Metabolism, Toxicity, Detoxification, Occurrence, Intake and legislations of Fumonisins - A review

ABSTRACT

Fumonisins are the group of mycotoxins generated usually by the *Fusarium spp*. in foods and feeds. However more than 15 isomers of fumonisin have been recognized, but the B series of fumonisins are the main and referral isomers of fumonisins. Fumonisin B can cause, leukoencephalomalacia in rabbits and horses and porcine pulmonary edema in swine. Also, fumonisin B is nephrotoxic, hepatotoxic, immunotoxic and carcinogenic. Fumonisin B blocks sphingolipid biosynthesis (hence, hinder the synthesis of ceramide) by a noticeable resemblance to sphingosine and sphinganine. This paper gives a review of the toxicity, occurrence, and mechanism of carcinogenicity, hepatotoxicity, nephrotoxicity, and immunotoxicity of fumonisins. Fumonisins are mainly found on several foods and feed in Africa, America, Europe, Asia, and Oceania. In this paper, we talk about current information on the worldwide contamination of feeds and foods by fumonisins. Because of economic losses induced by fumonisins and their hurtful effect on animal and human health, the various procedure for detoxifying infected feeds and foods have been illustrated in this review, containing; biological, physical, and chemical processes. Besides in this paper, we discuss dietary intakes and maximum limits of fumonisins in some countries.

Keywords: Fumonisins; Toxicity; Detoxification; Mechanism; Occurrence; Intake

1. INTRODUCTION

Fumonisins are a group of further than ten mycotoxins created by *Fusarium* species like*; F. globosum, F. oxysporum, F. proliferatum, F. verticillioides* and other species of *Fusarium, Alternaria alternata f. sp. lycopersici,* and *Aspergillus niger* [1, 2].
Fumonisins have a noncyclic structure (opposite of most mycotoxins). In this structure, there is a chain with 19- or 20- carbon aminopolyhydroxyalkyl that diesterified by tricarballylic acid groups (propane-1,2,3-tricarboxylic acid) Fig 1. Hitherto, various chemically associated series or groups of fumonisins were isolated. These series are consist of A, B, C, and P. The main detected forms of fumonisins in foods, are the B series of fumonisins [3]. Fumonisins B_1, fumonisins B_2, and fumonisins B_3 are the broadest mycotoxins between the more than 15 fumonisin forms that have been described until now [4].

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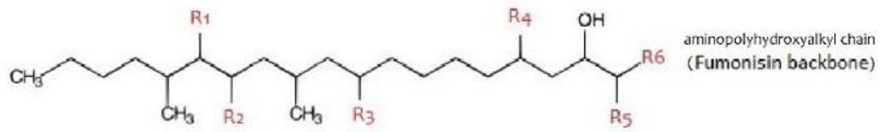

Fumonisins	Group					
	R1	R2	R3	R4	R5	R6
FA_1	TCA	TCA	OH	OH	$NHCOCH_3$	CH_3
FA_2	TCA	TCA	H	OH	$NHCOCH_3$	CH_3
FA_3	TCA	TCA	OH	H	$NHCOCH_3$	CH_3
FAK_1	=O	TCA	OH	OH	$NHCOCH_3$	CH_3
FB_1	TCA	TCA	OH	OH	NH_2	CH_3
FB_2	TCA	TCA	H	OH	NH_2	CH_3
FB_3	TCA	TCA	OH	H	NH_2	CH_3
FB_4	TCA	TCA	H	H	NH_2	CH_3
FC_1	TCA	TCA	OH	OH	NH_2	H
FP_1	TCA	TCA	OH	OH	3HP	CH_3
FP_2	TCA	TCA	H	OH	3HP	CH_3
FP_3	TCA	TCA	OH	H	3HP	CH_3
PH_{1a}	TCA	OH	OH	OH	NH_2	CH_3
PH_{1b}	OH	TCA	OH	OH	NH_2	CH_3
AP_1(Hydrolyzed FB_1)	OH	OH	OH	OH	NH_2	CH_3
N-(carboxymethyl) FB_1	TCA	TCA	OH	OH	$NH(C_2H_3O_2)$	CH_3
N-(deoxy-D-fructos-1-yl)B_1	TCA	TCA	OH	OH	$NH(C_6H_{11}O_5)$	CH_3
Fumonisin B1-di(methyl-α-D-glucopyranoside)	MG	MG	OH	OH	NH_2	CH_3

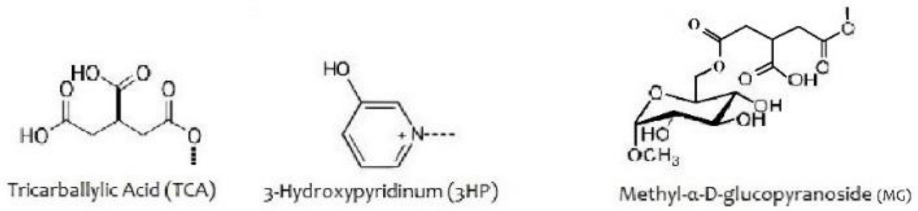

Fig. 1. Chemical structures of the fumonisins. From: [1, 2]

Fungi-producing fumonisin contaminated apple, barley, beef, breakfast cereals, black tea, corn, cornbread, corn flour, corn flakes, corn grits, corn snacks, basmati rice, crunchy nut, egg, milk, oats, polenta, popcorn, row corn, soybean, canned foods, tomato, tortilla, and wheat [5].
Intake of fumonisin B induced a different of toxic effect in animals, containing leukoencephalomalacia in horses [6], change in weight of the body and internal organ in broiler chicken [7, 8], pulmonary edema and hepatocellular necrosis in piglet [9, 10]. Moreover, renal and hepatic toxicity has been detected in different animal, containing rabbits, lambs, turkeys, mice, rats, and broilers [7, 11-14].
In human, fumonisins were increased risk of neural tube defects (NTD) and developing esophageal cancer [15, 16].

2. TOXICITY OF FUMONISINS

In the human and different animal, fumonisins beget some toxic effects such as carcinogenic, hepatotoxic, and nephrotoxic. Moreover, sensitivity to fumonisins is a different in human and varies animal, for example; based on [17] saying, rats are more sensitive to fumonisin B_1 than mice. We summarized in Table 1 disorder effects, dosage, duration and source of fumonisin.

Table 1. Some disorder effects induced by fumonisins

	Dosage and Fumonisin source	Duration	Effects
Human	Both FB1 and FB2 High corn intake higher risk than low corn intake	case–control study	Developing esophageal cancer
Human	FB1 in corn of three area of China, average of contamination was; 2.84, 1.27, and 0.65 mg/kg	1 year	Esophageal- and hepato-carcinogenesis
Human cells	Medicine with FB1 for 24, 48, 72 and 96 h		The proliferation of human esophageal epithelial cells (HEECs)
Women	Exposure to FB1 corn tortilla intake during the first trimester and before the pregnancy.	case–control study	Raise the risk of NTD
Lamb	Intraruminally; 11.1, 22.2, 45.5 mg fumonisin B1, B2, B3/kg b.w	9 days	Tubular nephrosis, mild hepatopathy, diarrhea, lethargy, death
Cattle	Feeding; 15, 31, 148 µg fumonisins /kg b.w	31 days	Increase in the AST, GGT, LDH, bilirubin, cholesterol and lymphocyte blastogenesis Mild microscopic liver lesions
Cattle	Intravenous; 1 mg fumonisin B1/kg b.w	7 days	Lethargy, the decrease in appetite Increase in Sa/So, proliferation and hepatocyte apoptosis, the proliferation of bile ductular cells, vacuolar change, proliferation of proximal renal tubular cells, apoptosis, and karyomegaly.
Broiler chicken	Feeding; 0, 100, 200, 300 or 400 mg fumonisin B1/kg b.w	21 days	The decline in body weight Increase in the liver-, proventriculus-, and gizzard-weights, Serum calcium, cholesterol, and AST
Broiler chicken	Feeding; 0, 75, 150, 225, 300, 375, 450, 525 mg fumonisin B1/kg b.w	21 days	Increase in liver and kidney weights, MCV, MCHC, Sa/So Histological lesions in the liver
Broiler chicken	Dietary; 0, 20, 40, 80 mg fumonisin B1/kg b.w	21 days	Increase in the Sa/So, GGT, AST, the weights of liver, proventriculus, spleen, kidney, and bursa of Fabricius.
Broiler chicken	Dietary; 0, 50, 100 or 200 mg fumonisin B1/kg b.w	21 days	Cell proliferation in response to mitogens, immunosuppress
Broiler chicken	Dietary; 300 mg fumonisin B1/kg b.w	21 days	Increase activities of AST, LDH, GGT

