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

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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.

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

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* (Scott, 2012; Shimizu et al., 2015).
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 (Jackson and Jablonski, 2004). In more than 15 Fumonisin forms, Fumonisins B_1, Fumonisins B_2, and Fumonisins B_3 are the broadest mycotoxins that have been described (Humpf and Voss, 2004).

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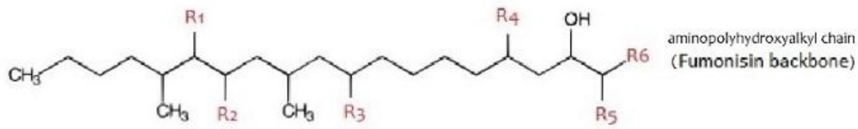

Fumonisins	Group					
	R1	R2	R3	R4	R5	R6
FA_1	TCA	TCA	OH	OH	$NHCOCH_3$	CH_3
FA_2	TCA	TCA	H	OH	$NHCOCH_3$	CH_3
FA_3	TCA	TCA	OH	H	$NHCOCH_3$	CH_3
FAK_1	=O	TCA	OH	OH	$NHCOCH_3$	CH_3
FB_1	TCA	TCA	OH	OH	NH_2	CH_3
FB_2	TCA	TCA	H	OH	NH_2	CH_3
FB_3	TCA	TCA	OH	H	NH_2	CH_3
FB_4	TCA	TCA	H	H	NH_2	CH_3
FC_1	TCA	TCA	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

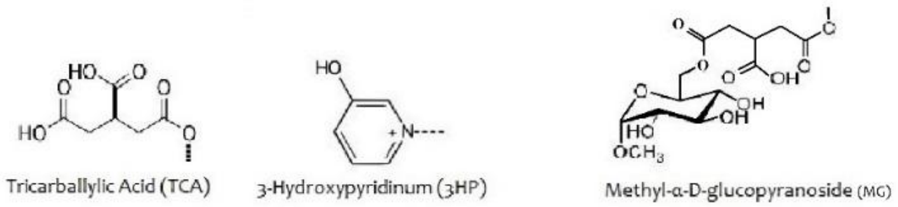

Fig. 1. Chemical structures of the Fumonisins (Humpf and Voss, 2004; Jackson and Jablonski, 2004).

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 (Soriano and Dragacci, 2004b).

Intake of fumonisin B induced a different form of toxic effect on animals, including leukoencephalomalacia in horses (Giannitti et al., 2011), change in weight of the body and internal organ in broiler chicken (Ledoux et al., 1992; Weibking et al., 1993a), and pulmonary edema as well as hepatocellular necrosis in piglet (Colvin et al., 1993; Pósa et al., 2016). Moreover, renal and hepatic toxicity are detected in different animals, such as rabbits, lambs, turkeys, mice, rats, and broilers (Edrington et al., 1995; Orsi et al., 2009; Voss et al., 1995; Weibking et al., 1993a; Weibking et al., 1993b).

In human, the risk of neural tube defects (NTD) and developing esophageal cancer is increased by Fumonisins (Missmer et al., 2006; Stockmann-Juvala and Savolainen, 2008).

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.

1. OCCURRENCE

Due to increase in global grain exchange, the fungi spread was transferred from one country to another (Placinta et al., 1999). 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.

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			(Mallmann et al., 2001)
Korea	0 to 2667.3	0 to 1521.1		(Choi et al., 2018)
France	Not detected			(Malmauret et al., 2002)
Spain	0.2 to 11.6	0.5		(Castella et al., 1999a)
UK	Not Detected	Not Detected	Not Detected	(Patel et al., 1997)
Corn				
Argentina	Average of Fumonisins in 2003: 10.2 and in 2004: 4.7 µg/kg			(Broggi et al., 2007)
Brazil	0.2 to 38.5	0.1 to 12		(Sydenham et al., 1992)
Brazil	5.45 to 10.59	3.62 to 10.31		(Hirooka et al., 1996)
Brazil	0.5 to 1.38	0.01 to 0.59		(Wild et al., 1998)
Brazil	0.2 to 6.1			(Vargas et al., 2001)
Brazil	78.92			(Mallmann et al., 2001)
Brazil	3.2	3.4	1.7	(Van Der Westhuizen et al., 2003)
Brazil	0.066 to 7.832	0.11 to 1.201		(Scussel et al., 2014)

