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REVIEW: TOXICITY OF THE MYCOTOXINS A POTENTIAL RISK FACTOR IN HEALTH

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ABSTRACT

Mycotoxin are naturally occurring toxic metabolites of fungi, that may be present in food product. Mycotoxinss encompass a wide spectrum of different chemicals and they effect many target organ and system, notably the liver, kidney, nervous system, endocrine system and other immune system. They are frequently found in product such as nuts, corn, rice etc. Five most important naturally occurring mycotoxin in human food and animal feed are aflatoxin, ochratoxin, deoxyvalenol, zearalenone and fumonisin. Most countries have established maximum tolerated levels for total aflatoxins ranging from 4-20ng/g . conventional risk assessment has helped manage the risk form of mycotoxin in developed countries but has not help in developing countries. Various mycotoxins may occur simultaneously depending on the environment and substrate condition. Considering the co-incident production very likely, human are always exposure to mixture other than individual compound. Therefore, future risk assessment should be considering mixture toxicity data. This particularly true for ochratoxin A and ochratoxin B, Citrinin and occasionaly for patulin as they are all provided by a number of penicillium and aspergillus species. This review emphasis the different type of mycotoxins and their toxicological effect on health. The study on mycotoxin demonstrated their toxigenic, nephrotoxic, hepatotoxic, carcinogenic, immunosuppressive and mutagenic charasteristics.

KEYWORDS: Mycotoxin, fungi, toxicological, health, aflatoxin, ochratoxin, fumonisin.

INTRODUCTION

Fungi are saprophytic decomposers, which are unable to produce food from sunlight or other energy sources.[1] Diseases caused by fungi are spread due to direct inhalation or implantation of spores. A spectrum of medical conditions can result from fungal exposure, similar to all infectious agents, This may range from a superficial skin disease such as tinea to invasive internal organ pathology such as pulmonary aspergillosis.[2] Mycotoxins are naturally occurring toxic and carcinogenic metabolites produced by fungi that excerts toxic effect on animals and humans. The toxic effect of mycotoxins on animals and humans referred as mycotoxicosis. The term mycotoxins was coined in 1962 in the aftermath of an unusual veterinary crisis near London, England during which approximately 100,000 turkey povlts died.[3] Mycotoxins are structurally diverse group of mostly small molecular weight compounds, they occur frequently in areas with a hot and humidity conditions and may develop on various foods and feeds, causing serious risk for human and animal health. Mycotoxins are secondary metabolites which have no biochemical significance on fungal growth and development, they vary from simple C4 compound eg: Moniliformin, to complex substance such as phomopsins.[4]

Human are exposed to mycotoxins as a result of consumption of plant derived foods that are contaminated with toxins also carry over of mycotoxins and their metabolites in animals products such as meat and eggs or exposure to air and dust containing toxins. These are produced by fungi of the genera aspergillus, fusarium and penicllium which commonly infect food crops.

Mycotoxins mainly produced by toxigenic molds and it is established that all molds are not toxigenic and also not all the secondary metabolites from molds are toxic. Storage, environmental and ecological condition are the various factors which contribute to the presence or production of mycotoxin in foods or feeds.[5] Their risk assessment of exposure which may be different for different countries of even groups of individuals with countries. The additive or synergistic effects of mycotoxins after combined exposure are rare but the

issue of combined toxicity is very complicated. Mycotoxins can interfere at cellular levels and thus interact with the toxicity of another mycotoxin.[6]

As a group mycotoxin cannot be classified based upon their mechanism of action. Different types of mycotoxins such as aflatoxins, ochrutoxin A, zearalenone, trichothecenes, patulin, ergot alkaloids.

Among these mycotoxins, such as aflatoxin B1 (AFB1), fumonisin B1 (FB1) and achratoxin A(OTA) are detected as more toxic to mammals. AF1 is classified under class I human carcinogen, FB1 & OTA classified as class 2B, patulin classified under group 3 carcinogen.[7] Ochratoxin and penicillic acid, ochratoxin and aflatoxin B1 and patulin and citrinin, fumonisin B1 and moniliformin are those frequently occurring combinations of mycotoxins in different plant products.