Broiler chicken Cobb 500	Orally and postnatal; 100 mg fumonisin B1/kg b.w	21 days	Increase in the liver weight, Sa/So, hepatic TBARS, Vit C, catalase
Chicken Embryos	Injection in air cell of chicken eggs; 0, 2, 4, 8, 16, 32, and 64 µg fumonisin/egg	In 72h of incubation	Not microscopic abnormalities but haemorrhages of the neck, thoracic area, and head of the dead embryos
Turkey	Dietary; 0, 100, 200 mg fumonisin B1/kg b.w	21 days	Increase in AST, alkaline phosphatase, MCV, MCH, liver-, kidney-, and pancreas-weights Biliary hyperplasia, , thymic cortical atrophy, hypertrophy of Kupffer's cells, and moderate broaden out of the proliferating hypertrophied zones of tibial physes The decrease in spleen and heart weights, body weight gains, cholesterol
Duck	Orally; 0, 5, 15, 45 mg fumonisin B1/kg b.w	12 days	Body weight gain was slightly retarded, liver hyperplasia Increase in liver weight, total protein, AST, Sa/So, LDH, GGT, cholesterol
Mouse embryos	Exposure of FB1	Long term Short-term	NTD; 65% in continuing experimentation and by almost 50% in temporary experimentation
Mice	Subcutaneous; 2.25 mg fumonisin B1/kg b.w	5 days	Hepatotoxic effects, increase in AST and liver enzymes in circulation
Mice	Dietary; 0, 14, 70, and 140µmol fumonisin B1 , B2, B3, hydrolyzed fumonisin B1, fumonisin P1, N-(carboxymethyl)fumonisin B1 or N-(acetyl)fumonisin B1/kg	28 days	Increase in whole bile acids, alkaline phosphatase, cholesterol, hepatocellular apoptosis, macrophage pigmentation, Kupffer cell hyperplasia, and hepatocellular hypertrophy.
Mice	Gavage; 1-75 mg fumonisin B1/kg	14 days	In the liver, mitosis, anisokaryosis, and hepatocellular single cell necrosis Increase in ALT, serum cholesterol, blood urea nitrogen in male, vacuolated lymphocytes and myeloid cells Mild decreases in ion transport of kidney
Mice	Dietary; 0, 1, 3, 9, 27, or 81 ppm FB1	13 weeks	Hepatopathy
Female B6C3F1	Fed 50 or 80 ppm FB1	2-year feeding	Hepatocellular adenomas and carcinomas

mice			
Rat	Dietary; 0, 1, 3, 9, 27, or 81 ppm FB1	13 weeks	Nephrosis
Male BD IX rats	Intake of 50 ppm FB1	Up to 2 years	Culminated in the appearance of hepatocellular carcinomas and cholangiocarcinomas
Male F344 rats	FB1	2-year feeding	No hepatocarcinogenic effects ,but FB1 caused renal tubule tumors
Male BD IX rats	0.08 and 0.16 mg FB/100 g of (bw)/day over	2 years	Induce cancer, mild toxic, and preneoplastic lesions
Rabbit	Gavage; 0, 31.5, 630 mg fumonisin B1/kg b.w	Single dose	Increase in AP, ALT, AST, GGT, urea, total protein, and creatinine
Rabbit	Gavage; 1.75 mg fumonisin B1/kg b.w	9,13 days	Focal small bilateral hemorrhages in the white matter cerebral, malacia, apoptosis in kidney and liver
Horse	Intravenously; 1.25-4 , 1-4 mg fumonisin B1/kg b.w	33-35 days	Lesions of LEM Apathy, incoordination, walking into objects, changes in temperament, paralysis of the lips and tongue,
Horse	Intravenously; 0.125 mg fumonisin B1/kg b.w	0-9 days	Apathy, trembling, paresis of the lower lip and tongue, reluctance to move, a wide-based stance, ataxia, tetanic convulsion, inability to drink or eat Focal necrosis in the medulla oblongata and severe edema in brains, bilaterally symmetrical.
Horse	Feeding; 160-3800 µg fumonisin B1/kg b.w 20-950 µg fumonisin B1/kg b.w		FB1 is the major fumonisin in LEM in horses
Arabian horse	Dietary; 12.490 µg fumonisin B1/kg b.w, 5.251 µg fumonisin B2/kg b.w		Blindness, hyperexcitability, four leg ataxia, circling, aimless walking, death Focal areas of hemorrhage, softening of the sub-cortical white matter and brown-yellow discoloration Microscopic brain lesions; wide areas of malacia within the white matter of the brainstem, cerebral hemispheres, and cerebellum
Pony	Feeding; 1-88 ppm fumonisin B1, B2, B3	120 days	Leukoencephalomalacia and hepatic necrosis

Pigs	Intravenously; 4.6-7.9 mg fumonisin B1/kg b.w Orally; 48-166 ppm FB1	15 days	Pulmonary edema and hepatic necrosis
Pigs	Dietary; 16 mg fumonisin B1/kg b.w		Hydrothorax, variably severe pulmonary edema, icterus and hepatocellular necrosis
Pigs	Dietary; 20 ppm fumonisin B1	42 days	Strong edema in the lung, mild degenerative changes in the kidneys, slight edema in the different interior organs
Gilt	Dietary; 0.1 g fumonisin B1/kg b.w	7, 27-80 days	Nodular hyperplasia in liver, hyperkeratosis, parakeratosis, formation of papillary, hyperplastic plaques in esophageal mucosa
Weaned piglets	Orally; 5 mg fumonisin B1/kg b.w	Single dose	Increase in cholesterol, alkaline phosphatase and highest Sa and Sa/So ratios in plasma and urine

2.1 Carcinogenicity

Contamination of wheat, corn and rice with Fumonisin B can increase the risk of esophageal cancer in human [16, 18, 19] by stimulating the proliferation of human esophageal epithelial cells (HEECs) [20]. Also, Mathur in 2001 observed some different effects of stimulation of the proliferation in liver cells consisted of a proliferation of bile ductular cells and hepatocyte proliferation in cattle [21].

In rats, continuing intake of FB_1 (up to 2 years) consequenced the introduction of renal tubule tumors, hepatocellular adenomas, cholangiocarcinomas, and carcinomas [22, 23].

2.2 Hepatotoxic Effect

[11] by performing histological examination demonstrated that the fumonisins could create a mild hepatopathy in lambs. But hepatotoxic effects of Fumonisins in cattle is more extensive than lamb, and consisted of increases in gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), cholesterol and bilirubin, and mild microscopic liver lesions [24] hepatic lesions were distinguished by the different severity of disorganized hepatic cords and hepatocyte apoptosis [21]. Therefore it is possible that cattle are more sensitive to Fumonisins than lamb.

