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Occurrence, toxicity, production and detection of *Fusarium* mycotoxin: a review

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Abstract

Fusarium mycotoxin contamination of both foods and feeds is an inevitable phenomenon worldwide. Deoxynivalenol, nivalenol, zearalenone, T-2 toxin and fumonisin B1 are the most studied *Fusarium* mycotoxins. Co-contamination of mycotoxins has also been studied frequently. *Fusarium* mycotoxins occur frequently in foods at very low concentrations, so there is a need to provide sensitive and reliable methods for their early detection. The present review provides insight on the types, toxicology and occurrence of *Fusarium* mycotoxins. It further elucidates various detection methods of mycotoxin production from *Fusarium* strains, with a special focus on chromatographic and immunochemical techniques.

Keywords: *Fusarium* mycotoxins, Toxicology, Occurrence, Detection

Introduction

Annually, 25–50% of crops harvested worldwide are contaminated with mycotoxins (Ricciardi et al. 2013). *Fusarium* head blight (FHB), also known as ear disease or scab, is a worldwide disease of wheat, corn, barley, rice and other small grains. Over the past decades, FHB has become one of the most serious fungal diseases, attributable to climate change and modern agricultural practices, causing tremendous economic losses worldwide (Osborne & Stein 2007). *Fusarium* mycotoxins are secondary metabolite produced by *Fusarium* species during growth and storage. They also have chemical and thermal stability. Furthermore, mycotoxins are passed from the contaminated feed to animals and eventually to humans. Mycotoxins exhibit both acute and chronic toxic effects in humans and animals. The outbreak of the *Fusarium* toxicity has been reported in many countries, such as Europe, Asia, Africa, New Zealand and South America (Marin et al. 2013). Therefore, to protect human health, some countries have continuously monitored the maximum levels of mycotoxins in foods and other commodities (Table 1) (Ferrigo et al. 2016; Moretti et al. 2017; Selvaraj et al. 2015).

Types and toxicities of *Fusarium* mycotoxins

Fusarium species produce three most important classes of mycotoxins namely: trichothecenes, zearalenone (ZEN), and fumonisins (FBs).

Trichothecenes

Trichothecenes are the most important class of *Fusarium* mycotoxins, and they are also the most diverse chemical composition. They belong to a large family that contains many chemically related mycotoxins. *Fusarium*, *Myrothecium*, and *Stachybotrys* can produce trichothecenes, although they come from taxonomically different genera. Trichothecenes are one of the potential threats to the health of humans and animals worldwide (Li et al. 2011).

Trichothecenes are extremely prevalent with molecular weights ranging from 200 to 500 Da. They include more than 200 toxins, which have a substantial sesquiterpenoid structure, with or without macrocyclic esters or ester ether bridges between C-4 and C-15. In addition, trichothecenes consist of 12,13-epoxyalkylene groups that are responsible for cytotoxicity, as well as 9,10 double bonds with different side-chain substitutions (McCormick et al. 2011). Trichothecenes

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Table 1 Allowable limits of *Fusarium* mycotoxins in food and feeds in certain countries and regions

Range	Toxin	Country	Applicable Products	Limit (μg/kg)
Food	DON	China	Cereals and their products	1000
		EU	Raw durum and oats, wet-milled corn	1750
			Unprocessed cereals other than hard wheat, oats, and corn	1250
			Cereal that can be consumed directly and cornflakes less than or equal to 500 μm in size	750
			Bread, snacks, desserts, and breakfast cereals	500
			Cereal-based foods for infants and young children	200
		America	Wheat for food milling	2000
			Final products made using edible wheat	1000
		Canada	Unpurified soft wheat in China	2000
			Soft wheat flour (adult food)	1200
			Soft wheat flour (baby food)	600
		Armenia	Wheat	700
			Barley	1000
		Belarus	Wheat	700
			Baby food	Prohibited
		Bulgaria	Grain and products made from grain for direct consumption or as processed food ingredients	1000
			Cereals which will be stored or subjected to further physical processing prior to consumption	2000
			Corn and corn products	1000
		Cuba	Imported cereals	300
		Cyprus	Grain	1200
		Serbia	Raw corn	1750
	ZEN	China	Wheat and flour	60
			Corn and corn flour (slag and slice)	60
		EU	Processed cereals for infants and young children	20
			Bread and breakfast cereals	50
			Grain products that can be eaten directly	75
			Corn, corn snacks, and corn breakfast cereals that can be eaten directly	100
			Corn flakes larger than 500 μm in size	200
			Corn flakes less than or equal to 500 μm in size	300
			Corn treated via wet grinding	350
			Refined corn oil	400
		Armenia	All foods	1000
		Austria	Wheat, rye, and hard wheat	60
		Belarus	Barley, wheat, and corn	1000
			Baby foods	Prohibited
		Bulgaria	Grain and processed grain products for direct consumption or for use as processed food ingredients	200
			Corn and corn products	200
		Chile	All foods	200
		Columbia	Sorghum	1000
		France	Grain and grain products	50
	FUMS	EU	Corn-based baby foods	200
			Corn snacks and corn breakfast cereals	800
			Corn, corn snacks, and corn breakfast cereals that can be eaten directly	1000
			Corn flakes larger than 500 μm in size	1400