AFLATOXIN

Aflatoxins was discovered during an epidemic of disease that wiped out more than 100,000 turkeys in 1960 s, was traced to the consumption of a mold contaminated peanut meal. These toxins were discovered to contain in all crops and food stuffs including corn, rice, wheat, barley and other variety of food and feeds. Milk and milk products are contaminated due to animal consumption of aflatoxin contaminated feeds.[8] Aflatoxin are a group of 20 chemically related metabolites produced by the food born fungi Aspergillus flavus and Aspergillus parasiticus. The several aflatoxins and their metabolits such as AFB_1, AFB_2, AFG1, AFG2, AFM1, AFM2 are named after their fluorescence umder Uv light as blue or green and relative mobility during TLC. Aflatoxin metabolitis (AFM) found in mammalian milk, where "M" denotes milk or mammalian metabolitis.[9] Aflatoxin associated with carcinogenicity and toxicity in human and animal population. Aflatoxicoses is the disease caused by the Aflatoxin consumption.

Where, acute aflatoxicosis leads to death and chronic aflatoxicosis results in cancer, immunesuppresion and other pathological conditions .The most toxic cause of the aflatoxin is potent liver carcinogen, causing hepatocellular carcinoma in human and wide varety of animal species . The magnitude of response influenced by age, weight, exposure to infectious agents, diet and the occurrence of other mycotoxins and pharmacologically active substance, laboratory models and agriculturally important species are mostly concerned for conducting thousands of studies on aflatoxin toxicity.[10] 65% of the AFB1 is cleared from the blood within 90 minute and the plasma half life is every short. In human liver homogenates thus half life of alfatoxins is tested and it was found approximately 13 minute, but the exact invivo half life of aflatoxin is unkown.[11] Ingestion of 2-6 mg/kg/day of aflatoxin over a month were estimated to produce hepatitis in India.[12] However suicide attempt with 1.5 mg/kg of pure aflatoxin resulted only in rash, nausea, headache.[13] In African countries aflatoxin detected in the blood of pregnant women, breast milk and neonatal umbilical code with seasonal variations.[14,15] Chlorophyllin protect against women AFB1 toxicity.[16]

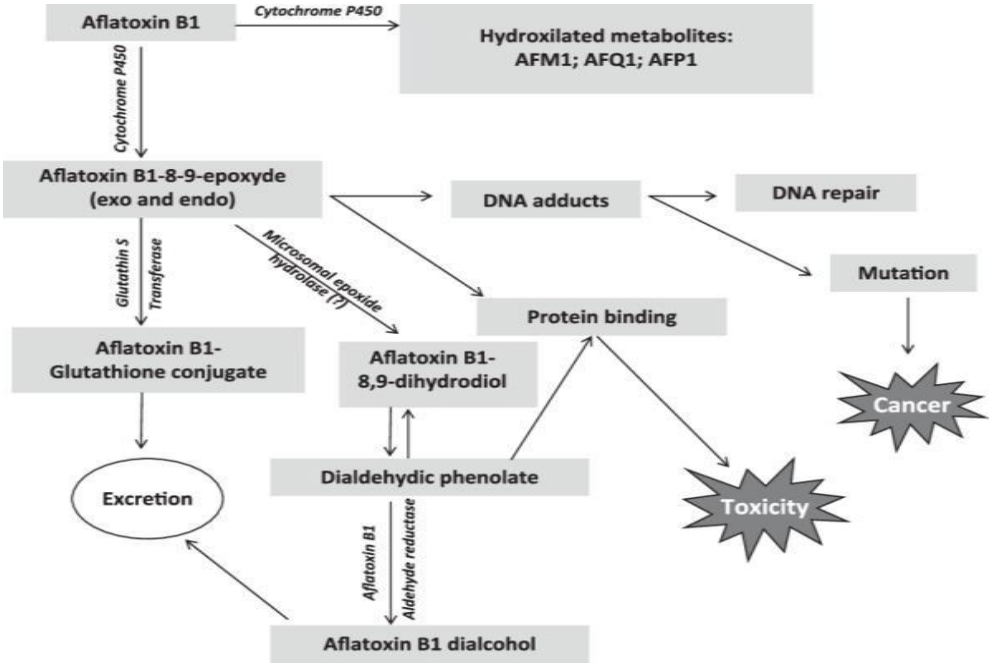

Fig 1: Overview of biotransformation pathways for aflatoxin B1.