In broiler chicken increasing dietary fumonisin B_1 caused the increase in liver weights, serum calcium, cholesterol, and AST levels. Also, biliary hyperplasia and multifocal hepatic necrosis were present in these chickens [8]. In researches of [7, 25], chickens fed with fumonisin B_1, sphinganine: sphingosine (Sa: So) ratio, serum glutamate oxaloacetate aminotransaminase (SGOT), levels of free sphinganine in the serum, AST ratios, LDH, and GGT were increased. Nonetheless, total liver lipids of chicks were decreased significantly. [26] demonstrated that subacute treatment of broiler chicks to fumonisin B_1 bring about hepatic oxidative stress simultaneously with SA/SO gathering. Also, TBARS (Thiobarbituric acid reactive substance) levels, catalase activity, and Vit C content were increased. Therefore (according to the measure of treatment with fumonisins) sensitivity to Fumonisin in broiler chicken is increased in compare with the latest research. Also, hepatotoxic effects of Fumonisins besides of change in the level of liver enzymes can influence other factors like Vit C content, TBARS, and even liver weight of broiler chicken.

Feeding the turkey with fumonisin B_1 caused increases in liver weights and serum AST levels. However, serum cholesterol, alkaline phosphatase, MCH (mean cell hemoglobin) and MCV (mean cell volume) were declined. Also, hypertrophy of Kupffer's cells and biliary hyperplasia were present in these turkeys [13].

Because of FB_1 in the plasma, cholesterol, total protein, alanine aminotransferase (ALT), LDH, GGT and SA/SO (sphinganine to sphingosine ratio) were rose. Liver weight growth with liver hyperplasia existed in ducks [27]. These effect of fumonisins in ducks probably created by SA to SO ratio and oxidative damages.

[28] declared that hepatic effects of FB_1 in mice were increased in liver enzymes like AST and ALT in circulation. Also, [17, 29] demonstrated that serum levels of the total bile acids, alkaline phosphatase, and cholesterol, were risen and hepatocellular hypertrophy, hepatocellular apoptosis, Kupffer cell hyperplasia, hepatocellular single cell necrosis, mitosis, anisokaryosis, and macrophage pigmentation were detected in the mice that fed with FB_1.

FB_1 in rabbits can cause a significant increase in alkaline phosphatase (AP), total protein, AST, ALT, and GGT. Also, degeneration of hepatocytes and apoptosis were the prominent degenerative changes in liver of rabbits [14, 30].

Because of fumonisin B_1, B_2, and B_3, hepatic necrosis in ponies occurred [31].

Effect of fumonisins in the liver of piglet was apoptosis, necrosis, hepatocyte proliferation, hyperplastic hepatic nodules (in chronic studies), icterus, and hepatocellular necrosis. Besides serum cholesterol, alkaline phosphatase, AST activities, and sphinganine and sphingosine concentrations in kidney, heart, lung, and liver were elevated. But there were no detectable portal triads or central veins, adjacent parenchyma, and the perilobular connective tissue was compressed [10, 32-34]. The hepatic changes especially disorganization in piglet by fumonisins probably is because of an acute pathway of this mycotoxin.

2.3 Kidney Toxicity

Fumonisin in the kidney of lambs revealed with tubular nephrosis [11].

Accumulation of sphingosine and sphinganine in the kidney of calves created renal lesion like vacuolar change, karyomegaly, apoptosis, dilatation of proximal renal tubules (that included protein and cellular debris) and the proliferation of proximal renal tubular cells [21].

Effect of fumonisin in the kidney of turkeys and broiler chicken was increasing in kidney weight [7, 13, 35].

In both sexes of rats, fumonisins decreasing in the kidney weight, nephrosis in outer medulla of rats (especially in female rats) was observed [12].

[14, 30] reported that the effect of fumonisin in the kidney of the rabbit was apoptosis and degeneration of renal tubule epithelium, also level of urea and creatinine were increased.

Fumonisins in the kidney of pigs create a mild degenerative change, and in the urine of pigs, the highest Sa/So ratio and Sa ratio were produced in the 48^{th} h [9, 33].

According to this researches, perhaps toxic effects of fumonisins in the kidney is not extensive such as liver and sensitivity of kidney of rodents and chicken to fumonisins is lesser than other animals.

2.4 Leukoencephalomalacia

Fumonisins (especially fumonisin B_1) are the causal factor in the development of LEM in horses [36].

The lethality rates, mortality, and morbidity in horses were 85.7%, 10%, and 11.6% respectively [6].

In horses with LEM because of fumonisins, the brain lesions were observed such as; severe to early bilaterally symmetrical edema of the brain, brown-yellow discoloration, focal necrosis in the medulla oblongata, focal or multifocal areas of hemorrhage, sporadically pyknotic nucleus all over the areas of rarefaction hemorrhage, softening of the sub-cortical white matter, cavitations crowded with proteinaceous edema with rarefaction of the white matter, mild percolation by infrequent eosinophils and neutrophils, intracytoplasmic eosinophilic globules, inflamed glial cells with plentiful eosinophilic cytoplasm, inflamed glial cells with plentiful eosinophilic cytoplasm, cell edges were separated, hyperchromatic, edema, necrosis, wide parts of malacia in the white matter of the cerebral hemispheres, cerebellum, and brainstem [6, 36, 37]. Perhaps these brain lesions (that were emerged by fumonisin in horses) leads horses to nervous signs, consisted mainly of; apathy, incoordination, walking into objects, changes in temperament, just in one horse paralysis of the tongue and lips, paresis of tongue and the lower lip, inability to drink or eat, a wide-based stance, reluctance to move, trembling, hyperexcitability, four leg ataxia, blindness, tetanic convulsion, aimless walking and circling developed by death [6, 36, 37].

Fumonisin created leukoencephalomalacia in rabbits, and the bilateral brain microscopic lesions consisted of small focal bleeding in the malacia, cerebral white matter, and bleeding in the hippocampus [30]. But as you see brain lesions and nervous signs because of leukoencephalomalacia in rabbits, is not extensive and prevalent like horses. Therefore the brain of horses is more sensitive than rabbits, to fumonisins.

2.5 Porcine Pulmonary Edema (PPE)

Usual damages in Fumonisin B-fed pigs were severe edema in the lung by inhibiting sphingolipid biosynthesis and phagocytosis in pulmonary macrophages and gathering of substance material in pulmonary capillary endothelial cells [9, 32].

The clinical sign in pigs because of pulmonary edema (induced by fumonisins) consisted of; hydrothorax and respiratory distress (reveal by getting up respiratory rate and effort with open mouth and abdominal breathing). Lethal pulmonary edema appears during 4 to 7 days after the daily feed or intravenous treatment of FB_1[10, 32].

2.6 Other Toxic Effects

Exposure to FB_1 during the first trimester and before the pregnancy emerged to get up the hazard of neural tube defects (NTD; because of defeat of the neural tube to close, embryonic defects of the spinal cord and brain happened) [15, 38].

Diarrhea and lethargy detected in fumonisin administrated lambs [11].

Feeding by fumonisin in calves has some effects such as; impairing the lymphocyte blastogenesis [24], lethargy, increasing of sphingosine and sphinganine concentrations in the heart, lung, and skeletal muscle. Elevate in the concentration of sphinganine, but not sphingosine, in brains of managed calves [21].

In broiler chicks, FB_1 had a bad effect on weight, water consumption, feed efficiency, and body [35]. Although decreasing in the body weight, but sthe weight of bursa of Fabricius, gizzard, and proventriculus was increased. Other effects of FB_1 consisted of diarrhea, thymic cortical atrophy, and rickets [8, 35].

Fumonisin B_1 in turkey appeared thymic cortical atrophy, and moderate enlarging of the proliferating and degenerating hypertrophied zones of tibial physis [13].

[39] reported that fumonisin in the egg could cause extreme hemorrhages of the thoracic area, head, neck of the dead embryos.

