globally, data confirm that high mycotoxin contamination is often linked to demanding weather (Pettersson, 2012). Regarding food products, the situation is quite similar and here we are talking about the fact that low levels of contamination are frequently observed in official controls, but the maximum levels are rarely exceeded in developed countries (Ayofemi et al., 2019). Since it is very difficult to eliminate mycotoxins from contaminated commodities, it is necessary to prevent their accumulation in agricultural commodities being the most effective strategy to combat the problem (Marroquín-Cardona et al., 2014). The most important preventive measures range from crop rotation and increasing resistance to inoculation with microbial antagonists. However, unfortunately, excessive levels of mycotoxins can occur despite all preventive measures. Therefore, continuous monitoring is essential and effective decontamination strategies are needed to deal with such contaminations. The prevalence of mycotoxins in food is equal to their presence in feed, although the concentrations detected are generally lower in food (Schatzmayr & Streit, 2013). Also, depending on the potential risk of transfer of each mycotoxin, feed contamination can also pose a safety hazard to food of animal origin and contribute to the intake of mycotoxins to humans (Pinotti et al., 2016).

AFLATOXINS

Aflatoxins are carcinogenic substances produced by the species *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxins are mainly found in grains, peanuts, cottonseed and tree nuts. *Aspergillus flavus* can invade corn and cottonseed in the field when there is drought stress, insect or hail damage, and the presence of excess moisture (Mahato et al., 2019). *Aspergillus parasiticus* can invade peanuts in the field and during harvest if there is excess moisture, such as heavy rains when the peanuts are drying. Aflatoxin-producing fungi can also invade during storage if moisture conditions become favorable for their growth (Sineque et al., 2017). Aflatoxins are a group of structurally related compounds, the most important of which are aflatoxins B_1, B_2, G_1, G_2, M_1 and M_2. Aflatoxins M_1 and M_2 are secondary metabolites of aflatoxin B and are eliminated through milk. Aflatoxins B_1 and B_2 are produced by strains of *A. flavus* and are most common in corn. These strains of *A. flavus* do not normally produce mycotoxins G and *Aspergillus parasiticus* produces aflatoxins B_1, B_2, G_1 and G_2. Thus, maize is most commonly contaminated with aflatoxins B_1 and B_2 and peanuts with aflatoxins B1, B2, G_1 and G_2 (Eaton & Gallagher, 2010). The best known mycotoxin found in human food and animal feed is aflatoxin B_1. In fact, aflatoxin B_1 is the most potent known hepatocarcinogen in mammals and is listed as a group I carcinogen by the IARC. The liver is the main target site of aflatoxin B_1. Acute aflatoxicosis has produced abdominal pain, vomiting, edema and even death. Aflatoxicosis outbreak was recorded four times in Kenya between 2004 and 2014, almost 600 people were affected and 211 deaths have been reported because of it (Ayofemi et al., 2019). In animals, aflatoxins can cause liver disease and are mainly associated with decreased production (milk, eggs, meat, etc.). Aflatoxin B_1 is a strong human carcinogen and high levels of exposure are known to cause liver cirrhosis and liver cancer. Aflatoxins can also cause immunotoxicity (Smith et al., 2020). FDA contamination limits for aflatoxin in grain products vary by commodity use. The contamination limit for most human foods is 20 ppb (µg/kg), but for milk and certain milk products it is 0.5 ppb (µg/kg) (Reg. (EC) No.1881/2006, Reg. (CE) No. 165/2010). Aflatoxin affects grain quality and marketability and is primarily a threat to the health of farm animals. This global scenario confirms that the contamination is highly dependent on the climatic conditions of the respective region. In general, environmental conditions such as excessive moisture, extreme temperatures, humidity, drought conditions, insect damage, cropping systems and some agronomic practices can cause stress and predispose field plants to mold and determine the severity of mycotoxin contamination (Zhang et al., 2018). The main climatic conditions leading to aflatoxin accumulation are high temperature, low rainfall and severe drought stress (Singh & Mehta, 2020).