Honduras	0.068 to 6.5			(Julian et al., 1995)
Uruguay	0.165 to 3.688			(Pineiro et al., 1997)
USA	0 to 1.614			(Tseng and Liu, 2001)
USA	0.058 to 1.976	0.054 to 0.890		(Li et al., 2001)
Venezuela	0.025 to 15.05			(Medina-Martínez and Martínez, 2000)
China	0.872 to 0.890	0.33 to 0.448		(Yoshizawa et al., 1994)
China	0.08 to 21	0.05 to 4.35	0.06 to 1.66	(GAO and YOSHIZAWA, 1997)
China	<0.05 to 25.97	<0.10 to 6.77	<0.10 to 4.13	(Ueno et al., 1997)
China	Total Fumonisins <0.5 to 16.0			(ZHANG et al., 1997)
China	0.058 to 1.976	0.056 to 0.89	0.053 to 0.385	(Li et al., 2001)
China	0.003 to 71.121			(Gong et al., 2009)
China	0.268	0.537	0.472	(Li et al., 2015)
China	0.0165 to 0.3159			(Shi et al., 2018)
India	0.07 to 8			(Shetty and Bhat, 1997)
India	<1 to 100			(Jindal et al., 1999)
Iran	1.270 to 3.980	0.190 to 1.175	0.155 to 0.960	(Shephard et al., 2000)
Iran	223.64			(Alizadeh et al., 2012)
Japan	<0.05 to 4.1	<0.1 to 10.2		(Ueno et al., 1993)
Philippines	Total Fumonisins 0.3 to 10			(Bryden et al., 1996)
Taiwan	0.63 to 18.8	0.05 to 1.4		(Yoshizawa et al., 1996)
Taiwan (Australia)	≤0.477			(Tseng and Liu, 2001)
Taiwan (USA)	≤1.614			(Tseng and Liu, 2001)
Taiwan (South	≤0.865	≤0.12		(Rheeder et al.,

Africa)				1994)
Taiwan (South Africa)	≤0.05 to 0.9	<0.05 to 0.25		(Rheeder et al., 1994)
Taiwan (Thailand)	≤0.334			(Tseng and Liu, 2001)
Vietnam	Total Fumonisins 0.3 to 9.1			(Bryden et al., 1996)
Australia	Total Fumonisins 0.3 to 40.6			(Bryden et al., 1996)
Australia	≤0.477			(Tseng and Liu, 2001)
Austria	<15			(Lew et al., 1991)
Croatia	0.01 to 0.06	0.01		(Doko et al., 1995)
Croatia	The highest concentrations Fumonisins 25.5, mean values of 4.509			(Pleadin et al., 2012)
Greece	0.1 to 0.56			(De Nijs et al., 1998a)
Portugal	0.09 to 2.3	0.25 to 4.45		(Doko et al., 1995)
Poland	0.01 to 0.02	<0.01		(Doko et al., 1995)
Romania	0.01 to 0.02	0.01		(Doko et al., 1995)
Spain	≤22	≤0.7		(Sanchis et al., 1995)
Spain	70 to 334	102 to 379		(Castellá et al., 1996)
Spain	0.2 to 19.2	0.2 to 5.9		(Castella et al., 1999b)
Spain	0.035 to 0.043	0.019 to 0.022		(Arino et al., 2007)
The Netherlands	Traces to 0.380			(De Nijs et al., 1998b)
The Netherlands	Traces to 3.35			(De Nijs et al., 1998a)
UK	0.2 to 6			(Preis and Vargas, 2000)
Benin	Total Fumonisins: 6.1 to 12 in 1999-2003			(Fandohan et al., 2005)
Ethiopia	0.606	0.202	0.136	(Getachew et al., 2018)
Ghana	0.011 to 1.655	0.01 to 0.77	0.07 to 0.224	(Kpodo et al., 2000)