Table 1 Allowable limits of *Fusarium* mycotoxins in food and feeds in certain countries and regions *(Continued)*

Range	Toxin	Country	Applicable Products	Limit (μg/kg)
			Corn flakes less than or equal to 500 μm in size	2000
			Corn treated via wet grinding	4000
		America	Edible corn	2000
	FB1 & FB2	Bulgaria	Corn and corn products	1000
	FB1	Cuba	Corn and rice	1000
	FB1	France	Grain and grain products	1000
	T-2	China	Distiller's dried grain with corn solubles for feed	100
			Formulated feeds for pigs and poultry	1000
		Armenia	All foods	100
		Belarus	Cereal, flour, and shelled oats	100
			Infant food	Prohibited
		Bulgaria	Grain and grain products for direct consumption and for use as processed food ingredients	100
Feed	DON	China	Formulated feeds for pigs, calves, and lactating animals	1000
			Formulated feeds for cattle and poultry	3000
		Austria	Pannage	500
			Feed for fattening poultry	1500
			Feeds for breeding poultry and laying fowl	1000
			Feeds for beef cattle	1000
		Canada	Feeds for livestock and poultry	5000
			Feeds for pigs, calves, and cows	1000
		Cuba	All feedstuffs	300
		Cyprus	All feedstuffs except coarse grain	7000
			Complete feeds for pigs	1000
			Complete feeds for poultry and fattening calves	5000
			Complete feeds for other animals	3000
		Serbia	Feeds	8000
	ZEN	China	Feeds and distiller's dried grain with corn solubles	500
		Austria	Feeds for breeding swine	50
		Canada	Feeds for gilts and sows	3000
		Cyprus	Feedstuffs	2000
			Complete feeds for piglets	1000
			Complete feeds for all pigs except piglets	1500
	T-2	Canada	Feeds for pigs and poultry	1000
	HT-2	Canada	Feeds for livestock and poultry	100

have been subdivided into four groups (A-D) based on the substitution mode of the core structure of 9-ene (EPT) by tricyclic 12,13- epoxidation. Type A toxins include T-2, HT-2, neosolaniol (ENNS), and diacetoxyscirpenol (DAS). Type B toxins include deoxynivalenol (DON) and its 3-acetyl and 15-acetyl derivatives, nivalenol (NIV), together with acetylated precursor of NIV [4-acetylnivalenol, also termed Fusarenon-X (FUX)]. Type C trichothecenes contain a C-7/C-8 epoxide, such as crotocin. Type D trichothecenes include roridin A, verrucarin A, and satratoxin H which have an extra loop that can link C-4 and C-15 (McCormick et al. 2011; Pinton & Oswald 2014). The structures of the trichothecenes are shown in Fig.1 and Table 2.

Deoxynivalenol

In recent years, FHB has once again become a major disease threatening food security, and this has led to renewed interest in trichothecenes, such as deoxynivalenol (DON) (Goswami & Kistler 2004; Van Egmond et al. 2007).

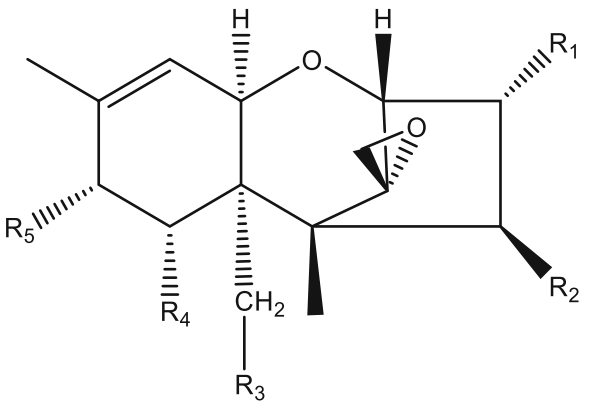

Fig. 1 Structures of trichothecenes (Marin et al., 2013)

DON is mainly produced by *Fusarium graminearum* and *Fusarium culmorum*. DON is chemically described as 12,13-epoxy-3α,7α,15-trihydroxytrichothec-9-en-8-one ($C_{15}H_{20}O_6$), crystallizes as colorless needles, stable at extreme temperatures (120–180 °C) and soluble in polar organic solvents such as aqueous acetonitrile, chloroform, methanol, ethanol and ethyl acetate (EFSA 2004a). DON causes vomiting (that is why it is also known as vomitoxin), digestive disorders, oxidative damage, and reproductive toxicities in animals and humans, however, this mycotoxin is not a human carcinogen (Berthiller et al. 2011). The International Agency for Research on Cancer (IARC) classified DON in group 3 (non-carcinogenic substances) (Ostry et al. 2017). DON causes biological barriers and affects cell and organ functions and viability (Maresca 2013). At cellular level, DON binds ribosomal peptide transferase active sites and activates cell kinases to inhibit protein and nucleic acid synthesis (Shifrin & Anderson 1999; Ueno et al. 1973). Many kinases have been affected, including extracellular signal-regulated kinases, mitogen-activated protein kinases (MAPKs) p38 and c-jun N-terminal kinases (Shifrin & Anderson 1999). DON triggers MAPK-mediated up-regulation of pro-inflammatory cytokine and chemokine expression, and apoptosis (Islam et al. 2006; Shifrin & Anderson 1999; Zhou et al. 2003). The effects of DON on the immune system are manifold. Due to the different mycotoxin concentrations, timing and duration of exposure, effects can be achieved from immunosuppression to immunostimulation. According to Peraica report, DON is a potent protein synthesis inhibitor that depresses the immune system, and causes dysphagia (Peraica et al. 1999). DON is regarded as a teratogen, neurotoxin, and immunosuppressant agent by The World Health Organization (WHO). In general, DON has been associated with chronic and fatal intoxication of human and animal by eating contaminated food and feed (Rotter et al. 1996).