OCHRATOXINS

Ochratoxins A (OTA), B (OTB), C (OTC) are a group of compounds developed by various species of *Penicillium* and *Aspergillus* that contaminate cereals, vegetables and compound feed. In laboratory conditions, most *Aspergillus ochraceus* strains produce OTB and OTC and in natural environmental conditions, the most predominant is OTA (Ostry et al., 2013). Ochratoxin A (OTA) is the most widespread and relevant fungal toxin in the field of mycotoxins. The results of research known over time show that in Europe at least part of the ochratoxin A in food comes from cereals and cereal products. Ochratoxin is mainly produced by *Aspergillus* and *Penicillium* species (Lhotská, 2016). Ochratoxin A is most often isolated from corn, sorghum, barley, wheat, oats and rye. It seems that barley, oats, wheat and corn, grains grown in Denmark and other Scandinavian countries, as well as in the Balkans and India, provide favorable conditions for the development of ochratoxigenic fungi, a fact that would explain such high levels of ochratoxin detected in these plant substrates (Sineque et al., 2017). In these specific climatic conditions approximately 20% of the examined samples were positive, the amount of ochratoxin A being of the order of ppm (Liang et al., 2016). Apart from cereals, ochratoxin A has been identified and isolated from many other substrates, such as soybeans, beans and fodder peas, green and roasted coffee beans, cocoa beans, wine and grape juice, beer, white and black pepper (Ayofemi & Adeyeye, 2019). It should be mentioned that in relation to coffee beans, research in recent years shows that approximately 80% of the ochratoxin A present in the green beans is destroyed by the roasting process, so that the amount of mycotoxin remaining in the substrate represents from a medical point of view a dose without pathogenic significance (Liu et al., 2020). Ochratoxin A contamination is mainly associated with insufficient drying or improper storage and unfortunately, it is found all over the world. In temperate regions, ochratoxin A contamination is mostly due to *Penicillium verrucosum* contamination, while *Aspergillus* species such as *A. carbonarius* account for ochratoxin production in warmer regions (Visagie et al., 2014). As for feed, ochratoxin A is most commonly found in grains, but it is known to contaminate soybeans and peanuts. Because fungal development often occurs in hotspots such as a high water activity zone, in stored grain the distribution of ochratoxin A in contaminated feed tends to be very heterogeneous (Ayofemi & Adeyeye, 2019). This fact represents a challenge in terms of ochratoxin contamination testing. Ochratoxin A has been classified as possibly carcinogenic to humans (Group 2B) (Sarrocco & Vannacci, 2018). Ochratoxin A has proven over time its carcinogenic, immunotoxic and nephrotoxic virtues, manifested extremely actively and vigorously towards humans and towards various animal species (Streit et al., 2013). The primary target site is the kidney. Animal studies have shown that ochratoxin A is a potent renal carcinogen (Kovalsky et al., 2016). The International Agency for Research on Cancer (IARC) has classified ochratoxin as possibly carcinogenic to humans in group 2B carcinogen. Based on epidemiological data, there is no significant evidence for human health risks associated with exposure to ochratoxin A. The primary effect of ochratoxin in all animals is nephrotoxicity. Regarding neurotoxicity, it has been reported that ochratoxin A can be seen as a possible cause of certain lesions, including brain lesions. Also, ochratoxin A is a strong teratogen for laboratory animals, being able to cross the placenta and accumulate in the fetal tissue, causing various morphological abnormalities. (Gallo et al., 2015).

DEOXYNIVALENOL AND OTHER TRICHOTHECENES

Deoxynivalenol (DON) belongs to the trichothecene group. This is one of the least acutely toxic but is of particular interest due to its high prevalence. More precisely, deoxynivalenol is classified as B-type trichothecene and is produced by *Fusarium culmorum* and *F. graminearum* (Palumbo et al., 2020). Contamination with deoxynivalenol is observed worldwide, with cereal crops such as wheat, corn or barley being the most frequently affected (Sineque et al., 2017). Deoxynivalenol is found predominantly in cereals such as wheat, barley, corn and to a lesser extent in oats, rice, rye, sorghum. Contamination of fodder, especially silage with deoxynivalenol is regularly observed. Cold and wet weather conditions favor DON production and it was found that the timing of precipitation influences the risk of contamination more than the amount of precipitation (Oldenburg et al., 2017). In animal husbandry, deoxynivalenol, also known as vomitoxin, primarily recalls negative effects, such as: refusal of feed and vomiting in pigs (Liang et al., 2016). This mycotoxin alters the immune response and intestinal functions. Poultry are not as sensitive to deoxynivalenol and feed refusal is only observed at very high concentrations (16-20 mg/kg feed). It is known that ruminants are the animal species least sensitive to deoxynivalenol, because the rumen microflora has the ability to detoxify this mycotoxin (Rocha et al., 2017). Mycotoxin concentrations were quite wide as ranges of variation, for example between 4 and 9000 pg/kg in barley samples. Deoxynivalenol concentrations > 2 to 5 ppm induce decreased feed intake and reduced weight gain and > 20 ppm induce vomiting and feed refusal (Zhang et al., 2018). However, concentrations as low as 1 ppm have been associated with feed refusal in pigs (Schenck et al., 2019). is the main fungal species that produces trichothecenes. Toxin T-2 and HT-2 are two of the most toxic members of the trichothecene group. They belong to the A-trichothecene type and are produced by F. sporotrichioides, *F. poae* and other *Fusarium* species. Oats and oat products were found to be particularly prone to contamination with high levels of T-2 and HT-2, followed by barley. Trichothecene contamination has been found to affect protein synthesis and exert immunotoxicity, hematotoxicity (Zhang et al., 2018). Ruminants are again protected by their microflora and have been shown to be the least sensitive to these toxins (Smith et al., 2020). Toxic effects of trichothecenes in animals (dairy cattle, pigs, broilers, and rats) include decreased plasma glucose, decreased blood cell and leukocyte counts, weight loss, food-toxic aleukia, and pathological changes in the liver and stomach (Bessaire et al., 2019). The toxins T-2 and deoxynivalenol are well-known inhibitors of protein synthesis (Khodaei et al., 2019). In general, trichothecenes exert a negative impact on the gastrointestinal tract, especially on intestinal absorption, integrity and immunity (Oldenburg et al., 2017).

