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Metabolism, Toxicity, Detoxification, Occurrence, Intake and Legislations of Fumonisins - A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Fumonisins are a group of mycotoxins generated by the *Fusarium spp*. in foods and feeds. More than 15 isomers of Fumonisin are recognized, and the B series of Fumonisins is the primary and referral isomer of Fumonisin. Fumonisin B can cause leukoencephalomalacia in rabbits and horses and porcine pulmonary edema in swine. Fumonisin B is also nephrotoxic, hepatotoxic, immunotoxic and carcinogenic. It blocks sphingolipid biosynthesis (and hinders the synthesis of ceramide) by a noticeable resemblance to sphingosine and sphinganine. This paper provides a review of the toxicity, occurrence, and mechanism of carcinogenicity, hepatotoxicity, nephrotoxicity as well as immunotoxicity of Fumonisins, which are primarily found on a variety of food and feed in Africa, America, Europe, Asia, and Oceania. In this paper, current information on contamination of feeds and foods by Fumonisins around the world is summarized. Because of economic losses induced by Fumonisins and their harmful effects on animal and human health, various procedures to detoxify infected feeds and foods have been illustrated in this review, including biological, physical, and chemical processes. Additionally, we discuss dietary intakes and maximum limits of Fumonisins in some countries.

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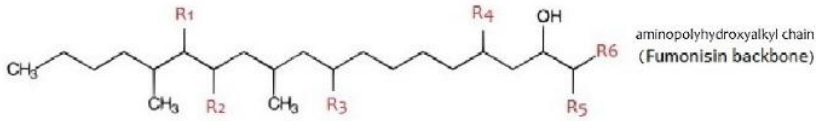
Keywords: Fumonisins; toxicity; detoxification; mechanism; occurrence; intake.

1. INTRODUCTION

Fumonisins are a group of more 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,* as well as *Aspergillus niger* [1,2].

Fumonisins have a noncyclic structure (in contrast to most mycotoxins), in which there is a chain with 19- or 20- carbon aminopolyhydroxyalkyl, diesterified by tricarballylic acid groups (propane-1,2,3-tricarboxylic acid) as shown in Fig 1. Hitherto, various chemically associated series or groups of Fumonisins were isolated. These series consist of A, B, C, and P. The main detected forms of Fumonisins in foods, are the B series of Fumonisins [3]. In more than 15 Fumonisin forms, Fumonisins B_1, Fumonisins B_2, and Fumonisins B_3 are the broadest mycotoxins that have been described [4].



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

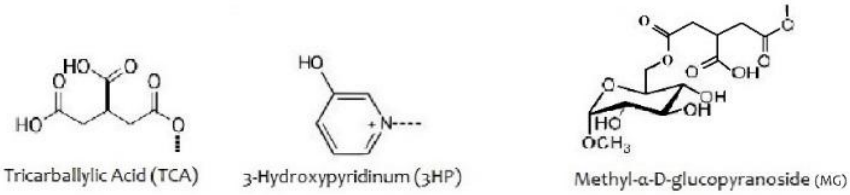


Fig. 1. Chemical structures of the Fumonisins [3,4]

Fungi-producing Fumonisin contaminates the following: 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 form of toxic effect on animals, including leukoencephalomalacia in horses [6], change in weight of the body and internal organ in broiler chicken [7,8], and pulmonary edema as well as hepatocellular necrosis in piglet [9,10]. Moreover, renal and hepatic toxicity are detected in different animals, such as rabbits, lambs, turkeys, mice, rats, and broilers [7,11-14].

In human, the risk of neural tube defects (NTD) and developing esophageal cancer is increased by Fumonisins [15,16].

2. METHODS

The current review is a narrative on Fumonisins, and the databases including Science Direct, PubMed, and Google Scholar are used to collect the published articles since 1980 through 2018. This paper is conducted using keywords: [*Fumonisin* OR *mycotoxin* OR *Fumonisin B* OR *Fusarium*] AND [toxicity OR detoxification OR degradation OR mechanism OR metabolism OR occurrence OR prevalence OR intake OR limitation]. The list of references of included articles was also searched to identify additional ones. After first screening by the title and abstract, eligible studies were downloaded and easy and suitable phrases were chosen. Inclusion criteria in our study included: (1) Full-text available. (2) Review, mini-review, original, narrative articles, and books. (3) Published paper in the English language (to avoid mistakes in translation process) among 1980 to the 2018 year. (4) Detect concentration of Fumonisin B1, B2, and B3 in barley, wheat, oat, rice, corn and corn product such as corn grits, corn flakes, corn flour, cornmeal, and corn kernel. The articles were excluded when they did not meet these criteria.

3. OCCURRENCE

Due to increase in global grain exchange, the fungi spread was transferred from one country to another [17]. In *Fusarium* fungi, this hazard is expected to be minimum whereas these phytopathogens are field sooner than storage organisms. Table 1 describes the global infection of animal feeds and foodstuffs with Fumonisins is described.

3.1 North and South America

Corn is the most prevalent source of Fumonisins (Table 1). The level of Fumonisins in South America is higher than North America, maybe because of their different climate conditions. For instance, the concentration of Fumonisin in corn in Brazil reaches to 38.5 mg/kg [18], while the percentage of Fumonisins in corn product of North America such as corn flour, corn grits, and corn flakes rarely reaches to 1 mg/kg. This decline probably proves that detoxification method was more effective for the controlling Fumonisins in North America in comparison with South America.

In Brazil, the incidence of Fumonisins in corn was detected by [18-24], and the contamination of corn with Fumonisins in Brazil usually decreased over 1999 to 2014.

The average of Fumonisins in corn of Argentina was 10200 µg/kg in 2003 and 4700 µg/kg in 2004 [25].

The infection of wheat, oat and barely by Fumonisins was also detected by Mallmann et al. [23].

3.2 Asia and Oceania

In China, the contamination of corn with Fumonisins was reported by GAO and Yoshizawa., [36], Gong et al. [39], Li et al. [33], Li et al. [40], Shi et al. [41], Ueno et al. [37], and Yoshizawa. [35]. 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, Zhang et al. [38] reported that in China total Fumonisins concentration was 0.5 to 16 mg/kg. In Iran, Shephard et al., [44] investigated infection of corn with fumonisin B_1, B_2, and B_3. Also, Alizadeh et al. [45] 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 were detected by Ueno et al. [46] in Japan.

Bryden et al. [47] declared 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.