Malawi	0.02 to 0.115	0.03		(Doko et al., 1996)
Morocco	1.930			(Zinedine et al., 2006)
Nigeria	0.164 to 2.09 (0.852)	0.046 to 0.710 (0.262)	0.010 to 0.186 (0.069)	(Akinmusire et al., 2018)
South Africa	<10 to 83			(Sydenham et al., 1990a)
South Africa	≤0.63	≤0.25		(Rheeder et al., 1994)
South Africa	0.05 to 117.5	0.05 to 22.9		(Rheeder et al., 1992)
South Africa	0.2 to 46.9	0.15 to 16.3		(Sydenham et al., 1990b)
South Africa	<0.2 to 2			(Dutton and Kinsey, 1995)
South Africa	0.012 to 8.514			(Mngqawa et al., 2015)
South Africa (Argentina)	0.05 to 0.7	<0.05 to 0.5	<0.05 to 0.5	(Stockenström et al., 1998)
South Africa (USA)	0.9 to 3.9	0.3 to 1.2	0.08 to 0.6	(Stockenström et al., 1998)
Tanzania	0.025 to 0.165	0.06		(Doko et al., 1996)
Zimbabwe	0.125	0.04		(Doko et al., 1996)
Corn flakes				
Argentina	0.002 to 0.038	Not detected		(Solovey et al., 1999)
Brazil	0.66	0.03		(Mac Jr and Valente Soares, 2000)
Uruguay	0.218	Not detected		(Pineiro et al., 1997)
USA	Total Fumonisins: <0.25			(Pohland, 1996)
USA	≤0.088	Not detected		(Castelo et al., 1998)
USA or Canada	0.012 to 0.155			(Kim et al., 2003)
Korea	0.018 to 0.143			(Kim et al., 2002)
China	0.001 to 0.171	<0.0002 to 0.025	0.0002 to 0.031	(Li et al., 2015)
Germany	Total Fumonisins <0.01 to 1			(Usleber and Märtlbauer, 1998)

Italy	0.01	Not detected	(Doko and Visconti, 1994)
Italy	0.020 to 1.092	0.006 to 0.235	(Solfrizzo et al., 2001a)
Nordic countries	0.005 to 1.030	0.004 to 0.243	(Petersen and Thorup, 2001)
Serbia	0 to 0.434 (0.067)	0 to 0.145 (0.019)	(Torović, 2018)
Spain	0.02 to 0.1		(Sanchis et al., 1994)
Switzerland	0.055		(Pittet et al., 1992)
The Netherlands	1.43		(De Nijs et al., 1998b)
Turkey	Not detected	Not detected	(OMURTAG, 2001)
South Africa	Not detected	Not detected	(Sydenham et al., 1991)
Corn flour			
Argentina	0.038 to 1.86	0.02 to 0.768	(Hennigen et al., 2000)
Brazil	≤1.46	≤0.51	(Mac Jr and Valente Soares, 2000)
USA	Total Fumonisins: <0.25 to 1		(Pohland, 1996)
China	0.06 to 0.2	<0.10	(Ueno et al., 1993)
Italy	3.54	0.84	(Doko and Visconti, 1994)
Nordic countries	0.017 to 0.86	0.007 to 0.024	(Petersen and Thorup, 2001)
Serbia	0 to 1.738 (0.162)	0 to 0.394 (0.042)	(Torović, 2018)
UK	Total Fumonisins 0.218		(Patel et al., 1996)
The Netherland	0.04 to 0.09		(De Nijs et al., 1998b)
Corn grits			
Argentina	0.092 to 0.494	0.02 to 0.1	(Hennigen et al., 2000)
Argentina	1.1	0.425	(Torres et al., 2001)
Brazil	0.17 to 1.23	0.05 to 0.3	(Mac Jr and Valente Soares, 2000)

USA	Average 0.6	Average 0.4		(Sydenham et al., 1991)
USA	Total Fumonisins: 0.251 to 1			(Pohland, 1996)
USA	Total Fumonisins: <0.25			(Pohland, 1996)
Japan	0.2 to 2.6	0.3 to 2.8		(Ueno et al., 1993)
China	0.0002 to 2.238	0.0002 to 0.547	0.0002 to 0.402	(Li et al., 2015)
Germany	0.0139			(Usleber et al., 1994)
Italy	3.76	0.9		(Doko and Visconti, 1994)
Nordic countries	0.007			(Petersen and Thorup, 2001)
Spain	0.03 to 0.09	Not detected		(Sanchis et al., 1994)
Switzerland	0 to 0.79	0 to 0.16		(Pittet et al., 1992)
South Africa	<0.05 to 0.19	<0.05 to 0.12		(Sydenham et al., 1991)
Corn kernel				
Bahrain	0.025			(De Nijs et al., 1998a)
China	5.3 to 8.4	2.3 to 4.3		(Ueno et al., 1993)
China	1.878	0.853		(Guo et al., 2016)
Nepal	0.05 to 4.6	0.1 to 5.5		(Ueno et al., 1993)
Indonesia	0.051 to 2.44	<0.376		(Ali et al., 1998)
Egypt	69 to 4495			(Fadl, 1997)
Ghana	0.07 to 33.1	0.06 to 12.3		(Kpodo et al., 2000)
Kenya	0.11 to 12			(Kedera et al., 1999)
Corn meal				
Argentina	0.06 to 2.86	0.061 to 1.09	0.018 to 1.015	(Solovey et al., 1999)
Argentina	0.603 to 1.171	0.717		(Torres et al., 2001)
Brazil	0.56 to 4.93	0.21 to 1.38		(Mac Jr and Valente Soares, 2000)
Canada	0.05			(Sydenham et al., 1991)