Nivalenol

Nivalenol (NIV) was detected from a virulent *Fusarium nivale* (Fn-2B), isolated from a farmland by Kokoda in 1963 in the Kumamoto region of Japan. Subsequently, Tani and Shigata (1979) found that the organism was lethal to rice, as it produced both NIV and FUX (Tatsuno et al. 1979). NIV (3,4,7,15-tetrahydroxy-12,13-epoxytrichothec-9-en-8-one) is produced mainly by *Fusarium graminearum*, *Fusarium crookwellense,* and *Fusarium nivale*. It co-occurs with FUX and DON in crops such as wheat, barley, and maize. NIV has been recently found in cereal-based products of European countries, and those of Brazil, Japan, Southeast Asia, and China (Turner 2010).

NIV and DON are similar in terms of chemical structure, and also share many toxicological properties such as causing nausea, vomiting, diarrhea, and eventually death. Both toxins inhibit protein synthesis, and increase the levels of stress-activated MAPKs and serum alkaline phosphatase. Gerez et al. (2015) found that the overall liver and kidney weights of female mice were reduced when NIV was added to feeds at up to 700 μg/kg body weight (bw)/day for 2 years. After NIV administration to mice at 12 ppm for up to 8 weeks, the serum IgA concentration increased and IgA became deposited on the

Table 2 Representation of different groups contained in trichothecenes structures

Type	Trichothecene	R_1	R_2	R_3	R_4	R_5	Chemical Formula	Molecular mass (amu)
A	Diacetoxyscirpenol	OH	$OCOCH_3$	$OCOCH_3$	H	H	$C_{19}H_{26}O_7$	366
A	Neosolaniol	OH	$OCOCH_3$	$OCOCH_3$	H	OH	$C_{19}H_{26}O_8$	382
A	T-2 Toxin	OH	$OCOCH_3$	$OCOCH_3$	H	$OCOCH_2CH(CH_3)_2$	$C_{24}H_{34}O_9$	466
A	HT-2 Toxin	OH	OH	$OCOCH_3$	H	$OCOCH_2CH(CH_3)_2$	$C_{22}H_{32}O_8$	424
B	Deoxynivalenol	OH	H	OH	OH	=O	$C_{15}H_{20}O_6$	296
B	3-Acetyldeoxynivalenol	$OCOCH_3$	H	OH	OH	=O	$C_{17}H_{22}O_7$	338
B	15-Acetyldeoxynivalenol	OH	H	$OCOCH_3$	OH	=O	$C_{17}H_{22}O_7$	338
B	Fusarenon X	OH	$OCOCH_3$	OH	OH	=O	$C_{17}H_{22}O_8$	354
B	Nivalenol	OH	OH	OH	OH	=O	$C_{15}H_{20}O_7$	312

glomerular mesangium, mirroring human IgA nephropathy (Gerez et al. 2015).

Among various *Fusarium* mycotoxins tested, NIV exerted one of the highest in vitro immunosuppressive effects on human peripheral blood mononuclear cells. NIV can inhibit the proliferation of human male and female mitogen-stimulated lymphocytes (Nagashima & Nakagawa 2014). At the mRNA level, NIV and DON modulate Th1-type cytokine expression differently at various doses, interacting with lymphocytes to inhibit cell proliferation by stimulating apoptosis (Severino et al. 2006). NIV is more toxic to human promyelocytic leukemia cell line HL60, human lymphoblastic leukemia cell line MLT-4 and rat aortic myoblast cell line A10 than DON (Nagashima & Nakagawa 2014).

The chronic effects of low oral NIV doses in animal models have been seldom explored, but several countries tolerate only low levels of trichothecenes in cereals (Gouze et al. 2007). China imposes no NIV limit on foods or feeds.

T-2 toxin and HT-2 toxin

The T-2 toxin [3-hydroxy-4-15-diacetoxy-8ct-(3-methyl butyryloxy) 12,13 epoxytrichothec-9-ene] contains an epoxy trichothecene loop. HT-2, a deacetylated form of T-2, is the principal metabolite of T-2. The toxicities of T-2 and HT-2 are similar, since both contain the epoxy sesquiterpenoid moiety. Consequently, the toxicity of T-2 may be partly attributable to HT-2 for T-2 is rapidly metabolized to HT-2 (Ndossi et al. 2012). Of all *Fusarium species*, *Fusarium langsethiae* seems to be the major producer of T-2 and HT-2 followed by *Fusarium poae* and *Fusarium sporotrichioides* (Glenn & Quillin 2007; Thrane et al. 2004). T-2 and HT-2 contaminate many grains, such as maize, oat, barley, wheat, rice, and soybeans.