Table 1. Occurrence of Fumonisins from human foods, cereals, and crops in various countries

Nation-seed	Fumonisin B_1 (mg/kg)	Fumonisin B_2 (mg/kg)	Fumonisin B_3 (mg/kg)	Reference
Barley				
Brazil	2.43			[23]
Korea	0 to 2667.3	0 to 1521.1		[26]
France	Not detected			[27]
Spain	0.2 to 11.6	0.5		[28]
UK	Not Detected	Not Detected	Not Detected	[29]
Corn				
Argentina	Average of Fumonisins in 2003: 10.2 and in 2004: 4.7 µg/kg			[25]
Brazil	0.2 to 38.5	0.1 to 12		[18]
Brazil	5.45 to 10.59	3.62 to 10.31		[20]
Brazil	0.5 to 1.38	0.01 to 0.59		[21]
Brazil	0.2 to 6.1			[22]
Brazil	78.92			[23]
Brazil	3.2	3.4	1.7	[24]
Brazil	0.066 to 7.832	0.11 to 1.201		[19]
Honduras	0.068 to 6.5			[30]
Uruguay	0.165 to 3.688			[31]
USA	0 to 1.614			[32]
USA	0.058 to 1.976	0.054 to 0.890		[33]
Venezuela	0.025 to 15.05			[34]
China	0.872 to 0.890	0.33 to 0.448		[35]
China	0.08 to 21	0.05 to 4.35	0.06 to 1.66	[36]
China	<0.05 to 25.97	<0.10 to 6.77	<0.10 to 4.13	[37]
China	Total Fumonisins <0.5 to 16.0			[38]
China	0.058 to 1.976	0.056 to 0.89	0.053 to 0.385	[33]
China	0.003 to 71.121			[39]
China	0.268	0.537	0.472	[40]
China	0.0165 to 0.3159			[41]
India	0.07 to 8			[42]
India	<1 to 100			[43]
Iran	1.270 to 3.980	0.190 to 1.175	0.155 to 0.960	[44]
Iran	223.64			[45]

Nation-seed	Fumonisin B_1 (mg/kg)	Fumonisin B_2 (mg/kg)	Fumonisin B_3 (mg/kg)	Reference
Japan	<0.05 to 4.1	<0.1 to 10.2		[46]
Philippines	Total Fumonisins 0.3 to 10			[47]
Taiwan	0.63 to 18.8	0.05 to 1.4		[48]
Taiwan (Australia)	≤0.477			[32]
Taiwan (USA)	≤1.614			[32]
Taiwan (South Africa)	≤0.865	≤0.12		[49]
Taiwan (South Africa)	≤0.05 to 0.9	<0.05 to 0.25		[49]
Taiwan (Thailand)	≤0.334			[32]
Vietnam	Total Fumonisins 0.3 to 9.1			[47]
Australia	Total Fumonisins 0.3 to 40.6			[47]
Australia	≤0.477			[32]
Austria	<15			[50]
Croatia	0.01 to 0.06	0.01		[51]
Croatia	The highest concentrations Fumonisins 25.5, mean values of 4.509			[52]
Greece	0.1 to 0.56			[53]
Portugal	0.09 to 2.3	0.25 to 4.45		[51]
Poland	0.01 to 0.02	<0.01		[51]
Romania	0.01 to 0.02	0.01		[51]
Spain	≤22	≤0.7		[54]
Spain	70 to 334	102 to 379		[55]
Spain	0.2 to 19.2	0.2 to 5.9		[56]
Spain	0.035 to 0.043	0.019 to 0.022		[57]
The Netherlands	Traces to 0.380			[58]
The Netherlands	Traces to 3.35			[53]
UK	0.2 to 6			[59]
Benin	Total Fumonisins: 6.1 to 12 in 1999-2003			[60]
Ethiopia	0.606	0.202	0.136	[61]
Ghana	0.011 to 1.655	0.01 to 0.77	0.07 to 0.224	[62]

Nation-seed	Fumonisin B_1 (mg/kg)	Fumonisin B_2 (mg/kg)	Fumonisin B_3 (mg/kg)	Reference
Malawi	0.02 to 0.115	0.03		[63]
Morocco	1.930			[64]
Nigeria	0.164 to 2.09 (0.852)	0.046 to 0.710 (0.262)	0.010 to 0.186 (0.069)	[65]
South Africa	<10 to 83			[66]
South Africa	≤0.63	≤0.25		[49]
South Africa	0.05 to 117.5	0.05 to 22.9		[67]
South Africa	0.2 to 46.9	0.15 to 16.3		[68]
South Africa	<0.2 to 2			[69]
South Africa	0.012 to 8.514			[70]
South Africa (Argentina)	0.05 to 0.7	<0.05 to 0.5	<0.05 to 0.5	[71]
South Africa (USA)	0.9 to 3.9	0.3 to 1.2	0.08 to 0.6	[71]
Tanzania	0.025 to 0.165	0.06		[63]
Zimbabwe	0.125	0.04		[63]
Corn flakes				
Argentina	0.002 to 0.038	Not detected		[72]
Brazil	0.66	0.03		[73]
Uruguay	0.218	Not detected		[31]
USA	Total Fumonisins: <0.25			[74]
USA	≤0.088	Not detected		[75]
USA or Canada	0.012 to 0.155			[76]
Korea	0.018 to 0.143			[77]
China	0.001 to 0.171	<0.0002 to 0.025	0.0002 to 0.031	[40]
Germany	Total Fumonisins <0.01 to 1			[78]
Italy	0.01	Not detected		[79]
Italy	0.020 to 1.092	0.006 to 0.235		[80]
Nordic countries	0.005 to 1.030	0.004 to 0.243		[81]
Serbia	0 to 0.434 (0.067)	0 to 0.145 (0.019)		[82]
Spain	0.02 to 0.1			[83]
Switzerland	0.055			[84]
The Netherlands	1.43			[58]
Turkey	Not detected	Not detected		[85]

Nation-seed	Fumonisin B_1 (mg/kg)	Fumonisin B_2 (mg/kg)	Fumonisin B_3 (mg/kg)	Reference
South Africa	Not detected	Not detected		[86]
Corn flour				
Argentina	0.038 to 1.86	0.02 to 0.768		[87]
Brazil	≤1.46	≤0.51		[73]
USA	Total Fumonisins: <0.25 to 1			[74]
China	0.06 to 0.2	<0.10		[46]
Italy	3.54	0.84		[79]
Nordic countries	0.017 to 0.86	0.007 to 0.024		[81]
Serbia	0 to 1.738 (0.162)	0 to 0.394 (0.042)		[82]
UK	Total Fumonisins 0.218			[88]
The Netherland	0.04 to 0.09			[58]
Corn grits				
Argentina	0.092 to 0.494	0.02 to 0.1		[87]
Argentina	1.1	0.425		[89]
Brazil	0.17 to 1.23	0.05 to 0.3		[73]
USA	Average 0.6	Average 0.4		[86]
USA	Total Fumonisins: 0.251 to 1			[74]
USA	Total Fumonisins: <0.25			[74]
Japan	0.2 to 2.6	0.3 to 2.8		[46]
China	0.0002 to 2.238	0.0002 to 0.547	0.0002 to 0.402	[40]
Germany	0.0139			[90]
Italy	3.76	0.9		[79]
Nordic countries	0.007			[81]
Spain	0.03 to 0.09	Not detected		[83]
Switzerland	0 to 0.79	0 to 0.16		[84]
South Africa	<0.05 to 0.19	<0.05 to 0.12		[86]
Corn kernel				
Bahrain	0.025			[53]
China	5.3 to 8.4	2.3 to 4.3		[46]
China	1.878	0.853		[91]
Nepal	0.05 to 4.6	0.1 to 5.5		[46]
Indonesia	0.051 to 2.44	<0.376		[92]
Egypt	69 to 4495			[93]
Ghana	0.07 to 33.1	0.06 to 12.3		[62]