In mice, fumonisins can cause adrenal cortical cell vacuolation and may cause increases in serum cholesterol. Vacuolated lymphocytes and myeloid cells were also detected in mice due to fumonisins [17].

Fumonisins in pigs had some effects such as; decrease in left ventricular dP/dT (max) (an indicator of heart contractility). But mean pulmonary artery pressure, heart rate, mean systemic arterial pressure, cardiac output, and pulmonary artery wedge pressure by obstruction of L-type Ca channels by get up sphinganine and/or sphingosine mass, were increased. Also in studies, parakeratosis, postpone in the pattern of papillary of the distal esophageal mucosa (part of stratum basale), hyperkeratosis, and hyperplastic nodules in the liver cell, esophageal plaques, and right ventricular hypertrophy were detected [32, 34].

3. METABOLISM AND MECHANISM OF FUMONISINS

Structure of fumonisin B has a noticeable similarity to sphinganine and sphingosine Fig. 2 both sphingosine and sphinganine are intermediates in the degradation and biosynthesis of sphingolipids. Furthermore, [40] reported that fumonisin B obstruct sphingolipid biosynthesis by specifically inhibiting sphingosine (sphinganine) N-acyltransferase, in vitro and situ.

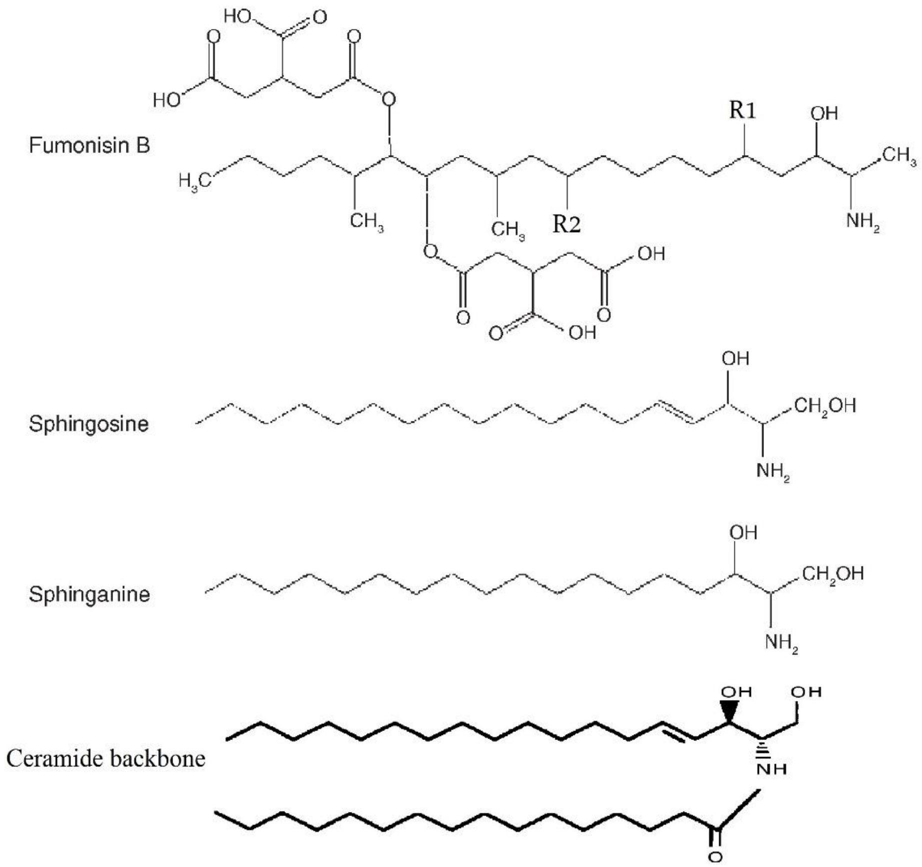

Fig. 2. Structures of fumonisin B, sphingosine, sphinganine and ceramide backbone[1]; [3]

Sphingolipids are a group of lipids that can detected in the whole of eukaryotic cells. All of the sphingolipids include a sphingoid (long-chain base backbone). Sphingolipids are urgent basic molecules and rule as regulators of a numeral of cell act [41]. In Fig. 3 location of working of fumonisin B-induced inhibition of the enzyme CER synthase, is presented.

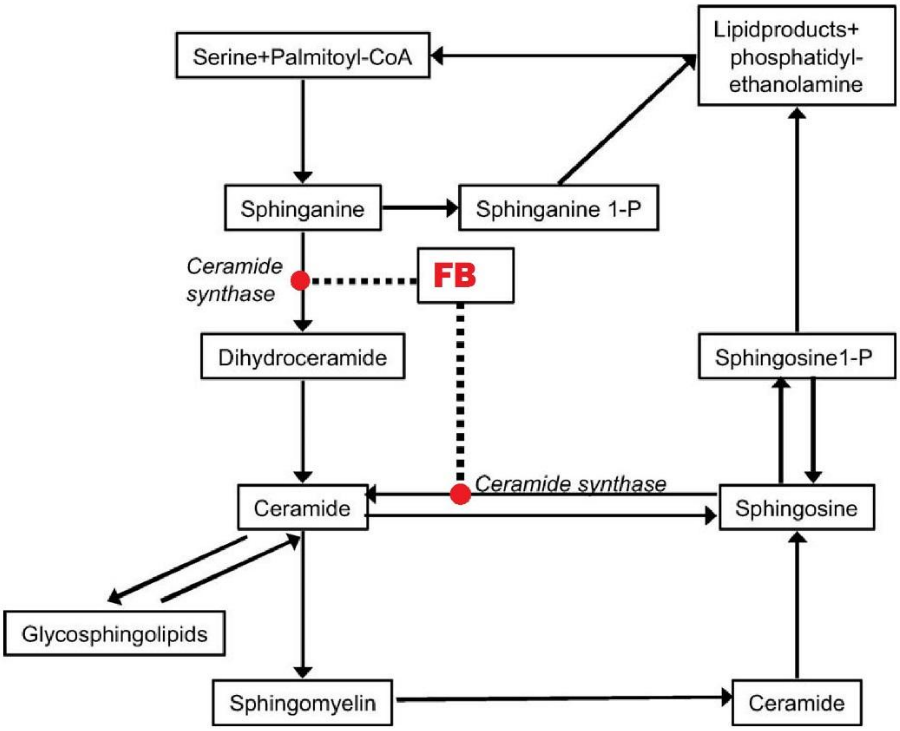

Fig. 3. A summarized scheme of the sites of action of fumonisin B-induced inhibition of the enzyme ceramide synthase on the pathway of de novo sphingolipid synthesis and turnover in mammalian cells and [4].

3.1 Mechanism of Fumonisins in Apoptosis and Cancer

Interruption of sphingolipid metabolism can cause the increase in available sphingoid backbone and their 1-phosphates, changing in compound sphingolipids, and decrease in the biosynthesis of ceramide (CER). Available sphingoid backbone induced cell death but fumonisin inhibition of CER synthase can restrain cell death influenced by ceramide [42].

Feedback of the apoptosis and carcinogenicity effects induced by fumonisin B_1 can be some mechanisms including oxidative damage, lipid peroxidation and maybe induction of hepatic, and renal tumors can happen [16]. Also, [43] discovered that FB_1 was able to promote the production of free radicals (by increasing the rate of oxidation) and by lipid peroxidation in membranes can accelerate chain reactions.

Increasing in sphinganine of tissue by FB was able to elevate beginning a cascade of cellular changes that probably product the carcinogenicity and toxicity by an unknown mechanism(s). However, in the following of sphinganine-induced cell proliferation and apoptosis and cancer incidence might be elevated [3].