T-2 is considered one of the most acutely toxic trichothecenes, causing a wide range of toxic effects in animals. Acute T-2 toxicity has been studied in rats, mice, guinea pigs, and pigeons, with the toxin administered intravenously, orally, subcutaneously, intraperitoneally, or intratracheally (Bouaziz et al. 2013). Symptoms of acute poisoning include nausea, vomiting, abdominal pain, diarrhea, bloody stools, cartilage tissue damage, weight loss, decreased immunity, decreased plasma glucose levels, and pathological changes in the liver and stomach. (Li et al. 2011). T-2 at 2, 000 μg/kg reduced lymphocyte numbers and caused hepatopancreatic necrosis in the black tiger shrimp. In addition, T-2 at 2, 500 μg/kg reduced body weight, feed ingestion, feed conversion, and hemoglobin concentration in rainbow trout. T-2 at 1, 000 μg/kg dose in catfish reduced intestinal immunity and increased mortality by up to 84% (Sehata et al. 2004). The main action of T-2 is to inhibit protein synthesis and secondary destruction of DNA and RNA synthesis (Doi et al. 2008).

T-2 can affect cell cycle, and induce chondrocytes, human astrocytes, mouse embryonic stem cells, pig primary hepatocytes, hematopoietic cells in bone marrow and spleen red pulp and epidermal basal cell apoptosis, indicating that T-2 can induce cell death with high proliferation activity (Fang et al. 2012; Shinozuka et al. 1998; Weidner et al. 2013).

In addition, T-2 targets the immune system, alters leukocyte counts, triggers delayed-type hypersensitivity, leads to depletion of certain hematopoietic progenitor cells, reduces antibody formation, and enhances allograft rejection and lectin promotion (Creppy 2002). Pigs and horses are among the animals that are most sensitive to T-2, the major effects of which are immunological and hematological in nature. In quail, T-2 reduced the activity of blood alkaline phosphatase, an enzyme that plays an important role in the innate immune response, increased the levels of glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase (Madheswaran et al 2004; Nemcsok & Boross 1982).

Zearalenone

Zearalenone (ZEN) or called ZEA, previously known as F-2 toxin, is a resorcyclic acid lactone [6-(10-hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcyclic acid lactone ($C_{18}H_{22}O_5$, MW: 318.36, CAS 17924–92-4)]. In mammals, the ketones in C-8 are reduced to two stereoisomeric metabolites (the a- and b-isomers). The structures of ZEN and its derivatives are shown in Fig. 2. Various ZEN metabolites are produced by fungi, but at lower concentrations. The relative concentrations of the individual toxins vary among host plants and geographical regions. These include several *Fusarium* species (*Fusarium graminearum*, *Fusarium culmorum*, *Fusarium crookwellense,* and *Fusarium equiseti*) that are known to also produce other toxins including DON, NIV, and FUX (Frizzell et al. 2011). ZEN is a whitish, crystalline toxin with a melting point of 164 °C–165 °C. ZEN is fat-soluble, insoluble in water, but soluble in alkalis and various organic solvents. ZEN is thermostable during storage, milling, processing, and cooking (EFSA 2004b). ZEN contaminates corn, barley, oats, wheat, sorghum, millet, rice, flour, malt, soybeans, and beer. ZEN derivatives [α-zearalenol (α-ZEN), β-zearalenol (β-ZEN), α-zearalanol (α-ZAL), β-zearalanol (β-ZAL), and zearalanone (ZAN) have been detected in corn stems, rice cultures, corn silage, corn products, and soya meal (Marin et al. 2011). The ZEN limits in corn and other cereals are currently in the range of 50 to 1000 μg/kg.

(Table 1). Several in vivo studies found that ZEN principally targeted the reproductive system. In laboratory animals, the toxic effects included changes in

reproductive tract, uterine enlargement, reduced fertility, increased embryo-lethal resorption, and changes in serum levels of progesterone and estradiol (Koraichi et al. 2012). ZEN and its metabolites α-ZEN and β-ZEN exert estrogenic effects, since they are structurally similar to estrogen; the toxins bind competitively to estrogen receptors, as found in pigs and sheep. In addition, ZEN exhibits relatively low acute toxicity (oral LD_{50} values > 2000–20,000 mg/kg bw) after oral administration in mice, rats, and guinea pigs (Schoevers et al. 2012). Furthermore, ZEN is immunotoxic, hepatotoxic, hematotoxic, nephrotoxic and enhances lipid peroxidation (Choi et al. 2012). ZEN induces liver lesions and subsequent hepatocarcinoma, and alters hepatic function in rabbits, rats, and gilts (Pistol et al. 2014). Recent studies indicated that ZEN may stimulate the growth of human breast cancer cells that express the estrogen receptors (Ahamed et al. 2001).