The childhood disease such as reye's syndrome and neonatal jaundice and kwashiorkor appears seasonally in tropical countries, which coincided with high concentration of aflatoxins, so it was believed that aflatoxin is an etiology of these diseases. Many studies have found that AFB1 and aflatoxicol were more

frequently occur in the serum, liver, urine and stool of children suffering from kwashiorkor.[17] Aflatoxins are detected in laboratory using high performance liquid chromatography (HPLC), gas chromatography ass spectrometry (GC- MS) and thin layer chromatography(TLC).

OCHRATOXINS

Ochratoxin are produced by pencillium and aspergillus species that comes in 3 secondary metabolite form A, B and C. the 3 forms differ in that achratoxin B (OTB) is a non chlorinated form of ochratoxin A (OTA) and that of ochratoxin C (OTC) is ethyl ester of ochratoxin A.[18] Based on animal studies OTA is easily absorbed through GIT mainly in the duodenum and jejunum.[19] There are no studies based on absorption via skin and inhalational route. The concentration of OTA found in decreasing order in kidney, liver, fat and muscle tissues.[20] Excretion is mainly through kidney. The elimination half life in animal studies was found to be 23.6 to 28.7 hour, as long as 35 days in monkeys.[21] OTA inhibits the synthesis of protein as well as DNA and RNA, also via lipid peroxidation they impair the endoplasmic reticulum membrane which leads to disruption of hepatic microsomal calcium homeostasis.[22] Ochratoxins are involved in human disease called endemic balken nephropathy, a chronic, wasting kidney disease associated with a high incidence of urinary tract tumor in eastern Europeans.[23] The most striking feature of OTA toxicity - even after short- term exposure enlargement of the nucleus and polyploidy of the proximal tubule, representation of the nuclear division without cytokinesis.[24] Genotoxicity results studies do not suggest that OTA is mutagenic or strong Genotoxin, consistent with the lack of formation of reactive Metabolite.[25] However, some authors suggested that genotoxicity plays a role and have an important role in OTA-induced tumorigenesis postulated the formation of DNA adducts as indicated by spots observed by 32P post-labeling.[26] OTA can be analyzed using TLC, HPLC and ELISA. Immunoassays such as ELISA can detect OTA in pg Areas. The possibility of cross reactions cannot be completely excluded. Other techniques should be there is used to confirm the OTA values.[27] The tolerance OTA values have been suggested as 1 ug / kg for baby food and 5 ug / kg for cereals.[28]

FUMONISINS

Fumonisis are group of mycotoxins produced by fusarium species are cancer inducing metabolites of F. proliferatum and F. verticillioides, these mycotoxins are structurally similar to sphingoid bases. This may cause cancer in rodents and affect the nervous system of horses. Among this group fumonisin B1 is the most impotant and potent mycotoxin. It has been implicated sporadic animal disease.[29] Toxic mechanism of fumonisin, which is involved in the inhibition of sphingolipid synthesis and leads to the disruption of sphingomyelin.[30] The FAO/ WHO Committee for Food Additives recommends a maximum tolerable intake with a consumption of 2 µg / kg body weight per day based on the NOEL and the safety factor of 100.[31] There are no reports or studies of the toxicity of this mycotoxin through inhalation exposure. Fumonisins are also involved in a handful of diseases such as liver cancer (in rats), bleeding (in the brain of rabbits) and nephrotoxicity in some animals.