In some studies following fumonisin B_1 treatment in different cells of human and animals, has been shown that apoptosis caused by fumonisin B_1 does not entail p53 or Bcl-2 group proteins and protect cells from the apoptosis by baculovirus gene (CpIAP). Baculovirus gene obstructs induced apoptosis by the tumor necrosis factor (TNF) pathway that caspase-8 was cleaved. The mitochondrial pathway perhaps is consisted of induced apoptosis by fumonisin B_1 by the actuation of Bid, release cytochrome c [16].

[20] reported that fumonisin B_1 in human normal esophageal epithelial cells (HEECs) stimulated the proliferation. Mechanism of the proliferation of HEECs is, decreasing in protein expression of cyclin E, p21, and p27 and increase in protein expression of cyclin D1.

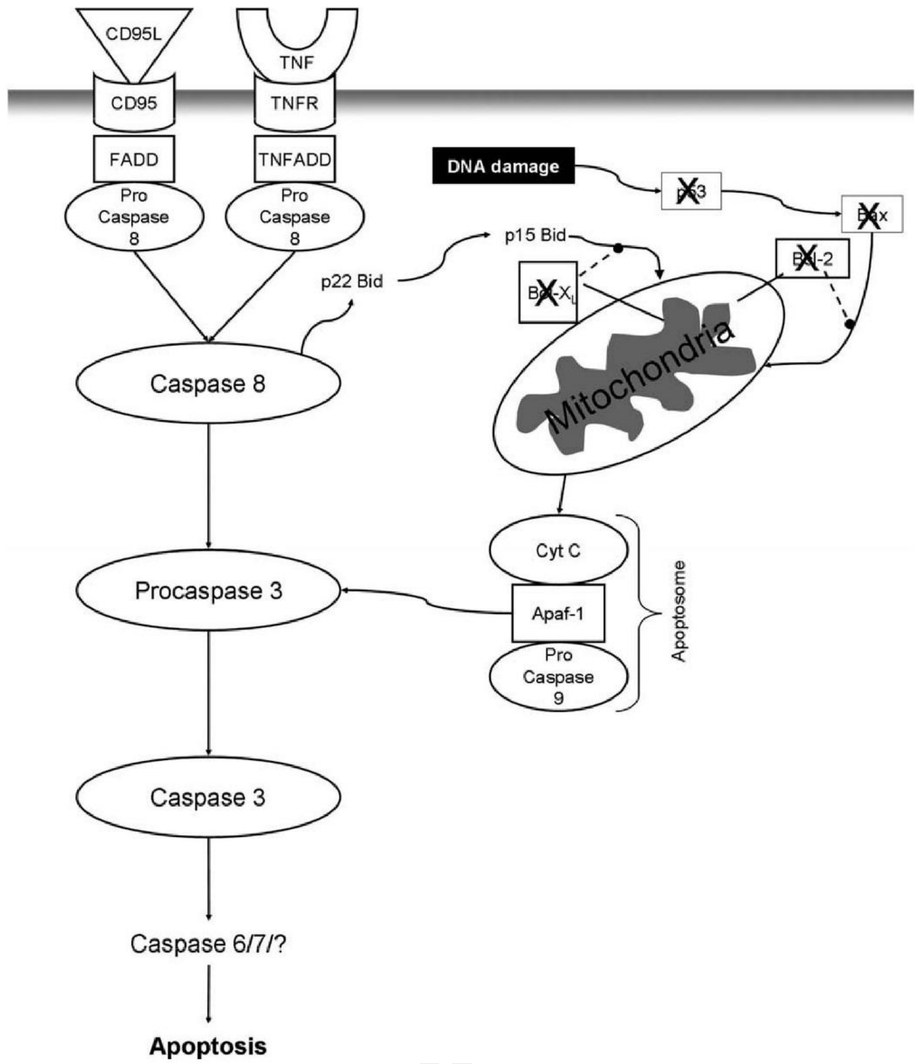

Fig. 4. A schematic landscape of the pathways conduct to apoptosis and the mechanisms probably consisted of fumonisin B1 -induced activation of caspase-3 resulted in apoptosis. X mark showed the mechanisms that do not consisted of the apoptosis caused by fumonisin B1 [4].

3.2 Mechanism of Fumonisins in Hepatotoxicity

Accumulation of sphingoid base because of induced fumonisin B_1 can induce TNF-α and make the hepatotoxicity in mice. Also, TNF-α receptor 1b is urgent mediating in the hepatotoxic responses by a rise in the circulation of liver enzymes [28].

3.3 Mechanism of Fumonisins in Immunotoxicity

Exposure to FB_1 in human dendritic cells; getting up the exhibition of IFN-γ and the associated chemokine CXCL9. Nevertheless, fumonisin B_1 may decline the lipopolysaccharide-induced liver and brain expression of IL-1β and IFN-γ in addition to the induced lipopolysaccharide expression of IL-1β, IL-6, and the chemokines CCL3 and CCL5 in human dendritic cells [16].
In piglets, fumonisin B_1 exposure can increase expression of IL-18, IL-8, and IFN-γ mRNA. But mRNA measure of TNF-α, IL-1β in piglet alveolar macrophages and levels of IL-4 may decrease [44]; [45].
After exposure to fumonisin B_1 in mouse, a getup expression of TNF-α and interleukin-1β (IL-1β) has been observed in kidney and the liver. Also, FB_1 can raise expression of IFN-γ, IL-1α, IL-18, IL-12, IL-10, and IL-6 in the liver of mouse [16].

3.4 Mechanism of Fumonisins in Some Disorder

[46] recommended that the fumonisin B_1-induced destruction of cardiovascular action may be one of the major elements provide to the happening of equine leukoencephalomalacia by the get up in serum and sphingosine concentrations and myocardial sphinganine.

Interruption of sphingolipid metabolism resulted in FB_1 before the pregnancy and during the first trimester may affect folate uptake and cause by a development risk of NTD [47]; [48].
FB_1 by the increase in sphingosine and/or sphinganine concentrations reduces the mechanical potency of the left ventricle and blocks L-type Ca channels. Pulmonary edema could generally caused by acute left-sided heart failure [49]; [50].

4. DETOXIFICATION OF FUMONISINS

Strategies of detoxification for infected feeds and foods to diminish or remove the toxic effects of fumonisins by biological, physical, and chemical processes are essential to boost food safety, hinder financial damage, and recover infected commodities. Data detected on biodegradation, detoxification, and binding procedures of fumonisins are abridged in Table 2.

Table 2. Biodegradation, detoxification, and binding processes of fumonisins

Process	Observation
Biological process	
Lactic acid bacteria (Micrococcus luteus, acillus subtilis)	Binding to FB1 and FB2
Sphingopyxis sp.	Hydrolysis of FB1 to HFB1
Saccharomyces	Decrase in FB1 and FB2
Lactobacillus strains (L. plantarum B7 and L. pentosus X8)	Removing fumonisins (FB1 and FB2)
Black yeasts Rhinoclodiella atrovirensa and Exophiala spinifera	Ester bonds was hydrolyzed of FB1
Candida parapsilosis	Mycelial growth inhibition
Physical process	
150–200 °C	87–100 % destruction of fumonisin B1 in corn cultures
Extrusion and roasting	60–70 % loss of FB1 and FB2
Extrusion	30 % loss of FB1 and FB2
Extrusion	92 % loss of fumonisin B1
Extrusion of drymilled products	Decrease in fumonisin accumulation by 30–90 % for mixing-type extruders and 20–50 % for non-mixing extruders
Baking corn	16 and 28 % loss of FB1
Frying corn chips	loss of 67 % of the fumonisin
Cooking and canning	Small influence on fumonisin measure (23%)
Ethanol–water extraction solvent at 80 °C	The most environmentally friendly, least toxic, and cheapest
Cholestyramine	Adsorption 85% of FB1
Activated carbon	Adsorption 62% of FB1
Ammonia process	Reduce FB1levels 30-45% No mutagenic potentials were apparent
Fructose	Obstruct the amine group of FB1, that is urgent for its toxicity
Chlorophorin	Reduced FB1 levels by 90–