FUMONISINS

Fumonisins are also counted among the mycotoxins produced by species of the genus Fusarium. In forage crops, these are most commonly produced by *F. proliferatum* and *F. verticillioides* (Jerome et al., 2018). The B-series fumonisins (FB_1, FB_2 and FB_3) are of greatest importance in terms of occurrence and toxicity, thus FB_1 is of greatest concern as it is the most widespread and toxic of the fumonisins. It was classified in class 2B, possibly carcinogenic to humans (Visagie et al., 2014). FB_1 contamination is frequently associated with corn and corn products. In a broader context, the classification of fumonisins as *Fusarium* mycotoxins is no longer 100% valid, as recently black Aspergilli, especially *A. niger*, have been found capable of producing fumonisins (Janik et al., 2021). We remind you that feed contaminated with fumonisins causes serious diseases, and here we are talking about pulmonary edema in pigs and leukoencephalomalacia in horses. In addition, fumonisins have been shown to be immunosuppressive, hepatotoxic and nephrotoxic just like other mycotoxins (Honma et al., 2004). Fumonisins, deoxynivalenol and zearalenona are considered to be the most important mycotoxins produced by Fusarium and in terms of animal health and economic losses they are the most relevant (Logrieco et al., 2018). Although FB_1 contamination is not very common in crops other than corn, mycotoxins produced by *Fusarium* in general are often found together in contaminated grains. In most cases, the resulting toxic effects are combinations of individual mycotoxin toxicity, but synergistic interactions with other mycotoxins have been observed with quite pronounced negative effects (Jouany, 2007). Unlike most mycotoxins, which are hydrophobic in nature, fumonisins are hydrophilic in nature, preventing their discovery until 1988 (Kovalsky et al., 2016). Fumonisins are frequently isolated from feed and food (sorghum, rice, corn, beer) and long-term research with FB_1 administered in feed demonstrated that this mycotoxin induced tumor formation in the kidney and liver (Marin et al., 2013). The metabolism of glycerophospholipids, as well as that of fatty acids and phospholipids, is also affected. FB_1 has the same structure as cellular sphingolipids, which are responsible for neurological and immunological diseases as well as cancer (Gallo et al., 2015). Fumonisins cause serious diseases in animals and induce esophageal cancer in humans. Human epidemiological studies in South Africa, Italy and China have shown that esophageal cancer is linked to the consumption of corn kernels containing fumonisins (Oldenburg et al., 2017). Consumption of moldy sorghum and corn contaminated with FB_1 has triggered severe poisoning with gastrointestinal disturbances and death in humans in India, and another outbreak caused neural tube disorders (birth defects of the brain, spine, or spinal cord), the last such study taking place along the Texas-Mexico border, China and South Africa, thus demonstrating the association with the consumption of corn contaminated with fumonisins (Kovalsky et al., 2016). In animals, fumonisins have been found to cause pulmonary edema and hydrothorax in pigs, leukoencephalomalacia in horses, and HCC in rats. Also, FB_1 causes reproductive damage in many animals. FB_1 negatively affects the livestock sector and food safety issues caused by FB_1 have also received widespread attention. (Palumbo et al., 2020).

