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Mycotoxins: The Hidden Danger in Foods

Aycan Cinar and Elif Onbaşı

Abstract

Mycotoxins are secondary metabolites synthesized by a variety of fungal species such as *Aspergillus*, *Penicillium*, *Fusarium*, and *Alternaria*. These secondary metabolites are toxic and have a significant impact if they enter the production and food chain. Mycotoxins have attracted worldwide attention because of their impact on human health, huge economic losses, and domestic and foreign trade. Although more than 400 mycotoxins have been identified, most studies have focused on aflatoxins (AF), ochratoxin A (OTA), *Fusarium* toxins, fumonisin (FUM), zearalenone (ZEA), trichothecenes (TCT), and deoxynivalenol/nivalenol due to food safety and economic losses. This chapter will be addressing the type of mycotoxins, its importance in food industry, preventive measures, and implementation of hazard analysis critical control point (HACCP) to control mycotoxin.

Keywords: mycotoxin, aflatoxins, ochratoxin A, *Fusarium* toxins, fumonisin, zearalenone, trichothecenes, deoxynivalenol/nivalenol, food industry, HACCP

1. Introduction

Mycotoxins are secondary toxic metabolites with a wide variety of chemical structures synthesized by fungi (mold) [1]. Mycotoxins are thought to be a kind of “chemical defense system” to protect mold from insects, microorganisms, nematodes, grazing animals, and humans [2]. Molds reproduce by means of spores, and their small molecular weight spores are easily disseminated to environment by wind. They cannot be affected by the adverse environmental conditions and can be present in the latent state for long periods. Moreover, when the environmental conditions are appropriate, spores return to vegetative form and can form into new mold colonies. Agricultural products can be contaminated with mold in pre-harvest via insect and bird damage and harsh weather condition damage such as hail damage. In addition, selected harvesting method is one of the most important reasons in contamination of the mold to the products. Improper storage, transport, and marketing can also cause the mold growth and synthesis of mycotoxins [3].

Mycotoxin can occur in food and agricultural products via many contamination pathways, at any stage of production, processing, transport, and storage (**Figure 1**) [4]. Factors that affect mold growth and mycotoxin production are temperature, relative humidity, fungicides and/or fertilizers, interaction between the colonizing toxigenic fungal species, type of substrate and nutritional factors, geographical location, genetic requirements, and insect infestation [5, 6].

Approximately 400 fungal secondary metabolites are known to be toxic, and one quarter of agricultural products have been reported to be contaminated with