	91%
Oxidizing agents	Little effects in FB1, but applicable because of the minimal cost and the minimal destruction of important nutrients
Bentonite	Adsorbed only 12% of the toxin FB1
Celite	Not effective
Chemical process	
Solution of SO2 at 60 °C for 6 h	Most impressive treatment to decline the measure of fumonisin B1
Acidic aqueous solution by the addition of NaNO2	Fumonisin B1 was significantly deaminated
NaCl solution	Fumonisin B1 had a little mass and that 86 % of the toxin could be eliminated
Ozone (O3)	No significant difference in FB1
Single Ca(OH)2 (nixtamalization) or with Na-HCO3 + H2O2 (modified nixtamalization)	reduction of 100% FB1 and 40% decresed toxicity of brine shrimp by Ca

4.1 Biological Methods

An enzymatic detoxification process is by recombinant enzymes from the bacterium *Sphingopyxis sp.* resulted in hydrolysis of fumonisin B_1 to HFB_1; deamination of HFB_1 by aminotransferase (a miss of the two tricarballylic side-chains via carboxylesterase) in the existence of pyridoxal phosphate and pyruvate. Lactic acid bacteria such as *Micrococcus luteus* and *Bacillus subtilis* bind to fumonisin B_1 and fumonisin B_2. Peptidoglycan bind to leastwise one tricarballylic acid part in the structure of FB_1 and especially FB_2 [2].

52.9% of FB_1 and 85.2% of FB_2 removed by two *Lactobacillus* strains (*L. pentosus X8* and *L. plantarum B7*), in the aqueous medium [51].

Fermentation using three different yeast strains (*Saccharomyces*) is a method for detoxification of fumonisins, thus a maximal decrease was observed in 28% and 17% for fumonisin B_1 and fumonisin B_2, respectively [52].

Hydrolyzing ester bonds of fumonisin B_1 by black yeasts (*Exophiala spinifera* and *Rhinoclodiella atrovirensa*) reported by [53].

Candida parapsilosis could inhibit mycelial growth of *Fusarium* species from 74.54% and 56.36%, and the maximum and minimum decrease in total created fumonisin was 78% and 12%, respectively [54].

Therefore we can remove 17 to 85 % of Fumonisins using the biological process, and *Lactobacillus* knew as the most effective strains for detoxification of Fumonisins.

4.2 Physical and Chemical Methods

Fumonisin B_1 needs a massive temperature (150–200 °C) to gain 87–100 % demolition in corn cultivation [53].

During extrusion of dry-milled products, decreasing in the measure of fumonisins was 20–50 % for non-mixing extruders and 30–90 % for mixing-type extruders [55]. For the production of cornflakes through the extrusion and roasting of raw corn, 60–70 % of fumonisins B_1 and B_2 were loosened. But removing of fumonisins only in the extrusion step was less than 30 % [56]. Destroying of fumonisin B_1 in extrusion processing of grits, was 92 % [56]. The economical, lowest toxic and most biodegradable solvent for fumonisin extraction is ethanol-water [57].

In baking corn muffins, removing of fumonisin during baked for 20 minutes were amidst 16 and 28 % at 175 °C and 200 °C respectively, also flotation the corn in water reduced the amount of fumonisin B_1, and frying corn chips for 15 minutes at 190 °C bring about a remove of 67 % of the fumonisin. But spiked corn masa fried at 140–170 °C (while degradation begins to take placed above 180 °C) has no significant loss of fumonisin B_1 [58],[59].

One of the most impressive management to decline the measure of fumonisin B1 is a 0.2 % solution of SO_2 at 60 °C for six hours [60]. But canning and cooking had a small influence on fumonisin measure [61].

In [62] studies, the adsorption capacity of cholestyramine for fumonisin B_1; 85% from a solution including 200 µg/ml FB_1, were reported.

Detoxification of corn with ammonia process reduced fumonisin levels (30 to 45 %), and no mutagenic potentials were found in the managed corn [63].

Obstruction the amine group of fumonisin B1 by reaction with fructose is another way to the detoxification of fumonisin B_1 [64].

The percentage of reduction of FB_1 in corn by single $Ca(OH)_2$ (nixtamalization) or with Na-HCO_3 + H_2O_2 (modified nixtamalization), was 100% [65].

Chlorophorin gets from vanillic acid, ferulic acid, caffeic acid, and iroko decreased FB_1 levels by 90–91% [66].

Treatment with oxidizing agents is an economical method for detoxification of fumonisin B_1, but this method isn't demonstrated in bioassays [65].

The acidic aqueous solution such as $NaNO_2$ can create deamination in fumonisin B_1, significantly [67].

In the floating section after treatment with NaCl solution, 86% of FB_1 were removed [68].

Celite and O3 couldn't make a significant difference in the level of FB_1, but bentonite adsorbed only 12% of the FB_1 [62, 69].

According to these reports, physical and chemical methods are the most effective way for detoxification of Fumonisin (in compare with the biological method), so it is necessary to intervention for remove the Fumonisin from feeds and foods.

5. OCCURRENCE

According to [70] using increases in global grain exchange, probably fungi spread from one country to another. In *Fusarium* fungi, this hazard expected to be minimum whereas these phytopathogens are field sooner than storage organisms. The global infection of animal feeds and foodstuffs with fumonisins is described in Table 3.

Table 3. Occurrence of fumonisins from human foods, cereals, and crops in various countries.

Nation-seed	Fumonisin B1 (mg/kg)	Fumonisin B2 (mg/kg)	Fumonisin B3 (mg/kg)
Barley			
Brazil	2.43		
France	Not detected		
Spain	0.2 to 11.6	0.5	
UK	Not Detected	Not Detected	Not Detected
Corn			
Argentina	Average of fumonisins in 2003: 10.2 and in 2004: 4.7 µg/kg		
Brazil	0.2 to 38.5	0.1 to 12	
Brazil	5.45 to 10.59	3.62 to 10.31	
Brazil	0.5 to 1.38	0.01 to 0.59	
Brazil	0.2 to 6.1		
Brazil	78.92		
Brazil	3.2	3.4	1.7

Honduras	0.068 to 6.5		
Uruguay	0.165 to 3.688		
USA	0 to 1.614		
USA	0.058 to 1.976	0.054 to 0.890	
Venezuela	0.025 to 15.05		
China	0.872 to 0.890	0.33 to 0.448	
China	0.08 to 21	0.05 to 4.35	0.06 to 1.66
China	<0.05 to 25.97	<0.10 to 6.77	<0.10 to 4.13
China	Total fumonisins <0.5 to 16.0		
China	0.058 to 1.976	0.056 to 0.89	0.053 to 0.385
China	0.003 to 71.121		
China	0.0165 to 0.3159		
India	0.07 to 8		
India	<1 to 100		
Iran	1.270 to 3.980	0.190 to 1.175	0.155 to 0.960
Iran	223.64		
Japan	<0.05 to 4.1	<0.1 to 10.2	
Philippines	Total fumonisins 0.3 to 10		
Taiwan	0.63 to 18.8	0.05 to 1.4	
Taiwan (Australia)	≤0.477		
Taiwan (USA)	≤1.614		
Taiwan (South Africa)	≤0.865	≤0.12	
Taiwan (South Africa)	≤0.05 to 0.9	<0.05 to 0.25	
Taiwan (Thailand)	≤0.334		
Vietnam	Total fumonisins 0.3 to 9.1		
Australia	Total fumonisins 0.3 to 40.6		
Australia	≤0.477		
Austria	<15		