Nation-seed	Fumonisin B_1 (mg/kg)	Fumonisin B_2 (mg/kg)	Fumonisin B_3 (mg/kg)	Reference
Kenya	0.11 to 12			[94]
Corn meal				
Argentina	0.06 to 2.86	0.061 to 1.09	0.018 to 1.015	[72]
Argentina	0.603 to 1.171	0.717		[89]
Brazil	0.56 to 4.93	0.21 to 1.38		[73]
Canada	0.05			[86]
Peru	0.66	0.13		[86]
USA	Average: 1	0.3		[86]
USA	Total Fumonisins: <0.25 to >1			[74]
China	<0.5 to 8.8	<0.5 to 2.8	<0.5 to 0.9	[95]
Turkey	0.25 to 2.66	0.55		[85]
South Africa	Average: 0.14	Average: 0.08		[86]
Oat				
Brazil	0.17			[23]
UK	Total Fumonisins not detected			[29]
Rice				
Iran	21.59			[45]
China 1999	3.410 to 16.79			[96]
China 2010	0.0001 to 0.00164			[96]
China 2014	0 to 0.74			[96]
UK	Total Fumonisins not detected			[29]
Wheat				
Brazil	24.35			[23]
Argentina_flour	0.0003	0.00124		[97]
France	Not detected			[27]
Spain	0.2 to 8.8	0.2		[28]
UK	Total Fumonisins not detected			[29]

Contamination of Taiwan's corn with Fumonisins was investigated by Rheeder et al. [49], Tseng and Liu. [32], and Yoshizawa et al. [48]. Increasing level of Fumonisins in Taiwan's corn declared that legislation and control programs in this country were not efficient and changing it seems necessary.

3.3 Europe

Doko et al. [51] published a review article on some information about the occurrence of Fumonisins from some European nations (Croatia, Poland, Portugal, and Romania). The highest concentration of Fumonisins in Croatia was 25.2 mg/kg, and the mean value was 4.509 mg/kg [52].

In Spain, contamination of corn with Fumonisins investigated by Arino et al. [57], Castellá et al. [55], and Sanchis et al. [54]. Also, Castella et al. [28] reported the concentration of Fumonisin B_1 and B_2 in wheat and barley. However, Fumonisin B_1 was not found in wheat and barley of France [27].

Lew et al. [50] reported the corn contamination with fumonisin B_1 in Austria.

In oat, barley and wheat of United Kingdom Patel et al. [29] have not detected Fumonisins but Preis and Vargas. [59] declared the concentration of fumonisin B_1 in corn of UK (0.2 to 6 mg/kg).

3.4 Africa

Albeit the majority of African territory has a weather distinguished by high temperature and humidity which is suitable for development of molds, little data is accessible on the occurrence of toxins of *Fusarium*. To a large extent, infection of the primary material is an expanding problem in Africa. Regulative problematic matters are not feasible in the territory of food retailing and exhibition, and mycotoxin issues now have been combined with some food infection in soe parts of Africa [98].

The maximum level of fumonisin B1 in researches on corn of South Africa is very high and achieved to 117.5 mg/kg in Rheeder et al., [67] and 8.514 in new literature by Mngqawa et al. [70].

Getachew et al., [61] detected the fumonisin B_1, B_2, and B_3 in corn of Ethiopia.

Evaluation of Fumonisins on corn products of Africa is low, and these investigations consisted of corn meal [86], corn kernel [94], and corn grits [86].

4. METABOLISM AND MECHANISM OF FUMONISINS

Structure of fumonisin B has a noticeable similarity to sphinganine and sphingosine. In Fig. 2 both sphingosine and sphinganine are intermediates in the degradation and biosynthesis of sphingolipids. Furthermore, D'mello et al. [99] reported that fumonisin B obstruct sphingolipid biosynthesis by specifically inhibiting sphingosine (sphinganine) N-acyltransferase, *in vitro* and *situ*.

Sphingolipids are a group of lipids which could be detected in the whole of eukaryotic cells. All of the sphingolipids include a sphingoid (long-chain base backbone). Sphingolipids are critical basic molecules and rule as regulators of a numeral of cell act [101]. In Fig. 3 presents location of working of fumonisin B-induced inhibition of the enzyme CER synthase, is presented.

4.1 Mechanism of Fumonisins in Apoptosis and Cancer

Interruption of sphingolipid metabolism can cause the increase in available sphingoid backbone and their 1-phosphates may change the compound sphingolipids and decrease the biosynthesis of ceramide (CER). Available sphingoid backbone induced cell death, but Fumonisins by inhibition of CER synthase can restrain cell death [102].

Feedback of the apoptosis and carcinogenicity effects induced by Fumonisin B_1 can be some mechanisms including oxidative damage, lipid peroxidation and maybe an induction of hepatic and renal tumors happens [16]. Also, Yin et al. [103] 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.

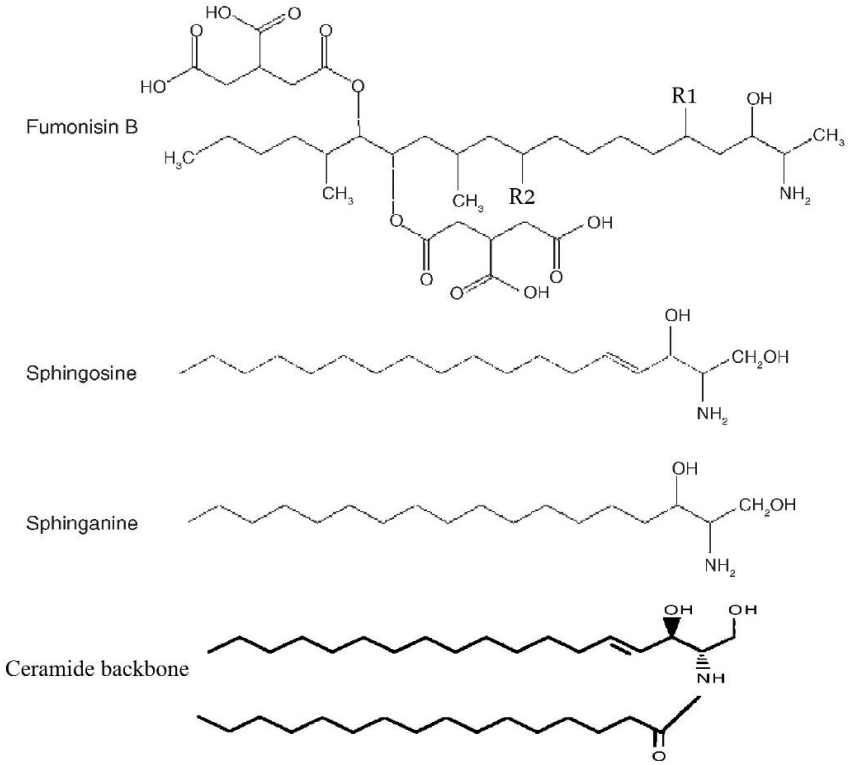


Fig. 2. Structures of fumonisin B, sphingosine, sphinganine and ceramide backbone [3,100]