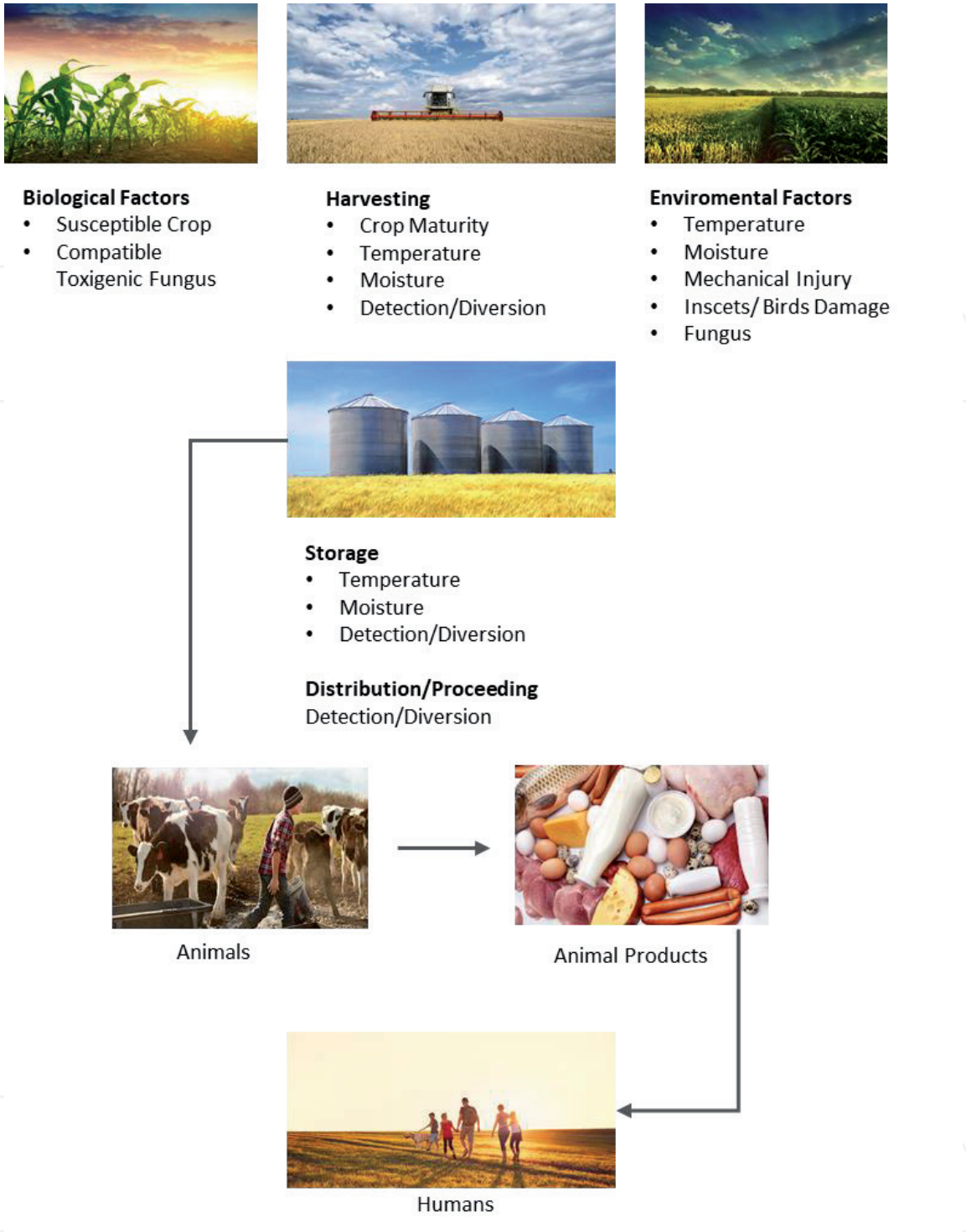


Figure 1.
Factors affecting mycotoxin occurrence in the food and feed chain [7, 8].

mycotoxins in the world [5–9]. While a type of mold may form more than one mycotoxin, a mycotoxin can be synthesized by many molds. The most common types of mold which are known to produce mycotoxins are *Aspergillus*, *Penicillium*, *Fusarium*, and *Alternaria* [10].

According to the result of many studies in poultry and mammals, mycotoxins can be carcinogenic, mutagenic, teratogenic, hepatotoxic, nephrotoxic, immunosuppressive, and embryotoxic [11]. The phenomenon of toxicity is called mycotoxicosis occurring after consumption of mycotoxin-contaminated product by human and animal [12].

Especially cereals, grains, nuts, oilseeds, fruits, dried fruits, vegetables, cocoa and coffee beans, wine, beer, herbs, and spices are major mycotoxin vectors since they are consumed by a large mass of people and animals [4]. Mycotoxins cause

different degrees of toxicity according to exposure time, mycotoxin amount, physiological state, and sensitivity of the organism in humans and animals.

In addition to risk of public health, mycotoxins generate high level of economical losses for food industry due to reduced crop yields, lost trade revenues (local and international), and livestock illnesses [13, 14]. Elimination of mycotoxin is quite though due to resistant to physical, chemical, and biological methods; however, some of the measures described in the following sections may help to prevent mycotoxin. The methods used for mycotoxin determination are chromatography such as high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), gas chromatography-mass spectrometry (GC-MS), and also enzyme-linked immunosorbent assay (ELISA) technique and biosensor-based screening methods [15]. Detection is complicated due to limitations in analytical methodology [16]. Therefore, prevention of mold contamination and mycotoxin synthesis is essential for food safety in food industry.

According to the Food and Agricultural Organization (FAO), 77 countries have established guidance and regulations on mycotoxin in food and feed to control the level of mycotoxin. On the other hand, 13 countries including African countries still do not have specific regulation for food safety [4].

2. Importance of mycotoxin in food industry

Ergotism is one of the oldest determined mycotoxicoses (disease) in human and results from consumption of the ergot body in rye or other grains infected by a parasitic fungus of the genus *Claviceps*. The history of this disease is based on the outbreak of Spartans in 430 BC [17]. The world has been met with mycotoxin term after an extraordinary death of nearly 100,000 turkeys in near London, England, in 1960 due to a peanut (groundnut) meal imported from Brazil, contaminated with secondary metabolites from *Aspergillus flavus* (aflatoxins) [18]. Scientists focused on the occurrence and toxicology of mold metabolite that could cause serious health and economic losses after this case. Aflatoxin (AF) is the term derived from the name of one of the molds that produces it, *Aspergillus flavus*. Mycotoxins have been affecting people since 1960, which is the time of the finding of mycotoxin, and this problem still persists worldwide.

Mycotoxins can occur in the food in several ways (**Figure 1**), but technically divided into two groups; first is mold growth as a pathogen plant in field, another one is grow on stored. After plant materials are contaminated with mold spores from soil and air, they easily contaminate other food source, production area, laboratory, and even kitchen of our homes. Certain species of mold are capable of mycotoxin synthesis; therefore, each food contaminated with mold always may not contain mycotoxins. Nevertheless, moldy products are considered to be risky products in terms of mycotoxin.

Mycotoxins appear in almost all kinds of animal feed and products such as wheat bran, noug cake, pea hulls, maize grain, milk and meat, and also human food such as cereal, fruit and vegetables, spice, etc. [5]. Consuming these foods creates serious health risks in human and all animal species. Mycotoxin intake by feed or food causes chronic intoxication rather than acute symptoms. Acute toxicity is observed in high-dose mycotoxin exposure, and symptoms show a rapid effect such as borborygmy, abdominal pain, diarrhea, etc. On the other hand, low-level mycotoxin exposure in long period causes serious impairments in the liver, kidney, and immune system organs and tissues. Therefore, mycotoxin plays a significant role in cancer in these organs [2]. Some important mycotoxin health effects are shown in **Figure 2**. Toxic effects on humans and animals of important mycotoxins are shown in **Table 1** [19].