Croatia	0.01 to 0.06	0.01	
Croatia	The highest concentrations fumonisins 25.5, mean values of 4.509		
Greece	0.1 to 0.56		
Portugal	0.09 to 2.3	0.25 to 4.45	
Poland	0.01 to 0.02	<0.01	
Romania	0.01 to 0.02	0.01	
Spain	≤22	≤0.7	
Spain	70 to 334	102 to 379	
Spain	0.2 to 19.2	0.2 to 5.9	
Spain	0.035 to 0.043	0.019 to 0.022	
The Netherlands	Traces to 0.380		
The Netherlands	Traces to 3.35		
UK	0.2 to 6		
Benin	Total fumonisins: 6.1 to 12 in 1999-2003		
Ethiopia	0.606	0.202	0.136
Ghana	0.011 to 1.655	0.01 to 0.77	0.07 to 0.224
Malawi	0.02 to 0.115	0.03	
Morocco	1.930		
South Africa	<10 to 83		
South Africa	≤0.63	≤0.25	
South Africa	0.05 to 117.5	0.05 to 22.9	
South Africa	0.2 to 46.9	0.15 to 16.3	
South Africa	<0.2 to 2		
South Africa (Argentina)	0.05 to 0.7	<0.05 to 0.5	<0.05 to 0.5
South Africa (USA)	0.9 to 3.9	0.3 to 1.2	0.08 to 0.6
Tanzania	0.025 to 0.165	0.06	
Zimbabwe	0.125	0.04	
Corn flakes			
Argentina	0.002 to 0.038	Not detected	

Brazil	0.66	0.03
Uruguay	0.218	Not detected
USA	Total fumonisins: <0.25	
USA	≤0.088	Not detected
USA or Canada	0.012 to 0.155	
Korea	0.018 to 0.143	
Germany	Total fumonisins <0.01 to 1	
Italy	0.01	Not detected
Italy	0.020 to 1.092	0.006 to 0.235
Nordic countries	0.005 to 1.030	0.004 to 0.243
Spain	0.02 to 0.1	
Switzerland	0.055	
The Netherlands	1.43	
Turkey	Not detected	Not detected
South Africa	Not detected	Not detected
Corn flour		
Argentina	0.038 to 1.86	0.02 to 0.768
Brazil	≤1.46	≤0.51
USA	Total fumonisins: <0.25 to 1	
China	0.06 to 0.2	<0.10
Italy	3.54	0.84
Nordic countries	0.017 to 0.86	0.007 to 0.024
UK	Total fumonisins 0.218	
The Netherland	0.04 to 0.09	
Corn grits		
Argentina	0.092 to 0.494	0.02 to 0.1
Argentina	1.1	0.425
Brazil	0.17 to 1.23	0.05 to 0.3
USA	Average 0.6	Average 0.4

USA	Total fumonisins: 0.251 to 1		
USA	Total fumonisins: <0.25		
Japan	0.2 to 2.6	0.3 to 2.8	
Germany	0.0139		
Italy	3.76	0.9	
Nordic countries	0.007		
Spain	0.03 to 0.09	Not detected	
Switzerland	0 to 0.79	0 to 0.16	
South Africa	<0.05 to 0.19	<0.05 to 0.12	
Corn kernel			
Bahrain	0.025		
China	5.3 to 8.4	2.3 to 4.3	
Nepal	0.05 to 4.6	0.1 to 5.5	
Indonesia	0.051 to 2.44	<0.376	
Egypt	69 to 4495		
Ghana	0.07 to 33.1	0.06 to 12.3	
Kenya	0.11 to 12		
Corn meal			
Argentina	0.06 to 2.86	0.061 to 1.09	0.018 to 1.015
Argentina	0.603 to 1.171	0.717	
Brazil	0.56 to 4.93	0.21 to 1.38	
Canada	0.05		
Peru	0.66	0.13	
USA	Average: 1	0.3	
USA	Total fumonisins: <0.25 to >1		
China	<0.5 to 8.8	<0.5 to 2.8	<0.5 to 0.9
Turkey	0.25 to 2.66	0.55	
South Africa	Average: 0.14	Average: 0.08	
Oat			

Brazil	0.17	
UK	Total fumonisins not detected	
Rice		
Iran	21.59	
UK	Total fumonisins not detected	
Wheat		
Brazil	24.35	
France	Not detected	
Spain	0.2 to 8.8	0.2
UK	Total fumonisins not detected	

5.1 North and South America

In the USA, the infection of corn by fumonisins was detected by [71] and [72].

Level of infection with fumonisin B_1 in corn of Honduras was 0.068 to 6.5 mg/kg [73].

In Brazil, the incidence of fumonisins was detected in corn by [74], [75], [76], [77], [78] and [79], the measure of contamination of corn with Fumonisins over 1999 to 2001 was increased. The infection of wheat, oat and barely by fumonisins was also detected by [78].

In Uruguay, research for checking measure of fumonisins in corn commodities showed the contamination of corn with fumonisin B_1 was 0.165 to 3.688 mg/kg [80].

[81] reported that the infection of corn with fumonisin B1 in Venezuela was 25 to 15050 ng/g.

The average of fumonisins in corn of Argentina was 10200 µg/kg in 2003 and 4700 µg/kg in 2004 [82].

Corn was the most prevalent source of Fumonisins in North and South America. Moreover, the level of Fumonisins in South America was higher than in North America, and perhaps it was because of different climate condition.

The percentage of Fumonisins in corn product such as corn flour were decreased; this decline probably proved that detoxification method was effective for the control of Fumonisins in America.

5.2 Asia and Oceania

In China, the contamination of corn with fumonisins was reported by [83]; [84], [85], [71], [86] and [87]. Based on these studies the most extreme concentration of fumonisin B_1, B_2 and B_3 were 25.97 mg/kg, 6.77 mg/kg and 4.13 mg/kg respectively. Also, [88] reported that in China total fumonisins concentration was 0.5 to 16 mg/kg. In Iran [90] investigated infection of corn with fumonisin B_1, B_2, and B_3. Also, [18] reported the corn's contamination with fumonisin B_1. The high concentration of Fumonisins in corn of Iran and China, justify the high prevalence of esophageal cancer in Iranian and Chinese people.

The contamination of corn with fumonisin B_1 and B_2 was detected by [89] in Japan.

[91] declared that the measure of total fumonisins in corn of Philippines and Vietnam was 0.3 to 10 mg/kg and 0.3 to 9.1 mg/kg, respectively.

Contamination of Taiwan's corn with fumonisins was investigated by [92], [72] and [93], increasing in level of Fumonisins in Taiwan's corn declared that legislation and control program in this country was not efficient and it is necessary to change their programmes.

The incidence of fumonisins in corn of India declared by [94] and [95].

[72] and [91] reported the contamination of corn in Australia and the highest fumonisins level was 40.6 mg/kg.

5.3 Europe

[96] published a review article on information about the occurrence of fumonisins from some European nations (Croatia, Poland, Portugal, and Romania). The highest concentration of fumonisins in Croatia was 25,200 ng/g, and the mean value was 4,509 ng/g [97].

In Spain, contamination of corn with fumonisins investigated by [98], [99], [100], and [101]. Also, [102] reported the concentration of fumonisin B_1 and B_2 in wheat and barley.
Fumonisin B_1 was not found in wheat and barley of France [103].
[104] reported the corn contamination with fumonisin B_1 in Austria.
In oat, barley and wheat of United Kingdom [105] have not detected fumonisins but [106] declared the concentration of fumonisin B_1 in corn of UK (0.2 to 6 mg/kg).

5.4 Africa

Albeit majority African territory has weather distinguished by high temperature and high humidity that suitable for the development of molds, little data is accessible on the occurrence of toxins of *Fusarium*. High infection of the basic material is a developing problem. Regulative problems are not accessible in the territory of food retailing and exhibition, and mycotoxin issues now have been combined with some food infection in some parts in Africa [107].
The infection of corn with fumonisins in South Africa was reported by [108], [109], [93], [110], [111] and [112]. Based on these studies the most extreme concentration of fumonisin B1, B2 and B3 were 117.5 mg/kg, 22.9 mg/kg and 0.6 mg/kg respectively.
A high measure of fumonisins (12 mg/kg) was also detected in corn from Benin [113].
[114] detected the fumonisin B_1, B_2, and B_3 in corn of Ethiopia.
Corn from Ghana and Morocco was also infected with fumonisins [115]; [116].