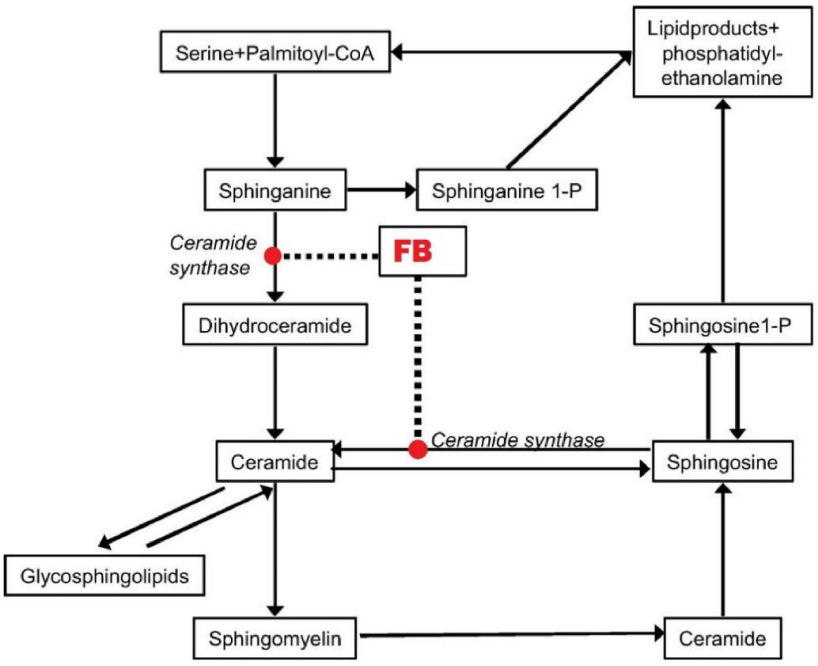


Fig. 3. A summarized scheme of the sites of action of fumonisin B-induced inhibition of the enzyme ceramide synthase on the pathway of de novo sphingolipid synthesis and turnover in mammalian cells and [16]

In some studies following Fumonisin B_1 treatment in different cells of human and animals, it has been proven 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 cleaved caspase-8. Probably, the mitochondrial pathway consists of induced apoptosis by Fumonisin B_1 by the actuation of Bid and release cytochrome c [16].

Wang et al. [104] reported that Fumonisin B_1 in human normal esophageal epithelial cells (HEECs) stimulated the proliferation, whose mechanism of HEECs is, decreasing in protein expression of cyclin E, p21, and p27 and increase in protein expression of cyclin D1.

4.2 Mechanism of Fumonisins in Hepatotoxicity

Accumulation of sphingoid base because of induced fumonisin B_1 can provoke TNF-α and make the hepatotoxicity in mice. Also, TNF-α receptor 1b is important mediating in the hepatotoxic responses by a rise in the circulation of liver enzymes [105].

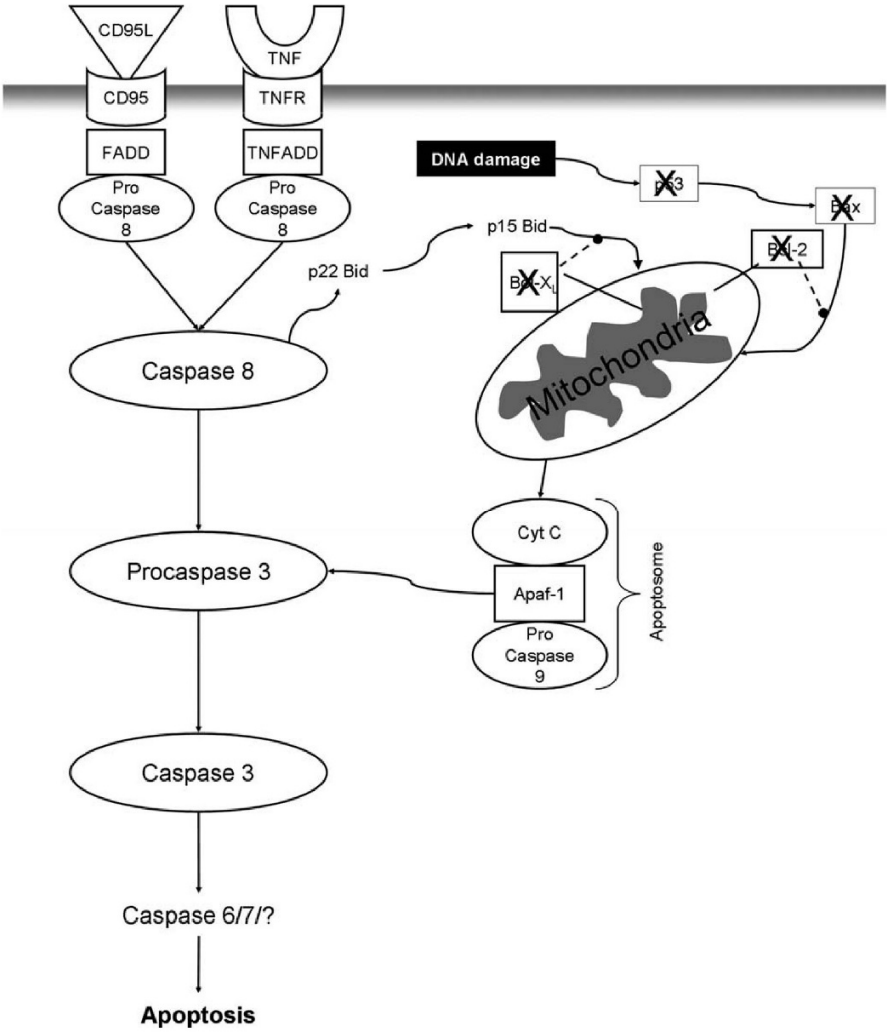


Fig. 4. A schematic landscape of the pathways conduct to apoptosis and the mechanisms probably consisted of fumonisin B1 -induced activation of caspase-3 resulted in apoptosis. X mark showed the mechanisms that do not consisted of the apoptosis caused by fumonisin B1 [16]

4.3 Mechanism of Fumonisins in Immunotoxicity

Exposure to FB_1 in human dendritic cells; increases 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 lipopoly-saccharide 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 [106,107].

After exposure to fumonisin B_1 in mouse, a raise 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].

4.4 Mechanism of Fumonisins in Some Disorder

Smith et al. [108] recommended that the induced Fumonisin B1 by the destruction of cardiovascular action can be one of the primary elements that trigger the occurrence of equine leukoencephalomalacia through the increase 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 development of the risk of NTD [109 and 110].