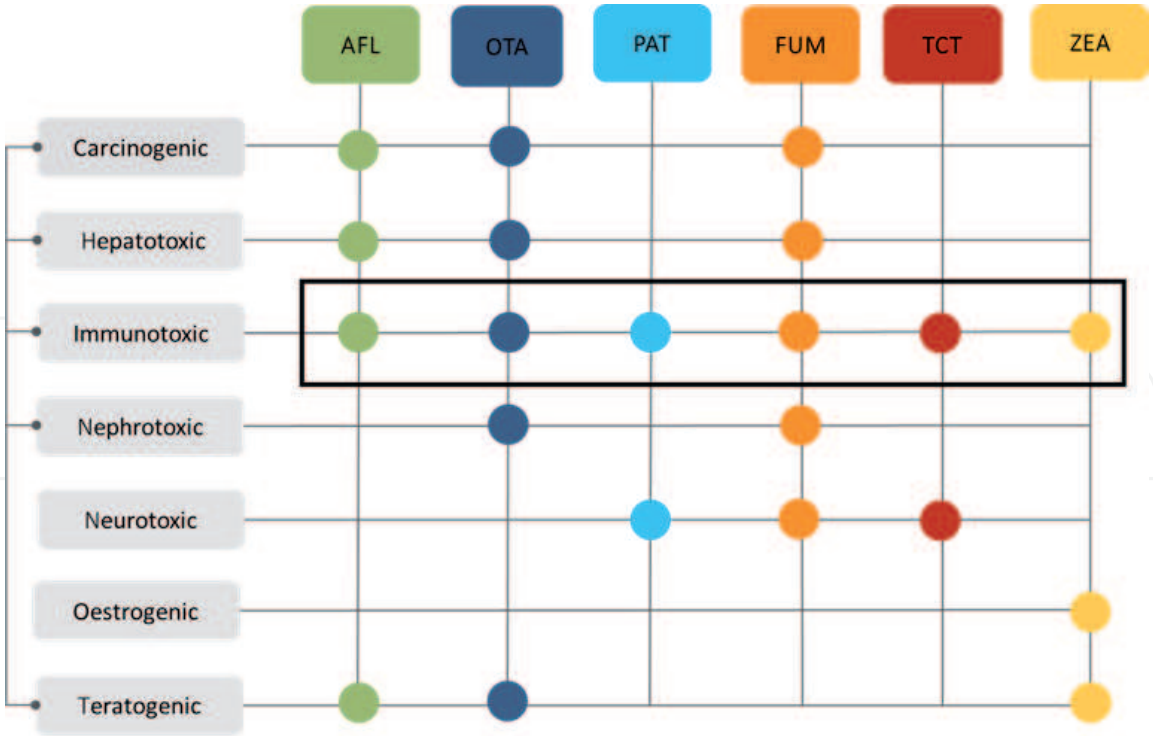


Figure 2. Aflatoxin (AFL), ochratoxin A (OTA), patulin (PAT), fumonisin (FUM), trichothecenes (TCT), and zearalenone (ZEA) mycotoxin health effects [20].

Mycotoxins have caused many serious outbreaks worldwide. There was an outbreak that occurred in 1967, and 26 people were poisoned because of the consumption of moldy rice for up to 3 weeks in Taiwan [21]. An outbreak of aflatoxicosis affecting humans, reported in India, led to the death of 100 people in 1974 [22]. Another outbreak was reported in India in 1995, affecting 1424 people due to sorghum and maize contaminated with fumonisin [23]. During January–June 2004, an aflatoxicosis outbreak in eastern Kenya resulted in 317 cases and 125 deaths [24].

Mycotoxin contamination in foods and fodder has been becoming a global concern day by day. According to Food and Agricultural Organization (FAO) reports, it is estimated that mycotoxin affects nearly 25% of the world’s crop each year and is causing huge agricultural product and industrial losses in billions of dollars [25]. For example, estimated annual loss in the United States is approximately \$ 0.5–1.5 billion [19]. The main effects of mycotoxins on national economies can be thought in five ways:

1. Product yield losses due to toxigenic mold diseases
2. Decrease in commercial value because of contaminated food and feed
3. Human and animal health losses due to harmful impacts associated with mycotoxin-contaminated food and fodder consumption
4. Cost of analysis of mycotoxin
5. Strategies to control mycotoxin contamination

Economic impacts are felt by agricultural chain such as manufacturer of plant and animal, especially cereal industry, consumers, and briefly all farm-to-fork steps.