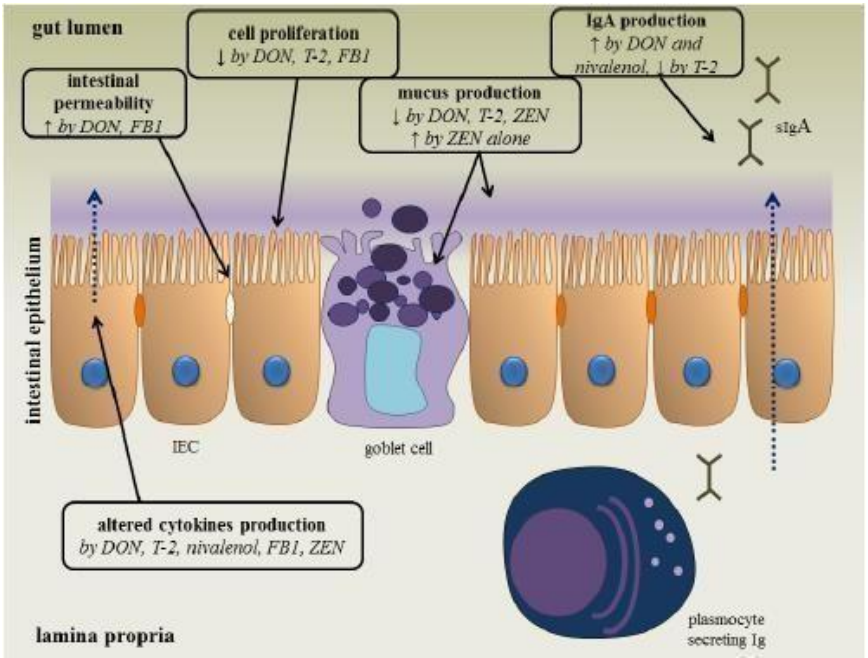

Fig 2: The effect of Fusarium mycotoxin on the intestinal epithelium. A variety of Fusarium mycotoxin change the different intestinal defence mechanisms including epithelial integrity, cell proliferation, mucus layer, immunoglobulins and cytokine production. (IEC: intestinal epithelium cell).

Apoptosis and esophageal cancer in humans.[32] According to FAO / WHO, the maximum tolerable every day uptake (TDI) of this toxin for humans is 2-4 mg / kg and for Animals 5-100 mg / kg.[33]

CITRININ

Citrinin is a secondary product of fungal metabolism, first isolated from Hetherington and Raistrick from a culture of Penicillium citrinum.[34] CTN has antibiotic properties against gram-positive o Bacteria, but it was never used as Drug due to its high nephrotoxicity.

The kidney is the main target organ of CTN toxicity, other target organs are the liver and bone marrow.[35] CTN has also been found to increase toxicity of OTA either additively or synergistically.[36] Its LD50 in the animal Models have been reported as approximately 50 mg / kg by oral Route. From a pathological point of view, citrinin damage includes the infiltration of liver fat and necrosis. Epidemiologically Citrinin has been associated with "yellow rice" Syndrome, but no systematic research has been done to the actual mycotoxin or the active ingredient responsible for this ill- defined disease.[37] Common methods for CTN Analysis are thin layer chromatography (TLC), high performance Liquid chromatography (HPLC) with UV or fluorescence detection and enzyme immunoassays. For the qualitative and quantitative determination of CTN LC-MS and GC-MS techniques are used.

PATULIN

Patulin is a toxin produced by the p.expansum, aspergillus, penicillium and paecilomyces fungi. p.expansum is particularly associated with a number of moldy fruits and vegetables, especially rotting apples and figs. Although patulin has not been shown to be carcinogenic, it has been reported to damage the immune system in animals.[38] However, in the 1960s it became clear that although it had antibacterial, antiviral and antiprotozoal activity, it was also toxic to animals and plants. After these revelations, it was classified as a real mycotoxin.[39] Although genotoxicity data was variable, most tests performed on mammalian cells were positive, while tests on bacteria were mostly negative.[40]

Patulin induced Carcinogenicity is currently questionable. The small amount of benign tumors observed only in animal studies at the site of administration (for Stomach- Papilloma and Glandular-Stomach adenoma) and the absence of malignant tumors were not considered sufficient evidence to make clear conclusions about carcinogenicity.