FB_1 increases sphingosine and/or sphinganine concentrations, reduces the mechanical potency of the left ventricle and blocks L-type Ca channels. Generally, pulmonary edema could be caused by acute left-sided heart failure [111,112].

5. TOXICITY OF FUMONISINS

In the human and various animals, Fumonisins beget some toxic effects such as carcinogenic, hepatotoxic, and nephrotoxic. Moreover, sensitivity to Fumonisins is different in human and varies in animals. For example, based on Bondy et al. [113] rats are more sensitive to fumonisin B_1 than mice. We summarized disorder effects, dosage, duration and source of fumonisin in Table 2.

5.1 Carcinogenicity

Contamination of wheat, corn and rice with Fumonisin B can increase the risk of esophageal cancer in human [16,45,114], by stimulating the proliferation of human esophageal epithelial cells (HEECs) [104]. Furthermore, Mathur et al. [117] observed some different effects of stimulation of the proliferation in liver cells consisted of a proliferation of ductular bile cells and hepatocyte proliferation in cattle.

In rats, continuing intake of FB_1 (up to 2 years) has consequences such as the introduction of renal tubule tumors, hepatocellular adenomas, cholangiocarcinomas, and carcinomas [130,132].

5.2 Hepatotoxic Effect

Fumonisins could create a mild hepatopathy in lambs [11]. Nonetheless hepatotoxic effects of Fumonisins in cattle is more extensive than lamb, and consists of increases in gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), cholesterol and bilirubin, and mild microscopic liver lesions [116]. Hepatic lesions were distinguished by the different severity of disorganized hepatic cords and hepatocyte apoptosis [117]. Therefore, Therefore, it is possible that cattle is more sensitive to Fumonisins than lamb.

Increasing dietary Fumonisin B_1 increased liver weight, serum calcium, cholesterol, and AST levels. Also, biliary hyperplasia and multifocal hepatic necrosis were present in broiler chicken [8]. In researches of Kubena et al. [121] and Weibking et al. [7] 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 increased. Nonetheless, total liver lipids of chicks decreased significantly. Subacute treatment of broiler chicks with Fumonisin B_1 bring about hepatic oxidative stress simultaneously by SA/SO gathering. Also, TBARS (Thiobarbituric acid reactive substance) levels, catalase activity, and Vit C content increased [122]. Therefore, (according to the measure of treatment with Fumonisins) sensitivity to Fumonisin in broiler chicken increased in comparison with the latest research. Additionally, 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.

Table 2. *In vivo* disorder effects induced by Fumonisins

	Dosage and Fumonisin source	Duration	Effects	Refrences
Human	Both FB1 and FB2 High corn intake higher risk than low corn intake	case–control study	Developing esophageal cancer	[16]
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	[114]
The human colon cell line HT-29	5 mg of FB1 was dissolved in PBS at a concentration of 1,380 uM	24 to 72 h	Main and early induction of Lipid peroxidation, assessing IL-8 secretion, increase in membrane microviscosity	[115]
Human cells	Medicine with FB1 for 24, 48, 72 and 96 h		The proliferation of human esophageal epithelial cells (HEECs)	[104]
Women	Exposure to FB1 corn tortilla intake during the first trimester and before the pregnancy.	case–control study	Raise the risk of NTD	[15]
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	[11]
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	[116]
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.	[117]
Bovine granulosa cell	0, 0.3, 1, 3, 10 µM of FB1	48 h	No effect on; cell proliferation, progesterone production, CYP11A1 and CYP19A1 gene expression, Slightly inhibited estradiol production Decreasing in serum-induced granulosa cell (GC) proliferation	[118]
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	[8]
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	[7]

	Dosage and Fumonisin source	Duration	Effects	Refrences
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.	[119]
Broiler chicken	Dietary; 0, 50, 100 or 200 mg fumonisin B1/kg b.w	21 days	Cell proliferation in response to mitogens, immunosuppress	[120]
Broiler chicken	Dietary; 300 mg fumonisin B1/kg b.w	21 days	Increase activities of AST, LDH, GGT	[121]
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	[122]
Broiler chicken	diet (18.6 mg FB1+FB2/kg	More than 17 days	Reduce in villus height and crypt depth of the ileum, Shift in the microbiota composition in the ileum Decreasing in abundance of Candidatus Savagella and Lactobaccilus spp Increase in Clostridium perfringens content caused to higher percentage of birds developed subclinical necrotic enteritis	[123]
Broiler chicken	Purified FB (0 or 10 ppm)	34 days	Higher feed-to-gain ratio than control, Serum nitric oxide (NO) levels were elevated	[124]
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	[125]
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	[13]
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	[126]
Mouse embryos	Exposure of FB1	Long term Short-term	NTD; 65% in continuing experimentation and by almost 50% in temporary experimentation	[127]
Mice	Subcutaneous; 2.25 mg fumonisin B1/kg b.w	5 days	Hepatotoxic effects, increase in AST and liver enzymes in circulation	[105]

	Dosage and Fumonisin source	Duration	Effects	Refrences
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.	[128]
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	[113]
Mice	Dietary; 0, 1, 3, 9, 27, or 81 ppm FB1	13 weeks	Hepatopathy	[12]
Mice	150 mg/kg diet of FB1	16 weeks	Decreasing in number of parietal cells, gastric mucosa height and mitotic index in the gastric glands, Mild to moderate gastric atrophy, proliferative activity of gastric glands lower than the control	[129]
Female B6C3F1 mice	Fed 50 or 80 ppm FB1	2-year feeding	Hepatocellular adenomas and carcinomas	[130]
Mice	8 mg/kg, i.p. for	4 days	No changes in the; Indirect nitric oxide (NOx) content, TBARS, ascorbic acid, organ-to-body weight ratio, organ-to-adrenal gland weight ratio or organ-to-brain weight Increasing in non-protein thiols (NPSH) levels in liver and lungs decreaseing in Ferric reducing antioxidant power (FRAP) content in liver and kidneys	[131]
Rat	Dietary; 0, 1, 3, 9, 27, or 81 ppm FB1	13 weeks	Nephrosis	[12]
Male BD IX rats	Intake of 50 ppm FB1	Up to 2 years	Culminated in the appearance of hepatocellular carcinomas and cholangiocarcinomas	[132]
Male F344 rats	FB1	2-year feeding	No hepatocarcinogenic effects ,but FB1 caused renal tubule tumors	[130]
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	[133]
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	[14]

	Dosage and Fumonisin source	Duration	Effects	Refrences
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	[134]
Rabbit	10 mg/kg fumonisin B1	4 weeks	Increasing in liver weight dramatically, change in active monovalent cation	[135]
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,	[136]
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.	[137]
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	[137]
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	[6]
Pony	Feeding; 1-88 ppm fumonisin B1, B2, B3	120 days	Leukoencephalomalacia and hepatic necrosis	[138]
Horses hoof cells	FB1 0.125–10 µg/mL	24 to 48 h	No effect on dermal or epidermal cells, increasing in supernatants of explants, reducing in lamellar integrity at noncytotoxic concentrations	[139]
Pigs	Intravenously; 4.6-7.9 mg fumonisin B1/kg b.w Orally; 48-166 ppm FB1	15 days	Pulmonary edema and hepatic necrosis	[140]
Pigs	Dietary; 16 mg fumonisin B1/kg b.w		Hydrothorax, variably severe pulmonary edema, icterus and hepatocellular necrosis	[10]
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	[9]