Mycotoxins	Genus/species	Major food	Toxic effects and diseases
Aflatoxin	<i>Aspergillus flavus</i> <i>A. parasiticus</i> <i>A. nomius</i> <i>Penicillium</i>	Cereals, feeds, oilseeds and pulp, coconut	Carcinogenic, hepatotoxicity, teratogenicity, decreasing immune systems, affecting the structure of DNA, hepatitis, bleeding, kidney lesions
Fumonisin	<i>Fusarium verticillioides</i> <i>F. culmorum</i>	Cereals, corn	Encephalomalacia, pulmonary edema, carcinogenic, neurotoxicity, liver damage, heart failure, esophageal cancer in humans
Ochratoxin OTA	<i>Aspergillus</i> <i>Penicillium</i> <i>A. ochraceus</i> <i>P. nordicum</i> <i>P. verrucosum</i>	Cereals, herbs, oil seeds, figs, beef jerky, fruits, and wine	Kidney and liver damage, loss of appetite, nausea, vomiting, suppression of immune system, carcinogenic
Patulin	<i>Aspergillus terreus</i> <i>A. clavatus</i> <i>Penicillium</i> <i>Penicillium carneum</i> <i>P. clavigerum</i> <i>P. griseofulvum</i>	Silage, wheat, feeds, apples, grapes, peaches, pears, apricots, olives, cereals	Neural syndromes, brain hemorrhage, skin lesions, skin cancer, lung, mutagenicity, antibacterial effect
Trichothecenes (T2, DON, DAS, HT2)	<i>Fusarium</i> <i>Cephalosporium</i> <i>Trichoderma</i> <i>Fusarium oxysporum</i>	Cereals, feeds, silage, legumes, fruits, and vegetables	Immune suppression, cytotoxic, skin necrosis, hemorrhage, anemia, granulocytopenia, oral epithelial lesions, GIS lesions, hematopoietic, alimentary toxic aleukia (ATA), hypotension, coagulopathy
Zearalenone	<i>Fusarium</i> <i>F. graminearum</i> <i>F. culmorum</i>	Cereals, corn, silage, timothy grass, fodder	Carcinogenic, hormonal imbalance estrogenic effect, reproductive problems, teratogenic

Table 1.
Name of some important mycotoxin-producing fungi, susceptible foods, and mycotoxin effects on humans and animals [19].

3. Worldwide important mycotoxin in food industry

3.1 Aflatoxins (AF)

Aflatoxins are a group of toxic secondary metabolites of filamentous fungi, *Aspergillus flavus*, *A. nomius*, and *A. parasiticus*, and the most important mycotoxins in the world for human food and animal feed [26]. On the other hand, recent studies have showed that *A. nomius*, *A. sergii*, *A. bombycis*, *A. minisclerotigenes*, *A. parvisclerotigenus*, *A. pseudocaelatus*, *A. pseudotamari*, and *A. ochraceoroseus* also have aflatoxigenic properties, but the occurrence of these species in nature is low [27]. The natural fungal multiplication subsequent to quantity of AF production is affected by various factors including environmental conditions (e.g., high temperature, moisture, and relative humidity), the presence of carbon dioxide and oxygen, mechanical damages, plant genre, insect infestation and amount of spores, and implementation of pesticides and fungicides [28, 29]. Among these, especially temperature and relative humidity are the most important effects of the formation and amount of AF as *A. flavus* has shown optimal growth at temperature from 29 to 35°C, maximum

aflatoxin production at 24° C, and no production at temperatures below 13°C or above 42°C and relative humidity below 70% [30]. Heat processing, such as ultra-high-temperature (UHT) treatment, pasteurization, roasting, and baking, and also cold storage do not affect aflatoxin in foods since they are fairly stable and resistant [31, 32]. Approximately more than 14 various chemical forms of AF are present in nature; however, the most dangerous ones are aflatoxins B1, B2, G1, and G2 [33]. The nomenclature of aflatoxins with these letters is based on the color they exhibit under ultraviolet radiation (B, blue, and G, green) [34]. Various food products especially grown in hot and humid regions of the world are susceptible to fungal invasion and aflatoxin production, including groundnuts, maize, various spices, tree nuts, cottonseed, pistachios, copra, wheat, rice, etc. [25]. AFB1 is converted into metabolized AFM1 and excreted in milk in both human and lactating animals [35]. The European Commission, Codex Alimentarius Commission, Germany, Turkey, Switzerland, France, Sweden, Belgium, Argentina, Iran, and Honduras have regulated an acceptable limit for AFM1 at 50 ng/L for infants, for raw, pasteurized, and UHT milk. On the other hand, the United States, Brazil, China, Bulgaria, Czech Republic, Kuwait, and Serbia have accepted 500 ng/L level for AFM1 [31]. Aflatoxin contamination causes huge economic and critical health problem due to their high toxicity. For example, aflatoxin contamination is estimated to cause damages to the corn industry in the United States ranging from US \$ 52.1 million to US \$ 1.68 billion [36]. They are carcinogenic, hepatotoxic, and teratogenic, decrease immune systems, poison the body through respiratory, and can directly affect the structure of DNA [37]. Of all the human health effects associated with aflatoxin exposure, the weight of evidence is strongest for aflatoxin-related liver cancer and secondarily of the synergism between aflatoxin exposure and chronic HBV infection in liver cancer risk [38]. In 1974, there was an outbreak of hepatitis due to aflatoxin in India, resulting in an estimated 106 deaths [22]. In 2004 the largest outbreak was ever recorded, where 317 people became ill and 125 people died because of consumption moldy maize which early harvested and stored improper harvested condition [39]. In 2013, countries in Europe, including Romania, Serbia, and Croatia, reported that nationwide milk was contaminated with aflatoxin [40].