Fumonisins

Fumonisins (FBs) were initially isolated from corn cultures of *Fusarium moniliforme* in South Africa (Gelderblom et al. 1988). The structures of these mycotoxins as shown in Fig. 3 and Table 3 were first reported by Marasas et al. in 1988 (Scott 2012). Subsequently, fumonisins have been isolated from other *Fusarium* species, such as *Fusarium verticillioides*, *Fusarium proliferatum* and *Alternaria alternata* f. sp. *lycopersici* (Bezuidenhout et al. 1988). It is divided into three types: FB1, FB2, and FB3, and are present as natural contaminant in foods and feeds. The molecular structures of fumonisins are shown in Fig. 1 (Soriano 2004). FB1 often contaminates corn and its products, and is the most abundant and most toxic FB. FB1 is a diester of propane-1,2,3-tricarboxylic acid and 2S-amino-12S,16R-dimethyl-3S,5R,10R,14S,15R-pentahydroxyeicosane, where the C-14 and C-15 hydroxy groups are esterified with the terminal carboxy group of propane-1,2,3-tricarboxylic acid (TCA). FB2 is a 10-deoxy FB1 while FB3 is a 5-deoxy FB1 (Soriano et al. 2005). The structures of the principal fumonisins are shown in Fig. 3. The symptoms induced by FBs are very broad, including neural tube defects in newborns, brain lesions in horses, pulmonary edema in pigs and cancer in experimental animals. Although FBs have no mutagenicity, they promote cancer development (Summerell & Leslie 2011). FBs are associated with human apoptosis, esophageal cancer and neural tube defects (Ahangarkani et al. 2014; Scott 2012). FBs can affect the progress of liver cancer in rats, cause bleeding in rabbit brains and have nephrotoxicity to other animals. In addition, FBs are also toxic to pigs, chickens and other farm animals (Ahangarkani et al. 2014). FB1 interferes with myelin synthesis, causes leukoencephalomalacia and liver necrosis in horses, leading to death. Pig intake of FB1 contaminated feed will cause pulmonary edema (Scott 2012). In rodent studies, liver and kidney are the main FB1 targets.

The mechanism by which fumonisin exerts toxic effects is complex. Structurally, fumonisins are similar to sphingoid base (a sphingolipid). They can inhibit the synthesis of ceramide synthase and block the biosynthesis of complex sphingolipids, thereby promoting the accumulation of sphingosine and sphinganine 1-phosphate (Wan et al. 2013). As sphingolipids play key roles in cellular regulation, dysfunctional sphingolipid metabolism may account for the observed toxicity. These lipids play an important role at the cellular level. They can maintain cell morphology, promote cell differentiation, regulate growth factor levels, and affect cell carcinogenicity and apoptosis. In addition, they also play a role in maintaining cell membrane structure, enhancing cell interaction and extracellular interaction.

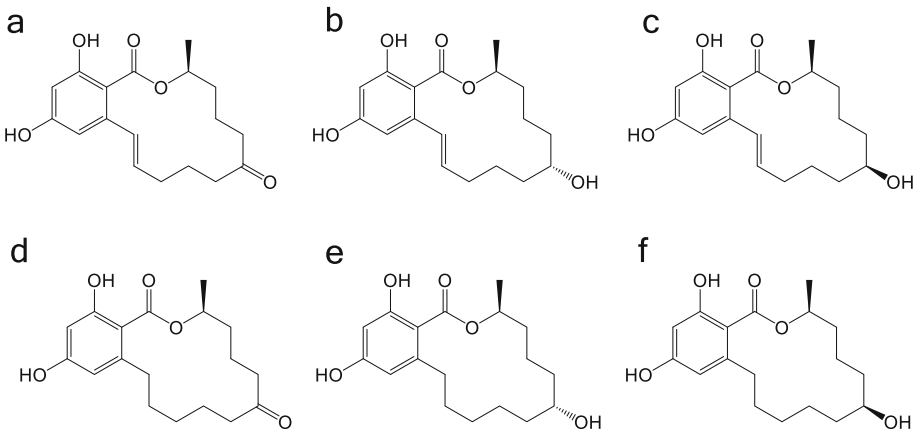

Fig. 2 Chemical structures of ZEN and its derivatives: (**a**) zearalenone, (**b**) α-zearalenol, (**c**) β-zearalenol, (**d**) zearalanone, (**e**) α-zearalanol, and (**f**) β-zearalanol (Marin et al., 2013)

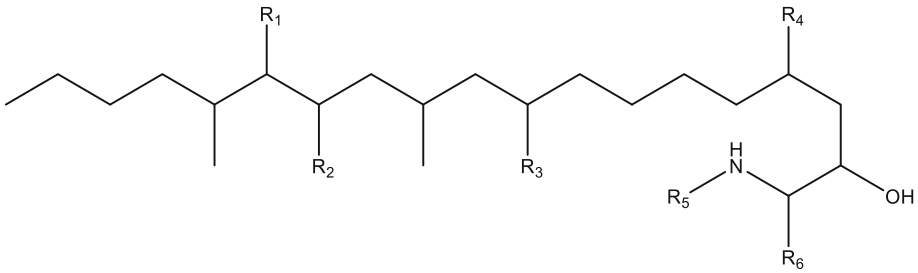

Fig. 3 Structures of the principal fumonisins in foods (FBs: fumonisins of group B) (Marin et al., 2013)

Moreover, sphingolipids also act as secondary messengers in various signal transduction pathways (Ahangarkani et al. 2014).

Occurrence of *Fusarium* mycotoxins in China

As early as the 1940s, there are some records about swine toxicosis fed with FHB contaminated wheat in China (Li, 1959). Wheat FHB has seriously occurred for many years in China with most recent epidemic of 2003, 2010, 2012, 2015, 2016 and 2018. As the staple food, wheat plays an important role to feed billions of people in China. The potential hazards of *Fusarium* mycotoxin contaminated cereals is a threat for human and animal.