	Dosage and Fumonisin source	Duration	Effects	Refrences
Pigs	Feeding; 10 mg/kg fumonisin B_1	4 weeks	Higher sphinganine/sphingosine ratio and gained less weight	[141]
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	[142]
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	[143]

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

In ducks, FB1 increased the level of cholesterol, total protein, alanine aminotransferase (ALT), LDH, GGT and SA/SO (sphinganine to sphingosine ratio) in the plasma. Also, FB1 resulted in the growth of liver weight by liver hyperplasia [126]. These effect of Fumonisins in ducks probably created by SA to SO ratio and oxidative damages.

FB_1 in mice decreased Ferric reducing antioxidant power (FRAP) content in liver and increased non-protein thiols (NPSH) levels [131] and liver enzymes like AST and ALT in circulation [105]. Moreover, FB1 caused an increase in serum levels of the total bile acids, alkaline phosphatase, and cholesterol, and created microscopic effect such as hepatocellular hypertrophy, hepatocellular apoptosis, Kupffer cell hyperplasia, hepatocellular single cell necrosis, mitosis, anisokaryosis, and macrophage pigmentation [113,128].

Effects of FB_1 on rabbits are a significant increase in liver weight [135], alkaline phosphatase (AP), total protein, AST, ALT, and GGT. Furthermore, degeneration of hepatocytes and apoptosis were the prominent degenerative changes in the liver of rabbits [14,134].

Because of fumonisin B_1, B_2, and B_3, hepatic necrosis in ponies occurred [138].

Effects of Fumonisins in the liver of piglet were apoptosis, necrosis, hepatocyte proliferation, hyperplastic hepatic nodules (in chronic studies), icterus, and hepatocellular necrosis. Besides, the serum cholesterol, alkaline phosphatase, AST activities, sphinganine and sphingosine concentrations in kidney, heart, lung, and liver were elevated. However, there were no detectable portal triads or central veins, adjacent parenchyma, and the perilobular connective tissue was compressed [10,142-144]. The hepatic changes especially disorganization in piglet by Fumonisins is probably because of an acute pathway of this mycotoxin.

5.3 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 [117].

Effect of fumonisin in the kidney of turkeys and broiler chicken was increasing in kidney weight [7,13,119].

In both sexes of rats, Fumonisins caused decrease in the weight of the kidney, nephrosis in outer medulla (especially in female rats) [12]. Ferric reducing antioxidant power (FRAP) content in the kidney of mice was decreased [131].

Bucci et al. [134] and Orsi et al., [14] reported that the effect of Fumonisin in the kidney of the rabbit was apoptosis and degeneration of renal tubule epithelium, it caused an increase in the level of urea and creatinine, too.

Fumonisins in the kidney of pigs created 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 [9,143].

According to these studies, 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.

5.4 Leukoencephalomalacia

Fumonisins (especially fumonisin B_1) are the causal factor in the development of LEM in horses [137]. The lethality rates, mortality, and morbidity in horses were 85.7%, 10%, and 11.6% respectively [6].

Because of Fumonisins in horses with LEM, brain lesions as the following were observed: 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 parts 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; separation of cell edges;

hyperchromatic; edema; necrosis; large parts of malacia in the white matter of the cerebral hemispheres; cerebellum; brainstem [6,136,137]. These brain lesions (emerged by Fumonisin in horses) is probable to lead horses to show nervous signs. These signs mainly include apathy; incoordination; walking into objects; changes in temperament; paralysis of the tongue and lips in one of the horses; 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 which ends to death [6,136,137].

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 [134]. However, brain lesions and nervous signs because of leukoencephalomalacia in rabbits, is not as extensive and prevalent as horses. Therefore the brain of horses is more sensitive than rabbits, to Fumonisins.

5.5 Porcine Pulmonary Edema (PPE)

Usual damage of Fumonisin B in pigs was severe edema in the lung by inhibiting sphingolipid biosynthesis, phagocytosis in pulmonary macrophages, and gathering of substance material in pulmonary capillary endothelial cells [9,144].

The clinical signs in pigs because of pulmonary edema (induced by Fumonisins) consisted of; hydrothorax and respiratory distress (revealed by increasing 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[10,144].

5.6 Other Toxic Effects

Exposure to FB_1 during the first trimester and before the pregnancy emerged to developed the hazard of neural tube defects (NTD; because of the defeat of the neural tube to close, embryonic defects of the spinal cord and brain happened) [15,140]. Also, Fumonisins in human colon cells caused to main and early induction of lipid peroxidation, assessing IL-8 secretion, and increasing in membrane microviscosity [115].

Feeding by fumonisin in calves has some effects such as; impairing the lymphocyte blastogenesis [116], decreasing in serum-induced granulosa cell (GC) proliferation [118], lethargy, increasing of sphingosine and sphinganine concentration in the heart, lung, and skeletal muscle. Raise in the concentration of sphinganine, but not sphingosine, in brains of managed calves [117], and have no effects on cell proliferation, progesterone production, CYP11A1 and CYP19A1 gene expression of bovine granulosa cell [118].

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

In broiler chicks, FB_1 had an adverse effect on weight, water consumption, feed efficiency, and body [119]. Also, Fumonisins reduced villus height and crypt depth of the ileum, the abundance of Candidatus Savella and Lactobacilus spp [123], and body weight, but Clostridium perfringens content (reason of subclinical necrotic enteritis), and the weight of bursa of Fabricius, gizzard as well as proventriculus increased. Other effects of FB_1 were diarrhea, thymic cortical atrophy, rickets [8,119], slightly inhibition in estradiol production [123], and elevation in the level of serum nitric oxide (NO) [124].

Henry and Wyatt. [125] reported that fumonisin in the egg could cause extreme hemorrhages of the thoracic area, head, and neck of the dead embryos in the egg.

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

In mice, Fumonisins can cause adrenal cortical cell vacuolation and mild to moderate gastric atrophy and may cause an increase in serum cholesterol. Vacuolated lymphocytes and myeloid cells were also detected in mice due to Fumonisins [113]. Also, Fumonisins decreased the number of parietal cells, proliferative activity of gastric glands, gastric mucosa height and mitotic index in the gastric glands [129]. In contrast, Dassi et al. [131] did not detect any change in the indirect nitric oxide (NOx) content, TBARS, ascorbic acid, organ-to-body weight ratio, organ-to-adrenal gland weight ratio or organ-to-brain weight.