3.2 Ochratoxin A

Ochratoxin A (OTA) is a natural mycotoxin produced mainly by fungal type of *Aspergillus* and *Penicillium* under optimum environmental conditions and storage especially tropical and subtropical regions such as Eastern and South Europe, Canada, and South America [41, 42]. There are three types of ochratoxins, namely A, B, and C. Especially, OTA is known as the most common and important one for public and animal health. Although people are exposed to OTA by inhalation or dermal contact, various foods are the main source of exposure to OTA including maize, sorghum, wheat, rice, barley, rye, bread, oats, flour, pasta, grapes, infant cereals, apples, peaches, strawberries, pears, oranges, figs, mangoes, wine, tomatoes, coffee beans, watermelons, nuts, rapeseed, sesame seeds, spice, soybeans, cocoa, peanuts, chickpeas, milk and milk-based baby formulae, eggs, cheese, yam, potatoes, garlic, onions, fish, pork, poultry, jerky, and dried beans [43]. Recently, the presence of OTA has been detected in bottled water [44], plant food supplement, and food coloring agent [45]. According to the European Commission report, the estimated adult exposure to OTA is as follows: 44% cereals, 10% wine, 9% coffee, 7% beer, 5% cacao, 4% dried fruits, 3% meat, 3% spices, and 15% others [46]. For the first time in 1970, the presence of OTA was detected in human blood in Balkans [47]. In the review of Malir et al., published data on OTA in human blood samples from healthy persons were compiled, and concentrations higher than 1.0 g/L were observed in several countries [48].

Huge amount of economic losses occurs resulting from OTA contamination on feed and food particularly livestock production. Exposure of OTA causes renal dysfunction (suspected in Balkan endemic nephropathy) and also is considered to be teratogenic, immunotoxigenic, nephrotoxic, carcinogenic, embryotoxic, hepatotoxic, and especially nephrotoxic in laboratory and farm animals [43, 49].

3.3 *Fusarium* toxins

Fusarium toxins are secondary metabolites synthesized by toxigenic molds including *Fusarium oxysporum*, *F. culmorum*, *F. roseum*, and *F. graminearum* [50]. Fumonisin (FBs), zearalenone (ZEA), trichothecenes, deoxynivalenol (DON), and nivalenol (NIV) are the most common *Fusarium* mycotoxin groups [51]. Recently fusaproliferin (FUS), beauvericin (BEA), enniatins (ENNs), and moniliformin (MON) are discovered but less studied [52]. *Fusarium* disease outbreak on cereal products such as wheat, barley, and maize causes worldwide economic losses due to yield loss and reduced grain quality, for example, losses in the United States of \$ 1–20 million in a normal year and \$31–46 million in a year [53]. *Fusarium* mycotoxin has both acute and chronic toxic effects and been shown to cause a wide variety of toxic effects in animals [54]. Spontaneous outbreaks of *Fusarium* mycotoxicosis have been reported in Europe, Asia, Africa, New Zealand, and South America. Moreover, chronic intake of these mycotoxins is reported on a regular and more widespread basis due to their global occurrence [55]. *Fusarium* mycotoxin limits specified in unprocessed cereals, milling products, and cereal foodstuffs are 200–1750 µg/kg for DON, 20–400 µg/kg for ZEN, and 200–4000 µg/kg for the sum of B1 + B2 fumonisins (FB1 + FB2 combined) according to the European Commission (19 December 2006).

3.3.1 *Fumonisin*

Fumonisin is generated by various fungal species such as *Fusarium verticillioides* and *F. proliferatum* also by *A. niger* and were discovered in 1988 in South Africa [56, 57]. Nowadays 28 types of fumonisin have been identified that are divided into four groups, fumonisins A (A1, A2, and A3), fumonisins B (B1, B2, and B3), fumonisins C (C4, C3, and C1), and fumonisins P (P1, P2, and P3), but the most important group of fumonisins is the B group, which contains fumonisins B1 (FB1), B2 (FB2), B3 (FB3) [58].

The International Agency for Research on Cancer (IARC) identified FB1 as possibly carcinogenic to humans (group 2B). Recent studies reported that FB1 causes an increased prevalence of esophageal and liver cancer in humans [59]. Furthermore, this mycotoxin has been found to have toxic effects against several organs (nervous and cardiovascular systems, liver, lung, kidney) in animals [60]. Fumonisin is largely found in corn and corn-based foods and also FB1 in rice, beer, sorghum, cowpea seeds, triticale, beans, asparagus, and soybeans [61].

3.3.2 *Zearalenone (ZEA)*

Zearalenone (ZEA), known as an estrogenic mycotoxin, is a secondary metabolite produced by *Fusarium* species such as *F. graminearum*, *F. culmorum*, *F. cerealis*, *F. equiseti*, *F. crookwellense*, and *F. semitectum* (mainly *F. culmorum* and *F. graminearum*) [62]. The main contamination source of ZEA is cereal-based foods such as maize, sorghum, wheat, rice, barley, oats, and also nuts, soybean, and sesame [63].

Several in vivo studies found that ZEA disrupts hormonal balance due to its similarity to naturally occurring estrogens [64]. The mycotoxin has high affinity for

estrogen receptors, causing reproduction and fertility disorders in mammals [65]. In addition, it is known that progressive exposure to endocrine-modulatory compound has been linked with carcinogenesis in human [64]. According to the European Food Safety Authority (EFSA) report in 2014, the bioavailability of toxin is up to 80% in human and animals such as rats, rabbits, and pigs [66]. Moreover, recent works report ZEA is metabolized in the liver and has shown hepatotoxic, immunotoxic, carcinogenic, and nephrotoxic effect in animal tests [67–69]. As this mycotoxin possesses such consumer health risks, the European Union (EU) has prescribed the limits of ZEA (20–350 µg/kg) for various processed and unprocessed cereals [66].