Temperature and rainfall are the key climatic factors that affect plants and their associated pathogens as well as mycotoxin concentrations in infected plants. In the middle-to-low valleys of the Huaihe and Yangtze Rivers, the most developed agro-production regions of China, the (typical) humid warm climate encourages FHB epidemics. In 2010, rainfall promotes wheat flowering, leading to the development of FHB, found as the common disease of wheat in Southern China. The total amount of wheat produced in 2010 in Jiangsu and An-hui was 100.81 and 120.65 million kg, respectively.

Li et al. (2014) sampled 76 cereals and oil products of the Yangtze Delta of China, and found that ZEN is the most prevalent toxin, with an incidence of 27.6% (9.2% higher than the legal limit). DON was detected in 7.9% of the samples (Rui Li et al. 2014). Han et al. reported the levels of DON, 3-ADON, and 15-ADON in wheat and maize samples from Shanghai, China. From 2009 to 2012, 58% of all maize samples and 80% of all wheat samples were contaminated by DON. In 2011 to 2012, all 50 wheat and maize samples evaluated were contaminated with low levels of 3-ADON and 15-ADON (Han et al. 2014). The authors collected 180 samples in Jiangsu Province from 2010 to 2012. The percentage of DON-positive samples was 74.4%, and that of ZEN-positive samples was 12.8%. The highest DON concentration was 41,157 μg/kg, far above the allowable limits (Ji et al. 2014). Li, BT, Liu, and Dong (2015) reported that 39.7% of maize samples were contaminated by FB1 and FB2 in Southwest China (Renjie Li., 2015). Recent studies have found that 30–80% corn grains have FB1 and FB2 in the corn grains planted in some provinces in China, and the mean mycotoxin concentration range is from 11 to 13,110 μg/kg (Feng et al. 2011; Wei et al. 2013). Several authors have investigated mycotoxin levels in various cereals and feeds. Table 4 summarizes data obtained over the past 28 years on *Fusarium* mycotoxin contamination of foods and feeds in China.

Production of Fusarium mycotoxins

The *Fusarium fujikuroi* species complexes (FFSC) and *Fusarium graminearum* species complexes (FGSC) are the major mycotoxin producers, respectively (O'Donnell et al. 2000). The FFSC produces fumonisins. *Fusarium verticillioides* is the main contaminant of corn, while *Fusarium proliferatum* is a polyphagous species that was found in many different crops.

Qiu et al. (2014) isolated *Fusarium* species from maize kernels from Jiangsu and Anhui Provinces, China. They also found that *Fusarium verticillioides* was the most prevalent species, followed by *Fusarium proliferatum,* and finally *Fusarium graminearum*. *FUM1* is a gene that plays a key role in fumonisin biosynthesis. They also reported that most *Fusarium verticillioides* strains have been detected to presence *FUM1* (Qiu & Shi 2014).

Table 3 Representation of different groups contained in fumonisins structures

	R_1	R_2	R_3	R_4	R_5	R_6
FB1	TCA	TCA	OH	OH	H	CH_3
FB2	TCA	TCA	H	OH	H	CH_3
FB3	TCA	TCA	OH	H	H	CH_3
FB4	TCA	TCA	H	H	H	CH_3

The FGSC contains 16 phylogenetically distinct species at least, which can cause FHB in a variety of crops and produce trichothecenes (O'Donnell et al. 2004). In North America and Europe, *Fusarium graminearum* is predominated in a survey of *Fusarium* species composition and population structure (Starkey et al. 2007). The distribution of *Fusarium asiaticum* and *Fusarium graminearum* is different in location, they are the main etiological agents of FHB in Japan and Korea (Gale et al. 2002; Lee et al. 2012; Suga et al. 2008). In China, both *Fusarium graminearum* and *Fusarium asiaticum* are widespread. In the colder northern regions of China, *Fusarium graminearum* isolates are the predominated. In the warm wheat growing areas, *Fusarium asiaticum* is found principally (Wang et al. 2008). *Fusarium* species differ in their responses to temperature and moisture, which perhaps influence their distributions in causing infections (Parikka et al. 2012). FGSC strains are usually classified into three trichothecene profiles according to the difference in the production of mycotoxins: (i) DON and 3-acetyldeoxynivalenol (3-ADON chemotype); (ii) DON and 15-acetyldeoxynivalenol (15-ADON chemotype), or (iii) NIV, its acetylated derivatives (NIV chemotype) (Ward et al. 2002). The analysis of the distribution of FGSC and trichothecene chemotypes in cereal crops will help to correctly understand the relationship between disease and mycotoxin pollution, so as to develop effective management strategies for controlling disease and mycotoxin pollution.

Detection of Fusarium mycotoxins

Mycotoxins can be detected by various techniques, which are broadly divided into instrumental and bioanalytical methods. However, each approach has merits and drawbacks; the method of choice depends on the detection requirements.