Fumonisins in pigs had some effects such as reduction 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) were increased by get up sphinganine and/or sphingosine mass. Also, in previous studies, parakeratosis, postpone in the pattern of papillary of the distal esophageal mucosa (part of stratum basale), hyperkeratosis, and hyperplastic nodules in the liver cells, esophageal plaques, and right ventricular hypertrophy were detected [141,142,144].

Effects of Fumonisins on hoof cells of horses were increasing in supernatants of explants, and decreasing in lamellar integrity at noncytotoxic concentrations, but Fumonisins didn't influence dermal or epidermal cells [139].

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 [145]. Daily intake of Fumonisins in different countries and foods, are summarized in Table 3.

In Soriano and Dragacci,. [145] and Creppy., [146] papers, 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 by the no-observed-effect-level (NOEL) of 0.2 mg/kg of body weight/day and a safety aspect of one hundred.

By means of simulation model, mean concentrations of Fumonisin B_1 in milk is evaluated 0.36 µg/kg. However, the pretended TDI from milk for females and males fell below European Union guidelines [147].

Orsi et al. [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.

7. MAXIMUM LIMITATION

Different variables may affect the foundation of tolerances for specific mycotoxins, such as delivery of mycotoxins through products; regulation of trade contact in different countries; availability of data of toxicological or dietary exposure; and accessibility of techniques for analysis [148].

Deadline level for Fumonisins in maize and other cereals, at the moment changes from 5 to 100000 µg/kg. Table 4 illustrates present laws of Fumonisins in feeds and foods, set by nations such as America, Africa, Europe, and Asia and described by [149,150].

8. 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 damages, and recover infected commodities. Table 5 includes data detected on biological, physical, and chemical processes for detoxification of Fumonisins in an abbreviated form.

8.1 Biological Methods

An enzymatic detoxification process of 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 binds to at least one tricarballylic acid part in the structure of FB_1 and especially FB_2 [2].

L. plantarum MYS6 is having potential probiotic attributes and antifungal activity against Fumonisin producing *F. proliferatum* MYS9 [183].

52.9% of FB_1 and 85.2% of FB_2 were removed by two *Lactobacillus* strains (*L. pentosus X8* and *L. plantarum B7*), in the aqueous medium [165].

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 [164].

Hydrolyzing ester bonds of fumonisin B_1 by black yeasts (*Exophiala spinifera* and *Rhinoclodiella atrovirensa*) reported by [166].

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 [167]. Therefore, we can remove 17 to 85 % of Fumonisins through the biological process, and *Lactobacillus* known as the most effective strains for detoxification of Fumonisins.

Table 3. Daily intake of Fumonisins for different countries and foods

Food	Nation	Intake (ng/kg of bw/day)	Explantion	Reference
Beer	USA	20 to 54	Camputed on the base of the 60 kg body weight	[151]
Cereal commodities	France	22.8	All children in france	[145]
Cereal commodities	France	4.6	All female adults in france	[145]
Cereal commodities	France	3.2	All male adults in france	[145]
Cereal commodities	France	9.96	All people in france	[145]
Cereal commodities	Germany	31.8	Users >14 years	[145]
Cereal commodities	Norway	430	6 month babies	[145]
Corn	Brazil	392	Camputed on the base of the 70 kg body weight from urban area	[73]
Corn	Brazil	1276	Camputed on the base of the 70 kg body weight from rural area people	[73]
Corn	Brazil	4.1	Conventional corn	[152]
		3.4	Organic corn	
		3.8	Total	
Corn	France	45.6	All children in france	[145]
Corn	France	12.4	All female adults in france	[145]
Corn	France	7.4	All male adults in france	[145]
Corn	France	9.96	All people in france	[145]
Corn	Germany	8.7	Users >14 years	[145]
Corn	Switzerland	30		[153]
Corn	The Netherlands	3.1	Adults	[145]
Corn	USA	80		[154]
Corn	USA	600000 to 2100000	Natural outbreak of LEM in horses	[155]
Corn	Zimbabwe	140 and 5760	Shamva district	[156]
Corn	Zimbabwe	180 and 8092	Makoni district	[156]
Corn commodity	Brazil	63.3	São Paulo population	[157]
Food with corn based	Argentina	0.73 to 2.29	Camputed on the base of the 70 kg body weight	[89]
Food with corn based	Brazil	maximum probable daily intake (MPDI): 256.07 average probable daily intake (APDI): 120.58		[158]
Food with corn based	Canada	89	All children	[159]
Food with corn based	Canada	190	Child users	[159]

Food	Nation	Intake (ng/kg of bw/day)	Explantion	Reference
Food with corn based	Denmark	400		[81]
Food with corn based	South Africa	14,000 to 440,000	A group of people exhibiting a high prevalence of human esophageal	[155]
Food with corn based	South Africa	5,000 to 59,000	A group of people exhibiting a less prevalence of human esophageal	[155]
Food with corn based	UK	30		[160]
Corn inferred commodities	Belgium	16.7		[145]
Corn inferred commodities	China	450 to 15,810 (Mean=3020)	Camputed on the base of the 50 kg body weight	[33]
Corn inferred commodities	Germany	10.4	Users >14 years	[145]
Corn inferred commodities	Italy	185.6	Italian users	[145]
Corn inferred commodities	Italy	24.6	All people in Italy	[145]
Corn inferred commodities	Norway	0.24	Adult male and female population	[145]
Corn inferred commodities	Norway	0.50	Adult male and female users	[145]
Corn powder	Argentina	79 to 198	For samples during 1996/1997 and January 1998	[87]
Corn pieces	Germany	69.8	Users >14 years	[145]
Corn pieces	Italy	283.6	Italian users	[145]
Corn pieces	Italy	15.9	All people in Italy	[145]
Food	Mexico	0.4 (0-23.2)	User in state of Morelos	[161]
Food	Burkina Faso	0.8 (0-2.4)	All users	[161]
Food	South Africa	3.8	User in Transkei	[161]
Food	South Africa	0	User in KwaZulu-Natal	[161]
Food	Guatemala	3.5	Urban area	[161]
Food	Guatemala	15.6	Rural area	[161]
Food	Guatemala	0.2-23	All users	[162]
Rice	France	12.1	All children in france	[145]
Rice	France	5.6	All female adults in france	[145]

Food	Nation	Intake (ng/kg of bw/day)	Explantion	Reference
Rice	France	5.6	All male adults in france	[145]
Rice	France	5.7	All people in france	[145]
Rice	Germany	0.6	Users >14 years	[145]
Wheat commodities	France	345.1	All children in france	[145]
Wheat commodities	France	230.8	All female adults in france	[145]
Wheat commodities	France	256	All male adults in france	[145]
Wheat commodities	France	240.08	All people in france	[145]
Wheat commodities	Italy	62.1	Italian users	[145]
Wheat commodities	Italy	10.6	All people in Italy	[145]
Food and feeds	Germany	bad case scenario: 21,000 mean case scenario: 1,100	German users	[163]

Table 4. Maximum limits for Fumonisins in feeds and foods in different countries [149,150]