3.3.3 *Trichothecenes (TCT)*

Trichothecenes are a large group of mycotoxins produced predominantly by *Fusarium* species although produced by other fungal genera such as *Trichoderma*, *Trichothecium*, *Stachybotrys*, *Verticimonosporium*, *Cephalosporium*, *Myrothecium*, and *Cylindrocarpum* spp. [70]. More than 200 different trichothecenes and trichothecene derivatives have been isolated. Trichothecenes are classified into four types (A–D). Type A and type B are the most prevalent type occurring widely in cereals [71, 72]. Type A trichothecenes such as T-2 and HT-2 toxins, diacetoxyscirpenol (DAS), monoacetoxyscirpenol (MAS), and neosolaniol (NEO) are synthesized mainly by *F. sporotrichioides* and *F. langsethiae*. On the other hand, type B including deoxynivalenol (DON), the co-contaminants 3- and 15-acetyl DON (3A-DON or 15A-DON), and fusarenon-X (FUS-X; synonym 4-acetylnivalenol) are mainly produced by *F. graminearum* and *F. culmorum* [73]. Moreover, another important type B member, nivalenol (NIV), is commonly synthesized by *F. poae* in cereals [74].

The mechanism of action of trichothecenes is based on the inhibition of protein synthesis in eukaryotes. This mycotoxin affects peptidyl transferase enzyme binding the 60S ribosomal subunit, thus causing the inhibition of protein translation and ribotoxic stress [75]. Also, Pestka reported these groups of mycotoxins cause immunosuppression or immune stimulation by affecting the leucocytes [76].

The family of trichothecenes has a significant impact on cereal and grain production due to health risk for human consumption, livestock feed, or malting purposes [77, 78]. According to report from the FDA, economic losses associated with mycotoxin ranges from USD 0.5 million to over USD 1.5 billion from aflatoxin (corn and peanuts), fumonisin (corn), and deoxynivalenol (wheat) in the United States. [72]. Hence, control of these mycotoxins is essential for human and animal health and economic reasons.

3.3.3.1 *Deoxynivalenol/nivalenol*

Deoxynivalenol (DON), known as vomitoxin, is the most commonly detected trichothecenes in grains such as wheat, barley, oats, rye, and corn and less often in rice, sorghum, and triticale [79]. Even though NIV presence of cereals appears generally to be lower than DON [80], it has been reported that the occurrence of NIV in of wheat and barley is as prevalent as that of deoxynivalenol (DON) in Japan [81]. According to animal toxicity studies, NIV shows higher toxicity than DON. The LD50 values for DON and NIV in tests in mice were 78 and 39 mg/kg, respectively, and DON and NIV, similarly to other trichothecenes, show inhibitor effect on cell metabolism such as protein, DNA, and RNA synthesis [82]. In addition, these mycotoxins affect cell division and mitochondrial functions [83, 84, 70]. Both mycotoxins exhibit major symptoms such as abdominal discomfort, diarrhea, vomiting, and inflammation of the throat, weight loss, and anorexia [85].

The World Health Organization (WHO) reported that trichothecenes shows fatal and chronic intoxications on human and livestock and also DON shows teratogenic, neurotoxic, and immunosuppressant effects [86].

According to the conducted BIOMIN World Mycotoxin Survey, DON appeared in 81% of livestock feed from 81 countries worldwide followed by fumonisins that were detected in 71% of samples. Therefore, DON is reported as the most common mycotoxin worldwide (<https://www.biomin.net/en/biomin-mycotoxin-survey/>).

4. Management of mycotoxin prevention

Food safety is a key component in public health issue, and a mycotoxin is a huge food safety risk in developing countries. Prevention is the most important and effective way in reducing fungal growth and mycotoxin production to ensure food safety. The following steps that explain prevention and control of mycotoxin occurrence include good agricultural practices (GAP) in field, control practices of harvesting and storage, physical methods (cleaning, milling, etc.), implementation of biotechnological application, biological control through the use of controlled atmosphere during storage, detoxification/degradation, and fermentation techniques.

Pre-harvesting is considered first and one of the most important stages to prevent mold growth and mycotoxin synthesis. Several strategies are available for the produce of healthy products and reduce the mold formation at pre-harvesting, including selection of plants according to the soil structure and production capacity, use of plant which is resistant to fungi and insects, irrigation time, make fertilization, use of insecticides to prevent insect damage [87].

Harvesting at the appropriate time periods (low moisture and full maturity) is essential for reducing the risk of a mycotoxin contamination since overmaturity creates sensitivity to mold growth. Additionally, suitable harvesting equipment and procedures should be used, and crops should be dried after maturity to both reduce grain moisture to safe levels [88].

The latest technological advances provided new paths in mycotoxin control strategies that include the use of a controlled atmosphere with inhibitory or a protective effect and use of naturally occurring compounds under different conditions and essential oils with antioxidant properties to decrease fungal growth and mycotoxin production in grains during storage [89]. Moreover, these strategies also include using regularly cleaned transport vehicles to prevent cross contamination of products; monitoring of temperature, humidity, aeration and pest infestation periodic during storage [90]; using mold inhibitors (propionic acid) to contaminated food and feed; and application of disinfectant such as sodium hypochlorite to storage area [91].