6. DIETARY INTAKE

In the European diet, the total intake of FB_1 has been evaluated at 1.4 µg/kg of body weight/week [117]. Daily intake of fumonisins in varies countries and foods, were summarized in Table 4.
In [117]; [118] articles, tolerable daily intake (TDI) of FB_1 was reported 800 ng/kg. Also, provisional-maximum-tolerable-daily-intake (PMTDI) of fumonisin was noted 2 µg/kg of body weight per day on by the no-observed-effect-level (NOEL) of 0.2 mg/kg of body weight/day and a safety aspect of one hundred.
Using the simulation model, mean concentrations of fumonisin B_1 in milk evaluated 0.36 µg/kg. Whenas the pretended tolerable daily intakes (TDI) from milk for females and males fell lesser European Union guidelines [119].
[14] demonstrated that feces are the major way of excretion of fumonisin B_1 in rabbits, by comparing the concentration of FB_1 in urine, liver, and feces.

Table 4. Daily intake of fumonisins for different countries and foods

Food	Nation	Intake (ng/kg of bw/day)	Explantion
Beer	USA	20 to 54	Camputed on the base of the 60 kg body weight
Cereal commodities	France	22.8	All children in france
Cereal commodities	France	4.6	All female adults in france
Cereal commodities	France	3.2	All male adults in france
Cereal commodities	France	9.96	All people in france
Cereal commodities	Germany	31.8	Users >14 years
Cereal commodities	Norway	430	6 month babies
Corn	Brazil	392	Camputed on the base of the 70 kg body weight from urban area
Corn	Brazil	1276	Camputed on the base of the 70 kg body weight from rural area people
Corn	Brazil	4.1 3.4	Conventional corn Organic corn

		3.8	Total
Corn	France	45.6	All children in france
Corn	France	12.4	All female adults in france
Corn	France	7.4	All male adults in france
Corn	France	9.96	All people in france
Corn	Germany	8.7	Users >14 years
Corn	Switzerland	30	
Corn	The Netherlands	3.1	Adults
Corn	USA	80	
Corn	USA	600000 to 2100000	Natural outbreak of LEM in horses
Corn	Zimbabwe	140 and 5760	Shamva district
Corn	Zimbabwe	180 and 8092	Makoni district
Corn commodity	Brazil	63.3	São Paulo population
Food with corn based	Argentina	0.73 to 2.29	Camputed on the base of the 70 kg body weight
Food with corn based	Brazil	maximum probable daily intake (MPDI): 256.07 average probable daily intake (APDI): 120.58	
Food with corn based	Canada	89	All children
Food with corn based	Canada	190	Child users
Food with corn based	Denmark	400	
Food with corn based	South Africa	14,000 to 440,000	A group of people exhibiting a high prevalence of human esophageal
Food with corn based	South Africa	5,000 to 59,000	A group of people exhibiting a less prevalence of human esophageal
Food with corn based	UK	30	
Corn inferred commodities	Belgium	16.7	
Corn inferred commodities	China	450 to 15,810 (Mean=3020)	Camputed on the base of the 50 kg body weight
Corn inferred commodities	Germany	10.4	Users >14 years
Corn inferred commodities	Italy	185.6	Italian users
Corn inferred commodities	Italy	24.6	All people in Italy
Corn inferred commodities	Norway	0.24	Adult male and female population
Corn inferred commodities	Norway	0.50	Adult male and female users
Corn powder	Argentina	79 to 198	For samples during 1996/1997 and January 1998
Corn pieces	Germany	69.8	Users >14 years

Corn pieces	Italy	283.6	Italian users
Corn pieces	Italy	15.9	All people in Italy
Rice	France	12.1	All children in france
Rice	France	5.6	All female adults in france
Rice	France	5.6	All male adults in france
Rice	France	5.7	All people in france
Rice	Germany	0.6	Users >14 years
Wheat commodities	France	345.1	All children in france
Wheat commodities	France	230.8	All female adults in france
Wheat commodities	France	256	All male adults in france
Wheat commodities	France	240.08	All people in france
Wheat commodities	Italy	62.1	Italian users
Wheat commodities	Italy	10.6	All people in Italy
Food and feeds	Germany	bad case scenario: 21,000 mean case scenario: 1,100	German users

7. MAXIMUM LIMITATION

There are different variables that may affect the foundation of tolerances for specific mycotoxins, such as the delivery of mycotoxins through products, regulations of trade contact in different countries, availability data of toxicological or dietary exposure, and the accessibility of techniques for analysis [120].

Deadline level for fumonisins in maize and other cereals, at the moment change from 5 to 100000 µg/kg. Present laws of fumonisins in feeds and foods set by nations from America, Africa, Europe, and Asia and described by [121]; [122] and denoted in Table 5.

Table 5. Maximum limits for Fumonisins in feeds and foods in different countries [138]; [139]

Country	**Maximum limit (µg/kg)**	**Commodity**
Bulgaria (FB1, FB2)	1000	Maize and processed products thereof
Cuba (FB1)	1000	Maize, rice
France (FB1)	3000	Cereals & cereal products
Iran (FB1, FB2)	1000	Maize
Singapore (FB1, FB2)	Not given	Corn & corn products
Switzerland (FB1, FB2)	1000	Maize
Taiwan (FB1)	Based on the result of risk evaluation	Maize commodities
USA (FB1, FB2, FB3)	2000	Disinfected dry milled corn commodities (e.g. corn grits, flaking grits, corn meal, corn flour with fat content of <2.25%, dry weight basis)
	3000	purified corn purpose of popcorn
	4000	Total of partially disinfected dry milled corn commodities (e.g. corn grits, flaking grits, corn meal, corn flour with fat content of <2.25%, dry weight basis);
	5000	dehydrated milled corn bran; purified corn purpose of

		masa production
	20000	
		Corn and corn derived purpose of rabbits and equids
	30000	
		Corn and corn derived purpose of catfish and swine
	60000	Corn and corn derived purpose of breeding mink, breeding poultry, and breeding ruminants (contains hens laying eggs and lactating dairy cattle for human use)
	100000	
	10000	Mink upbringing for pelt output and Ruminants >3 months old upbringing for slaughter
		Poultry upbringing for slaughter
		Pet animals and all other species or classes of livestock
European Union fumonisins	2000 1000	Unprocessed maize Maize products for human
European Union (FB1, FB2)	50 5	Animal feeds except Equines Feeds of Equines
Food and Drug Administration (FB1, FB2, FB3)	30 5	Animal feeds except Equines Feed of Equines

CONCLUSION

Fumonisins can cause fatal diseases in animals and classified as a potential human carcinogen. In this review as the main aspects presents results on studies concerning the ability of Fumonisins to cause varies toxicity effects in different part of body in human and animal, compare and evaluation of Fumonisins occurrence in many countries, effect of different detoxification method for removing the Fumonisins, mechanism of toxicity in cells of human and animals, evaluation the intake of Fumonisins in various consumers of and comparing the limitation of Fumonisins in several countries.

The authors suggestion for future investigation about Fumonisins are; estimate the reproductive effects of fumonisins, refresh and expand the information about the occurrence of fumonisins in different parts of the world, extend masked Fumonisins in detoxification researches, improve the legislation about Fumonisins to change daily intake of these mycotoxins, more notice to mechanisms of Fumonisins on different types of animals and cells, cell-cell interactions, exposure pathway, and exposure measures.

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