Chromatographic methods

There are many kinds of instrumental detection methods for mycotoxins. Thin layer chromatography (TLC) is a qualitative or semi quantitative method with the longest history in the detection of mycotoxins. High-performance liquid chromatography (HPLC) can couple with different detectors. These detectors include ultraviolet (UV) detection, diode array detection, fluorescence detection or mass spectrometric detection. Gas chromatography can couple with electron capture detection, flame ionization detection (FID), or mass spectrometry (MS) detection (Lippolis et al. 2008; Visconti & De Girolamo 2005). These methods afford high accuracy and precision, and are used for both quantitative and qualitative analyses. However, they are expensive, require skilled personnel and longer periods for sophisticated sample preparation (Elliott 2011). Thus, instrumental methods are not suitable for normal laboratories or field environments. Chromatographic techniques involving UV and FID are principally employed in confirmatory contexts, thus facilitating compliance with regulations. Occasionally, such techniques serve as reference methods for validation of immunochemical tests.

MS has indisputable advantages of high sensitivity, high selectivity, high throughput and accuracy, making multi-residue analysis possible. Quick, easy, cheap, effective, rugged, and safe (QuEChERS) approaches for sample preparation allow analysis of a wide range of matrices and analytes, and further allowing the simultaneous extraction of the amount of mycotoxins. However, QuEChERS approaches reduce analytical sensitivity, and require preconcentration steps. Alternatively, isotope dilution quantification can improve sensitivity in the absence of preconcentration (Anfossi et al. 2016).

High resolution MS (HRMS) and tandem MS/MS allow (possibly) identification of unknown compounds by analyzing structural information of the compounds. The use of non-selective extraction protocols followed by mass screening employing HRMS or MS/MS has allowed identification of new masked mycotoxins and new members of known groups. The rapid multi-residue LC-MS/MS methods have been used to evaluate mycotoxins level in food and feed.

Immunochemical methods

Immunoassays based on antibody-antigen reactions are very useful for routine analyses, as these techniques are simple and have been used for rapid mycotoxin detection (Zherdev 2014). Recently, several immunological techniques have been developed, including enzyme-linked immunosorbent assays, time-resolved immunochromatographic assays, enzyme-linked aptamer assays, chemiluminescence immunoassays, fluorescence immunoassays, fluorescence resonance energy transfer immunoassays, and metal-enhanced fluorescence assays (Chauhan et al. 2016). Aptamer is an important parameter in these detection techniques. It can bind a variety of peptides, proteins, amino acids, and organic or inorganic molecules, all of which have high affinity and specificity (Torres-Chavolla & Alocilja 2009). Jodra et al. (2015) developed an electrochemical magneto-immunosensor to detect FB1 and FB2. The sensor was made of magnetic beads and disposable carbon screen-printed electrodes. Liu et al. (2014) constructed an ultrasensitive immunosensor based on mesoporous carbon and trimetallic nanorattles with special Au cores. The lower detection limit of ZEN was 1.7 pg/mL, and the assay was found to exhibit good stability and reproducibility.

Because of the strong selectivity of molecular recognition mechanisms, it is difficult to simultaneously assay different compounds or discover new toxins. Osward

Table 4 Contamination of *Fusarium* mycotoxins in foods and feeds in China

Product	Number	toxin	positive samples (%)	Province	Reference
Corn	120	DON	74.2	Shanxi	Wei et al., 2017
		3-A-DON	16.7		
		15-A-DON	74.2		
		NIV	27.5		
		ZEN	49.2		
		FB1	74.2		
		FB2	82.5		
		FB3	70.0		
		T-2	5.0		
		HT-2	17.5		
	215	DON	84.65	Twelve provinces	Ma et al., 2011
		ZEN	69.30		
		T-2	46.05		
		HT-2	16.28		
	42	DON	47.6	Anhui and Henan	Xiong et al., 2009
		ZEN	78.6		
	111	DON	16.2	Anhui	Lu et al., 1994
	105	DON	61.9	Hebei	Liu et al., 1993
	284	DON	66.6	Six provinces: Henan, Hubei, Sichuan, Jilin, Guangxi, and Guangdong	Wang et al., 2007
	204	DON	50.5	Seven provinces: Henan, Hebei, Guangxi, Anhui, Sichuan, Ghongqing, and Jiangsu	Li et al., 2011
		ZEA	41.7		
	50	FBs	26	Shangdong	Yan et al., 1999
	70	FBs	44.3	Jilin	Sun et al., 2003
	50	FBs	38.00	Hubei	Lv et al., 2005
Wheat	100	NIV	35	Shanghai	Li et al., 1997
	100	DON	53.0		
	41	DON	97.6	Anhui and Henan	Xiong et al., 2009
		ZEN	68.3		
	439	ZEN	31.9	National	Luo et al., 1989
	815	DON	49.2		
	329	DON	69.3	Anhui	Lu et al., 1994
	200	ZEN	61.0	Twenty-six provinces	Cheng et al., 2014
		DON	89.0		
		T-2	42.0		
	190	DON	66.3	Six provinces: Henan, Hubei, Sichuan, Jilin, Guangxi, and Guangdong	Wang et al., 2007
	162	DON	88.8	Seven provinces: Henan, Hebei, Guangxi, Anhui, Sichuan, Ghongqing, and Jiangsu	Li et al., 2011
		ZEN	22.9		
	183	DON	37.99	National	Wu et al., 2009
		FBs	87.34		
		T-2	97.38		
		ZEN	16.02		
	56	DON	89.3	Anhui and Jiangsu	Cui et al., 2013
	50	DON	30	Ten regions of China, including Shandong, Hebei, Jilin, et al.	Wang. et al., 2014
	50	FBs	94	Shangdong	Yan et al., 1999