TRICHOTHECENES

Trichothecenes mycotoxin are toxic sesquiterpenoid metabolites produced by fungi that contaminate cereal based foods and built environment.Trichothecenes are divided into four Groups. The most common contaminants are deoxynivalenol (DON), nivalenol (NIV), diacetoxyscirpenol (DAS), while T-2 toxin is less common. Values in the range from 0.5 to 40 mg / kg T-2, DON and NIV are detected in foods such as corn, rice, wheat.

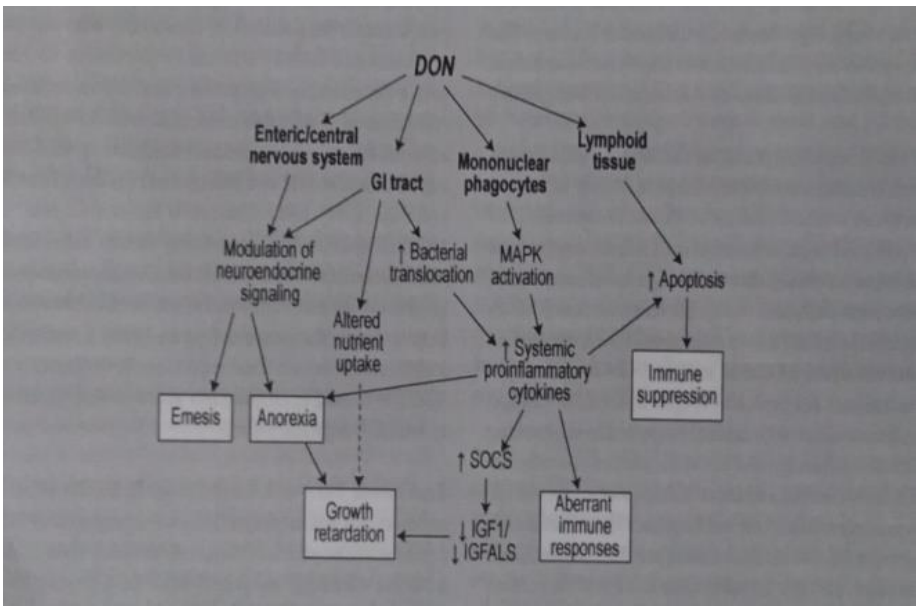

Fig 3: Potential mechanism that underline DON-induced toxicity in experimental animals.

Tricothecenes of groups A and B are quickly absorbed from the GI tract. Although human data on inhalation and skin contact absorption are not available, in vitro and animal studies show that tricothecenes are poorly absorbed by intact skin.[41] The mechanism of toxicity in turn involves the inhibition of protein and DNA synthesis. They also create general cytotoxicity by inhibiting the mitochondrial electron transport system. The LD50 of tricothecenes is between 0.5 and 300 mg / kg depending on the route of administration and animal model. TLC methods are non-specific and insensitive to the detection of tricothecenes. GCMS and LCMS

were used to determine trichothecenes in trace concentrations. HPLC is also a reliable and sensitive method for the detection of trichothecenes.[42]

FACTORS AFFECTING THE PRODUCTION OF MYCOTOXINS

A major difficulty in assessing the risk of mycotoxin to human and animal health is the variety of factors that affect the production or presence of mycotoxins in food or feed. Factors affecting mycotoxin production and Contamination can be classified as physical, chemical and biological. Physical factors include Environmental conditions that promote the colonization of fungi and the mycotoxin production, such as Temperature, relative humidity and insect infestation. Chemical factors include the use of Fungicides and / or fertilizers. Exposures such as drought, rising temperatures and increasing relative humidity can selectively change the colonization and metabolism of mycotoxigenic fungi and thus mycotoxin production. Biological factors are based on the interaction between the Colonization of toxigenic fungi and substrates.[9] The biological factors were further broken down into intrinsic factors, including types of fungi, strain specificity, strain variation and instability of the toxigenic properties.