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); dehydrated milled corn bran; purified corn purpose of masa production
	5000	Corn and corn derived purpose of rabbits and equids
	20000	Corn and corn derived purpose of catfish and swine
	30000	Corn and corn derived purpose of breeding mink, breeding poultry, and breeding ruminants (contains hens laying eggs and lactating dairy cattle for human use)
	60000	Mink upbringing for pelt output and Ruminants >3 months old upbringing for slaughter
	100000	Poultry upbringing for slaughter
	10000	Pet animals and all other species or classes of livestock
European Union Fumonisins	2000	Unprocessed maize
	1000	Maize products for human
European Union (FB1, FB2)	50	Animal feeds except Equines
	5	Feeds of Equines
Food and Drug Administration (FB1, FB2, FB3)	30	Animal feeds except Equines
	5	Feed of Equines

Table 5. Biological , physical , and chemical processes of Fumonisins

Process	Observation	Refrence
Biological process		
Lactic acid bacteria (*Micrococcus luteus*, *Acillus subtilis*)	Binding to FB1 and FB2	[2]
Sphingopyxis sp.	Hydrolysis of FB1 to HFB1	[2]
Saccharomyces	Decrase in FB1 and FB2	[164].
Lactobacillus strains (*L. plantarum* B7 and L. pentosus X8)	Removing Fumonisins (FB1 and FB2)	[165]
Black yeasts *Rhinoclodiella atrovirensa* and *Exophiala spinifera*	Ester bonds was hydrolyzed of FB1	[166]
Candida parapsilosis	Mycelial growth inhibition	[167]
Physical process		
150–200°C	87–100% destruction of fumonisin B1 in corn cultures	[166]
Extrusion and roasting	60–70% loss of FB1 and FB2	[168]
Extrusion	30% loss of FB1 and FB2	[168]
Extrusion	92% loss of fumonisin B1	[168]
Extrusion	34-95% reduction of Fumonisins	[169]
Extrusion of drymilled products	Decrease in fumonisin accumulation by 30–90 % for mixing-type extruders and 20–50% for non-mixing extruders	[170]
Baking corn	16 and 28% loss of FB1	[171]
Frying corn chips	loss of 67% of the fumonisin	[171]
Cooking and canning	Small influence on fumonisin measure (23%)	[172]
Ethanol–water extraction solvent at 80°C	The most environmentally friendly, least toxic, and cheapest	[173]
Cholestyramine	Adsorption 85% of FB1	[174]
Activated carbon	Adsorption 62% of FB1	[174]
Ammonia process	Reduce FB1levels 30-45% No mutagenic potentials were apparent	[175]
Fructose	Obstruct the amine group of FB1, that is important for its toxicity	[176]
Chlorophorin	Reduced FB1 levels by 90–91%	[177]
Oxidizing agents	Little effects in FB1, but applicable because of the minimal cost and the minimal destruction of important nutrients	[178]
Bentonite	Adsorbed only 12% of the toxin FB1	[174]
Celite	Not effective	[174]

Chemical process		
Solution of SO2 at 60°C for 6 h	Most impressive treatment to decline the measure of fumonisin B1	[179]
Acidic aqueous solution by the addition of NaNO2	Fumonisin B1 was significantly deaminated	[180]
NaCl solution	Fumonisin B1 had a little mass and that 86% of the toxin could be eliminated	[181]
Ozone (O3)	No significant difference in FB1	[182]
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	[178]

8.2 Physical and Chemical Methods

Fumonisin B_1 needs a massive temperature (150–200°C) to gain 87–100% demolition in corn cultivation [166].

During extrusion of dry-milled products, reduction of the measure of Fumonisins was 20–50% for non-mixing extruders and 30–90% for mixing-type ones [184]. For the production of cornflakes through the extrusion and roasting of raw corn, 60–70% of Fumonisins B_1 and B_2 were loosened; however, removing of Fumonisins only in the extrusion step was less than 30% [168]. Destruction of Fumonisin B_1 in extrusion process of grits, was 92% [168]. The economic, lowest toxic and most biodegradable solvent for Fumonisin extraction is ethanol-water [173].

In baking corn muffins, removing Fumonisin during the baking process for 20 minutes were amidst 16 and 28% at 175°C and 200°C, respectively. Additionally, flotation of the corn in water reduced the amount of Fumonisin B_1, and frying corn chips for 15 minutes at 190°C brings about a 67% remove of the Fumonisin. However, spiked corn masa fried at 140–170°C (while degradation begins to take place above 180°C) has no significant loss of Fumonisin B_1 [171 and 185].

One of the most impressive management to cause declination of the measure of Fumonisin B1 is a 0.2% solution of SO_2 at 60°C for six hours [179]. Nevertheless, canning and cooking had a small influence on fumonisin measure [172].

In paper of Solfrizzo et al. [174] the adsorption capacity of cholestyramine for fumonisin B_1 was 85% from a solution including 200 µg/ml FB_1.

Detoxification of corn with ammonia process reduced fumonisin levels (30 to 45%), and no mutagenic potentials were found in the managed corn [175].

Obstruction in the amine group of fumonisin B1 by reaction with fructose is another way to the detoxification of fumonisin B_1 [176].

The percentage of reduction in FB_1 in corn by single $Ca(OH)_2$ (nixtamalization) or with $NaHCO_3$ + H_2O_2 (modified nixtamalization), was 100% [178].

Chlorophorin gets from vanillic acid, ferulic acid, caffeic acid, and iroko decreased FB_1 levels by 90–91% [177].

Although treatment with oxidizing agents is an economical method for detoxification of Fumonisin B_1, this method isn't demonstrated in bioassays [178].

The acidic aqueous solution such as $NaNO_2$ can create deamination in fumonisin B_1, significantly [180].

In the floating section after treatment with NaCl solution, 86% of FB_1 were removed [181].

Celite and O3 couldn't make any significant difference in the level of FB_1, but bentonite adsorbed only 12% of the FB_1 [174,182].

According to these reports, physical and chemical methods are the most effective ways of detoxification of Fumonisin (in comparison with the biological method), so that an intervention is necessary for removing the Fumonisin from feeds and foods.

9. CONCLUSION

Fumonisins can cause fatal diseases in animals and are classified as a potential human carcinogen. In this paper, we reviewed the aspects of studies concerning the ability of Fumonisins to cause various toxicity effects in different parts of body in human and animal. We evaluated and compared occurrence of Fumonisins in several countries. We also evaluate the effects of different detoxification method for removing the Fumonisins, mechanism of toxicity in cells of human and animals, the intake of Fumonisins in various consumers, and to compare the limitation of Fumonisins in countries mentioned above.

For future investigation about Fumonisins, the authors suggest estimating the reproductive effects of Fumonisins; improving the information about the occurrence of Fumonisins in different parts of the world; extending masked Fumonisins in detoxification researches; improving the legislation about Fumonisins to change daily intake of these mycotoxins; growing attention to mechanisms of Fumonisins in different types of animals and cells; cell-cell interactions; exposure pathways; and finally the exposure measures.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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