Table 4 Contamination of *Fusarium* mycotoxins in foods and feeds in China *(Continued)*

Product	Number	toxin	positive samples (%)	Province	Reference
	40	FBs	72.5	Jilin	Sun et al., 2003
	52	FBs	55.77	Hubei	Lv et al., 2005
	330	T-2	80	Nine provinces: Shandong, Henan,Hebei, Hubei, Liaoning, Shanxi, Anhui,Jiangsu, and Shanghai	Yang et al., 1992
	37	T-2	76.9	Guizhou	Chen et al., 1995
	174	T-2	58.05	Beijing	He et al., 1998
Flour	158	DON	84	Anhui, Beijing, Henan, Jilin, Shandong	Han et al., 2017
		DON-3-G	24		
		3-A-DON	84		
		15-A-DON	61		
		NIV	22		
		ZEN	77		
	125	DON	96.80	Twelve provinces	Ma et al., 2011
		ZEN	72.80		
		T-2	74.40		
		HT-2	24.80		
	50	DON	54	Hebei	Liu et al., 1993
	132	DON	92.4	Anhui	Lu et al., 1994
Rice	18	DON	44.44	Twelve provinces	Ma et al., 2011
		ZEN	38.89		
		T2	61.11		
		HT2	11.11		
	51	ZEN	3.9	Guangxi	Li et al., 2011
	40	FBs	95	Shangdong	Yan et al., 1999
	60	FBs	38.3	Jilin	Sun et al., 2003
	49	FBs	32.65	Hubei	Lv et al., 2005
Feeds	205	ZEN	62.5	National	Zhou et al., 2014
		DON	85.83		
	341	DON	45.4	Twenty-eight provinces	Chen et al., 1997
		ZEN	35.8		
		T2	24.2		
Combined feeds	47	DON	100	Guangxi	Jiang et al., 2011
		ZEN	100		
		T2	100		
		FBs	100		

et al. (2013) designed an analytical array that can detect several targets separately in spatially distinct regions. Song et al. (2014) developed an immuno-chromatographic strip test device that simultaneously detect at least 10 different toxins (AFs, DON and analogs thereof, and ZON and analogs thereof). Wang et al. (2013) reported that they developed a unique spectral addresses which can simultaneous detection of many mycotoxins in peanuts. Those mycotoxins include AFB1, DON, ZON, and T-2.

In comparison to chromatographic methods, immunochemical methods afford greater selectivity in terms of monitoring mycotoxin levels which is very important to ensure food safety in developing countries. In addition, due to global changes in climate and the environment, the level of contamination by fungi and their mycotoxins will increase in the future. Risk management requires routine application of efficient control programs such as optimally employing immunoassays.

Conclusion

In conclusion, the study of *Fusarium* mycotoxins has attracted increasing attention. Many studies have addressed the toxicokinetic profile, mycotoxin persistence

and accumulation. The progress of mycotoxin analysis highlights the limitations currently being understood due to their effective impact on animal and human health in food. Co-contamination by several toxic compounds and identification of new compounds in the mycotoxin family both require new toxicological studies to assess. In addition, food from crops is susceptible to fungal contamination, and it has been clearly demonstrated that animals fed the contaminated feed can transmit mycotoxins. Some regulations, especially those established by the European Union, have gradually recognized the risk of contamination by mycotoxins in the food chain. Mycotoxin levels should be monitored routinely and continuously, as the annual levels may vary depending on environmental moisture, climate, temperature changes, plant disease status, and insect pest numbers. Effective management of food safety risks is required, especially including the use of rapid and sensitive immunological techniques.

Abbreviation

CSPE: Carbon screen printed electrode; DAD: Diodearray; DAS: Diacetoxyscirpenol; DON: Deoxynivalenol; ECD: Electron capture; ENNS: Neosolaniol; EPT: 12, 13 epoxytrichothec-9-ene; ERK: Extracellular-signal regulated kinase; FBs: Fumonisins; FD: Fluorescence; FFSC: *Fusarium fujikuro*i species complex; FGSC: *Fusarium graminearum* species complex; FHB: Fusarium Head Blight; FID: Flame ionization; FRET: Fluorescence resonance energy transfer; FUX: Fusareno-X; GC: Gas chromatography; HPLC: High-performance liquid chromatography; HRMS: High-resolution MS; IARC: Agency for Research on Cancer; JNK: Jun N-terminal kinase; MAPKs: Mitogen-activated protein kinase; MC: Mesoporous carbon; MS: Mass spectrometry; NIV: Nivalenol; QuEChERS: Quick, easy, cheap, effective, rugged, and safe; TLC: Thin-layer chromatography; UV: Ultraviolet; ZAN: zearalanone; ZEN: Zearalenone; α-ZAL: α-zearalanol; α-ZEN: α-zearalenol; β-ZAL: β-zearalanol; β-ZEN: β-zearalenol

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Authors' contributions

JS, JX and FJ conceived and designed the paper; FJ collected, analyzed literatures and wrote the paper; DH edited the table and figure; AOO and MPM reviewed and edited the manuscript. All authors read and approved the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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