Such intrinsic factors underscore the difficulty of risk assessment of mycotoxin exposure due to mold contamination. The toxigenic properties can vary over time and if the mycoecology changes, the toxin can be reduced.[43]

TOXICITY INDUCED MY MYCOTOXIN

cases. The mycotoxic effects can occur Increase the severity of depressive symptoms or the presence of a mood disorder.[45] Mycotoxins have some significant effects on the circadian rhythmic process, which leads to it deprivation of sleep, in which an acute and temporary increase in NKC activity is observed.

Neurologic Toxicity

Few cross-session surveys report that mold exposure is associated with neurological symptoms. Ergot poisoning can cause convulsions and hallucinatory effects. It has been suspected that 3-nitropropionic acid, which is produced by arthrinium species, causes "moldy sugar cane poisoning" with symptoms such as dystonia, convulsions and coma.[44] Recent reports of tricothecene exposure do not describe specific neurological findings. Psychological confusion can be observed in patients who are exposed Mold and mycotoxins; in some cases it can become a solid clinical condition. Temporary attention malfunction, cognitive and brain memory systems is commonly called Delirium. In our patients who are susceptible to mold, we see different degrees of a changed mental state Status, usually with changed attention, and faulty short-term memory. The most important presentations for patients with chronic toxic mold exposures were headache, general debilitating pain, nosebleeds, fever, cough, memory loss, Depression, mood swings, sleep disorders, anxiety, chronic fatigue, dizziness and in Seizures can occur in some

Renal Toxicity

Ochratoxins produced by Penicillium and Aspergillus associated with endemic nephropathy in the Balkans.[46] There is a case report indicating that acute kidney failure was due for inhaling ochratoxins in the air. The climate in endemic areas favors mold production and the common nephrotoxic mycotoxins that contaminate food in mild climates are OTA, Citrinin and Fumonisin B1 (FB1). Exposure to OTA and other mycotoxins can therefore be considered as etiology of EN and urothelial tumors.

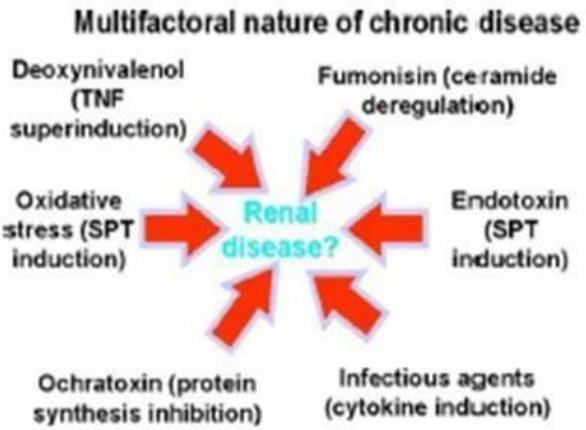

Fig 4: A theorectical example of mycotoxin and an infectious agent acting in concert to initiate or exacerbate renal dysfunction.

Infants with IPH-related stachybotrys exposure suffered from electrolyte disturbances, non-ionic gap acidosis, and proteinuria, but this can be related to shock Syndrome instead of mycotoxin effects.[47]

It It should be noted that there are no trichothecenes in the air were isolated or correlated with kidney toxicity.

Pulmonary Toxicity

when mycotoxins are ingest.ed, they can cause chronic inflammation of the lungs. Mycotoxins may also trigger COPD in farm animals. "pulmonary mycotoxicoses" was used to describe a patient who had inhaled large amounts of mycotoxin and developed respiratory symptoms.[48] This person presented with cough, respiratory problems distress, fever, fatigue, interstitial or alveolar Infiltrates and leukocytosis. The condition was self-limited and the patient recovered with no rest deficits. Unfortunately, no effective treatment for exposure to mycotoxin is currently available. The mechanism of mycotoxin-induced lung injury is still unclear. Although Trichothecene is manufactured by Stachybotrys are potent protein synthesis inhibitors, Pulmonary bleeding cannot be fully explained by this mechanism. Although using some experimental animal studies Stachybotrys have shown hemorrhagic changes in these exposures were

intratracheal or intranasal in the lungs. The direct instillation of mold spores or mycotoxins through the trachea or nose has questionable physiological and clinical relevance Spores larger than an aerodynamic diameter of 10 microns is unlikely reaches lower respiratory tract through inhalation exposure.[49] Other studies and reports of Respiratory involvement have not been provided Support pathological and laboratory findings of Lung disease. Current epidemiological and toxicological information indicate a temporary inflammation or irritant effect as a result of mycotoxin.