Some studies have shown that using physical methods (dehulling, washing, sorting, and cleaning of visible moldy seed) reduces different mycotoxin species in foods regardless of grain genre [70]. Scudamore and Pascale et al. [92] and Patel [93] observed a reduction of T-2 (62%) and HT-2 (53%) and DON (50%) in wheat seeds after cleaning. Scudamore and Patel also reported a 32% reduction in fumonisin levels in corn in an industrial enterprise [94]. Moreover, milling is an important effect in the reduction of *Fusarium* mycotoxins in grains especially wet milling of maize which has shown to result in the degradation of mycotoxins [95].

One of the best applicable strategies for the prevention of mycotoxin formation is the cultivation of fungal infestation-resistant plants and improvement of the genetic composition to suppress mycotoxin production [96]. The benefits of biotechnological applications were observed with Aflasafe. Aflasafe is a biocontrol

product that includes a blend of four fungal species covered over grains which reduce aflatoxigenic fungi that produce AFs in maize and groundnuts (<https://aflasafe.com/>).

Mycotoxins are resistant to heat and cannot be completely destroyed under normal cooking process. On the other hand, mycotoxin reduction has been determined after heating, and this may be the result of reactions changing the chemical structure [70]. Ryu et al. reported heat treatment (at temperature 120–160°C) causes a reduction between 66 and 83% of ZEN [97]. Scott and Lawrence also reported a reduction of 60–100% of fumonisins with a heat treatment at 190°C (60 min) and 220°C (25 min).

Biological control of mycotoxins via detoxification/degradation offers a promising alternative method [98]. Recently the effectiveness of fermentation for the reduction and elimination of mycotoxins has also been proven. Studies documented in the literature generally show that mycotoxins are reduced by conversion, detoxification, binding, degradation, and decontamination after food fermentation [99]. Modification of the chemical structure of the mycotoxin molecule, removal or detoxification/inactivation, and adhesion to bacterial cell walls provide a reduced toxicity during fermentation [99]. Implementation of these preventive methods cannot solve the problem alone; also it must be an integral part of an integrated food safety management system based on the hazard analysis and critical control point (HACCP).

5. Implementation of HACCP to mycotoxin control

HACCP is a food management system where food safety is addressed through the analysis, control, and monitoring of physical, chemical, and biological hazards from raw material manufacturing, supply, and handling to production, distribution, and consumption of the finished product [100]. The National Advisory Committee on Microbiological Criteria for Foods (NACMCF) published a guideline about HACCP containing seven basic principles, decision tree, and all plans in 1992 [101]. Implementation of HACCP is an effective strategy for prevention, control, and periodic monitoring of mycotoxin in all stages from field to the consumer. There are 12 successive steps recommended to implementation of HACCP system. Previous HACCP studies can be researched to set up tasks from 1 to 5 that specify each food process, and tasks required for mycotoxin control begin at 6 (Principle 1).

1. Establish the HACCP team.
2. Describe the product.
3. Identify the product's intended use.
4. Draw up the commodity flow diagram.
5. Confirm the flow diagram on-site.
6. Identify and analyze hazard(s) (Principle 1).
7. Determine the critical control points (CCPs) (Principle 2).
8. Establish critical limits for each (CCP) (Principle 3).
9. Establish a monitoring procedure (Principle 4).

- 10. Establish corrective action (Principle 5).
- 11. Verify the HACCP plan (Principle 6).
- 12. Keep record (Principle 7).

Principle 1: identify and analyze hazard—food safety hazards for HACCP programs are divided into three groups: biological (bacteria, viruses, parasites, etc.), chemical (cleaning agents, pest control, pesticides, biocides, mycotoxin), and physical (glass or metal fragments, jewelry, etc.). Mycotoxins are identified as biological hazards because they are secondary metabolites of mold and also identified as a chemical hazard that appears as residues in food.

Principle 2: determine critical control points (CCPs)—determining CCPs is an essential step which is decided using the HACCP decision tree to eliminate or prevent a food safety hazard or reduce it to an acceptable level. Dried figs and other dried fruits, pistachios and other edible nuts and cereals, and also animal feed such as maize, groundnut cake, cottonseed cake, babassu, palm kernel cake, copra cake, etc. are susceptible to mycotoxin in planting, harvesting, production, storage, and transport according to EC regulations. Mycotoxins can be considered a CCP for these products. For example, *Aspergillus flavus* is a CCP in maize production. It is a pathogenic fungus which colonizes in broken kernels in stored maize. High concentration of aflatoxin can cause public health problem, rejection of the final product or product recalls, litigation, etc. [102].

Principle 3: establish critical limits—critical limits must be defined and verified for each CCP. Mycotoxin acceptable limits can be set by country regulation and customer or producer specification which is below of the regulatory mycotoxin limit (Table 2).

Principle 4: establish a monitoring system for each CCP—identifying an appropriate, sensitive, and rapid monitoring method which applies physical, chemical, and biological measurement or observations for each critical control point. HPLC, GC, ELISA, OWLS-based biosensors, rapid test kits, etc. are used to detect mycotoxin level.