ZEARALENONE

Like the mycotoxin deoxynivalenol, zearalenone (ZEN) is produced by fungi of the genus *Fusarium*, the best known being *F. culmorum, F. graminearum* and *F. heterosporum* (the species that produce ZEN) (Rashedi M. et al., 2011). As in the case of other mycotoxins, the risk of contamination is the highest in cereal crops. Also, silage, feed and straw are prone to contamination with zearalenone (Fink-Gremmels et al., 2019). The acute toxicity of zearalenone is at a lower level and the adverse effects are caused by the interaction with the estrogen receptor. Consequently, zearalenone produces fertility problems with estrogenic symptoms such as vulva swelling and uterine enlargement (Oldenburg et al., 2017). Among animals, pigs are the most sensitive to zearalenone exposure, while poultry are tolerant, and there are few studies of adverse effects in birds, as feed is unlikely to contain zearalenone in sufficiently high concentrations. Data on dairy cows is limited, but it is known that there is a low reaction to zearalenone contamination (Anfossi et al., 2016). In animals, the main effect of zearalenone contamination is estrogenic, and pigs are clearly the most affected farm animals. It is well known that zearalenone is a non-steroidal estrogenic mycotoxin, involved in reproductive disorders of farm animals (pigs, cattle and sheep) but also causes hyperestrogenic syndromes in humans (Bueno et al., 2015). Other studies on the effects of zearalenone have revealed problems on the reproductive system, such as the enlargement of the uterus, early decline in fertility, problems of the reproductive tract, but also an abnormal level of progesterone and estradiol (Palumbo et al., 2020). In addition, another issue exemplifies that the ingestion of food contaminated with zearalenone during pregnancy resulted in a reduction in fetal weight and a reduced embryo survival rate (Jensen et al., 2019). This is because zearalenone has a structure that allows it to bind to the mammalian estrogen receptor, even if the affinity is lower compared to natural estrogens (Cheli et al., 2913). In addition, zearalenone has been shown to be hepatotoxic, hematotoxic, immunotoxic, and genotoxic. Even if the reproductive organ is the main target of this mycotoxin and has the role of inducing toxicity, adverse effects on the gastrointestinal tract have also been reported (Danezis et al., 2016). It is worth noting that the effects of zearalenone ingestion on the gastrointestinal tract are not as harmful as the other mycotoxins (Marroquín-Cardona et al., 2014). Metabolites of zearalenone (α- and β-zearalenol) were found to significantly ($P < 0.05$) decrease cell integrity, the study showed that zearalenone and its metabolites acted differently in the gut, and modulation of gene expression was responsible for the carcinogenic effects of it (Smith et al., 2020). Despite all these problems, pigs that ingested this mycotoxin did not show changes in villus height, mucosal thickness or goblet cell number (Rashedi et al., 2011). In short, zearalenone plays a negative role in the health of the intestine and beyond, even if no particular histological changes were observed (Claeys et al., 2020). Mycotoxins can cause a variety of adverse health effects and pose a serious health threat to both humans and animals (Figure 1).

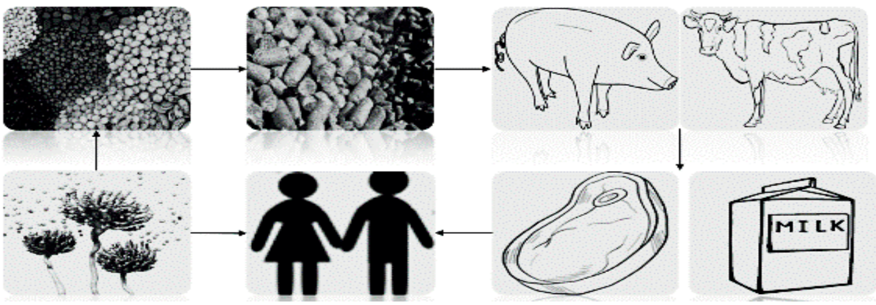

Figure 1. The chain of contamination with mycotoxins

The effects of some mycotoxins in food give signals with acute symptoms, with symptoms of severe disease that set in quickly after consumption of mycotoxin-contaminated food products (Sarrocco & Vannacci, 2018). Other mycotoxins that are found in food and not only have been linked to long-term health effects, such as even inducing cancer but also an immune deficiency. Of the several hundred mycotoxins identified to date, about a dozen have gained the most attention because of their serious effects on animal and human health and their occurrence in feed, food (Rocha et al., 2017).

CONCLUSIONS

Most grains are susceptible to mycotoxin contamination, which means that because of this, all animals are at risk of contamination. Mycotoxins trigger adverse and toxic effects in animals and affect health and productivity. Extreme weather phenomena trigger the growth and development of cultivated species, hence the presence of mycotoxins in cereals affects the agricultural and animal husbandry sectors, which represent a challenge for the future. The control along the entire traceability route contributes to ensuring the quality of the grains, in this way ensuring two important factors: quality and safety. The control of mycotoxins eliminates their entry into the agri-food chain and, in this way, the health of animals and people, as well as the environment, is protected.

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