Gastrointestinal Toxicity

Mold contaminated food and possibly Mycotoxins are known to cause nausea, vomiting, Abdominal pain and diarrhea when ingested.[44] The mechanism of toxicity is related to direct toxicity effects on GI mucosal surfaces.

Teratogenicity

Animal Studies have also shown mycotoxic effects on Fertility and embryo implantation Treatment of pregnant mice at 5 mg / kg, i.p. Ochratoxin A on days 7–12 of gestation resulted in increased prenatal mortality., T-2 toxin (1.0 mg / kg) was a prenatal growth retarder and a teratogen. Trichothecenes has been shown that limb and tail abnormalities occur in animals Studies . Aflatoxins are teratogenic for most animals examined models. Ergot has been shown to trigger an abortion due to their oxytocic or uterine contraction effects.[50] Zearalenone can cause infertility and fetal malformation due to estrogenic effects.[51] It is also important to point out that these exposures were all through oral administration.

REGULATION AND MANAGEMENT

Mycotoxin problems worsen if handling and storage practices ever lead to mold growth. The ability to diagnose and verify mycotoxicosis is an important forensic aspect of mycotoxin problems.[52] To control the mycotoxin contamination, feed processors and grain mill operators keep the grain at less than 14% moisture. The feed components must be dry, oxygen-free and treated with mold inhibitors. Delivering contaminated feed to susceptible animals can lead to a reduced growth rate, illness and death. People who have enough food can usually avoid foods that are heavily contaminated by mycotoxin. Chemical treatment and processing are anthropogenic factors that can reduce food or feed contaminated with mycotoxin. Bentonite and aluminosilicate clays used as binders have been shown to reduce AF poisoning in pigs, rats, cattle and poultry without causing digestive problems when mixed with AF contaminated feed.[53] The antioxidant ethoxyquin has been recognized as a potent anti-aflatoxigen agent that has been established in humans as a potential chemoprotective agent against the carcinogenic effects of AFB1.[54] Fumonisin contamination was reduced using fungisides such as cyproconazole and tebuconazole, and fungisides such as itraconazole and amphotericin B have been shown to effectively control the aflatoxin-producing Aspergillus species.[55] Practices such as crop rotation, planting date and irrigation management have only limited effects on the infection and subsequent contamination with mycotoxins. Government agencies, private organizations,non-government organizations and national media networks could raise awareness of what mycotoxin is and the risks it poses to human and animal health.

CONCLUSION

Fungi can damage many organ systems. In addition to infections and allergies, fungi can produce mycotoxins and organic chemicals, which are responsible for various toxicological effects in certain circumstances. Mycotoxin-related diseases in humans clearly show a connection between the intake of food contaminated with mycotoxin and diseases, in particular liver, gastrointestinal and carcinogenic diseases. There is currently no supporting evidence that inhaling mold or mycotoxins indoors is responsible for other serious health effects than temporary irritation and allergies in immunocompetent people. For a better understanding of mycotoxin absorption, suitable animal models are required, which correspond to the principles of inhalation toxicology, metabolism and disease relationship indoors. A solid epidemiological methodology is urgently required to connect people who are exposed to known mycotoxin concentrations with precisely defined endpoints or disease entities. Most official regulations and control methods are based on high-performance liquid technologies (e.g. HPLC) by international bodies. There is no specific treatment or antidote for most mycotoxins. Supplementing with vitamins and selenium can be helpful and providing high quality protein.

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