Principle 5: establish a corrective action—Corrective action must be established when monitoring result indicates that there is a deviation of target CCP

Crops and tolerated levels of mycotoxins (μgkg^{-1})					
Country	Mycotoxins	Rice	Maize	Spices	Fruit juices
Brazil	AFB1/AFG1	30	30	30	30
China	AFB1	10	20	—	—
France	FB1	1000	1000	—	—
Hungary	Total AF	50	50	-	-
	OTA	5	5	-	-
Japan	AFB1 Patulin	10	10	10	—
The United States	Total AF	20	20	20	-
	Patulin	-	-	-	50
Turkey	AFB1	2	2	5	-
	Patulin	-	-	-	-

Table 2.
Global regulation of mycotoxin contamination in agricultural products [103].

Step/CCP	Hazard analysis		Monitoring			Corrective action
	Hazard	Control	Critical limit	Monitoring	Frequency	
Pre-harvest/ growing	Low soil moisture leading to plant stress during kernel development	Irrigate	Lower limit of critical water activity (aw) (check with your agronomist/extension staff for an exact value)	Measure soil moisture and record	Weekly on Monday morning	Additional irrigation; record amounts
	Insufficient soil nutrients leading to plant stress during kernel development	Fertilize	N, P, and K applications as recommended for hybrid by local agronomists (insert the values)	Fertilizer applied (appropriate for soil type and hybrid); amounts and type recorded	As recommended for hybrid	Additional fertilizer; record amounts added
	Insect attack leading to damaged kernels	Integrated pest management (IPM) plan	Insect population within acceptable limits as determined by control program	Visual inspection and sample, with results recorded	Weekly	Apply pesticide in accordance with IPM plan
Harvest	Damage to kernels from harvester	Harvest when kernels are dry	Moisture content $\leq 14\%$	Measure and record grain moisture	Prior to harvest	Delay harvest till kernels are dried enough
Storage	Excessive moisture content of kernels	Do not store until kernels are dry	Moisture content $\leq 14\%$	Measure and record grain moisture	Immediately prior to storage	Dry mechanically
	Insect attack, allowing fungi to penetrate kernels	IPM plan	No evidence of insect or rodent infestation using inspection protocols specified in IPM plan	Visual inspection with results recorded	Weekly	Apply pest control methods in accordance with IPM plan
	High ambient humidity and temperature	Aerate grain to control temperature and humidity	Temperature and humidity within limits recommended in industry literature	Measure and record humidity, ambient temperature, and airflow	Daily during storage	Adjust aeration time of day or airflow to achieve desired temperature and humidity

Table 3.
HACCP plan of maize [102].

value. Taking appropriate corrective actions immediately is essential to producing safe food [103]. Corrective actions must ensure that the CCP is taken under control. Corrective action sample of maize production is given in **Table 3**.

Principle 6: establish verification procedures—regularly at the specified intervals, it must be verified by checking whether the levels of mycotoxin in the final product are within acceptable levels. The following steps are used for verification:

- Microbiological and/or chemical tests can be used to confirm which product is meeting CCP.
- Asking questions especially to CCP employees.
- Internal or external audit by independent person to check whether HACCP system is being implemented.

Principle 7: establish documentation and record keeping—record keeping is an evidence of how you identify, monitor, and verify each hazard. HACCP plan, flowchart of product, product description, HACCP team, hazard analysis documents, analysis result sheet, etc. are required for monitoring whether control of each hazard is appropriate or not.

6. Conclusion

Mycotoxin is a well-known food safety risk, which is a threat to human and livestock health, and has high economic significance in food industry. Recently, the food industry has become aware of the new term modified mycotoxins introduced by Rychlik et al. (masked mycotoxin) [104]. Food safety risk has risen since masked mycotoxins which pose many difficulties including the unknown occurrence/co-occurrence of these compounds and their toxicological properties. In addition, Lorenz et al. reported that the European Food Safety Authority (EFSA) has taken into account efforts to address this emerging issue in food safety by developing strategies on how to evaluate potential added health risk due to the occurrence of modified mycotoxins [104].

Mycotoxigenic molds are difficult to prevent and control due to their widespread presence in nature. Prevention of mycotoxin synthesis in all stages of food processing is an essential point for public health and economic reasons. Many practices used for prevention of mycotoxin include good agricultural practices (GAP) in field, control practices of harvesting and storage, physical methods (cleaning, milling, etc.), implementation of biotechnological application, biological control through the use of controlled atmosphere during storage, detoxification/degradation, and fermentation techniques.

Meanwhile a number of techniques for mycotoxin control and management prove to be quite costly and/or unenforceable in some cases. On the other hand, using fermentation process for appropriate process has been recommended for mycotoxin reduction by Adebisi et al. [99]. In the future, more emphasis should be given to nanotechnology and genetic engineering practices in the development of durable product types to ensure food safety.

In addition to these applications, food safety management systems such as HACCP, GAP, and good manufacturing practices (GMP) should be integrated at all stages of production, transport, and storage, in order to minimize contamination in food industry. Also fairly new food safety system including threat assessment

critical control points (TACCP), vulnerability critical control points (VACCP), and hazard analysis and risk-based preventive controls (HARPC) should be investigated and implemented to ensure an effective control system.

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