Peru	0.66	0.13		(Sydenham et al., 1991)
USA	Average: 1	0.3		(Sydenham et al., 1991)
USA	Total Fumonisins: <0.25 to >1			(Pohland, 1996)
China	<0.5 to 8.8	<0.5 to 2.8	<0.5 to 0.9	(Groves et al., 1999)
Turkey	0.25 to 2.66	0.55		(OMURTAG, 2001)
South Africa	Average: 0.14	Average: 0.08		(Sydenham et al., 1991)
Oat				
Brazil	0.17			(Mallmann et al., 2001)
UK	Total Fumonisins not detected			(Patel et al., 1997)
Rice				
Iran	21.59			(Alizadeh et al., 2012)
China 1999	3.410 to 16.79			(Sun et al., 2017)
China 2010	0.0001 to 0.00164			(Sun et al., 2017)
China 2014	0 to 0.74			(Sun et al., 2017)
UK	Total Fumonisins not detected			(Patel et al., 1997)
Wheat				
Brazil	24.35			(Mallmann et al., 2001)
Argentina_flour	0.0003	0.00124		(Cendoya et al., 2018)
France	Not detected			(Malmauret et al., 2002)
Spain	0.2 to 8.8	0.2		(Castella et al., 1999a)
UK	Total Fumonisins not detected			(Patel et al., 1997)

1.1 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 (Sydenham et al., 1992), 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 (Scussel et al., 2014), (Sydenham et al., 1992), (Hirooka et al., 1996), (Wild et al., 1998), (Vargas et al., 2001), (Mallmann et al., 2001) and (Van Der Westhuizen et al., 2003), 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 (Broggi et al., 2007).
The infection of wheat, oat and barely by Fumonisins was also detected by (Mallmann et al., 2001).

1.2 Asia and Oceania

In China, the contamination of corn with Fumonisins was reported by (Yoshizawa et al., 1994); (Ueno et al., 1997), (GAO and YOSHIZAWA, 1997), (Li et al., 2001), (Li et al., 2015), (Gong et al., 2009) and (Shi et al., 2018). 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., 1997) reported that in China total Fumonisins concentration was 0.5 to 16 mg/kg. In Iran (Shephard et al., 2000) investigated infection of corn with fumonisin B_1, B_2, and B_3. Also, Alizadeh et al. 2012, reported the corn's contamination with fumonisin B_1 (Alizadeh et al., 2012). 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. 1993, in Japan (Ueno et al., 1993).
Bryden et al. (1996), 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 (Bryden et al., 1996).
Contamination of Taiwan's corn with Fumonisins was investigated by (Yoshizawa et al., 1996), (Tseng and Liu, 2001) and (Rheeder et al., 1994). [37]. 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.

1.3 Europe

Doko et al. (1995), published a review article on some information about the occurrence of Fumonisins from some European nations (Croatia, Poland, Portugal, and Romania) (Doko et al., 1995). The highest concentration of Fumonisins in Croatia was 25.2 mg/kg, and the mean value was 4.509 mg/kg (Pleadin et al., 2012).
In Spain, contamination of corn with Fumonisins investigated by (Sanchis et al., 1995), (Arino et al., 2007), (Castellá et al., 1996), and (Castella et al., 1999b). Also, Castella et al. 1999, reported the concentration of Fumonisin B_1 and B_2 in wheat and barley (Castella et al., 1999a), however, Fumonisin B_1 was not found in wheat and barley of France (Malmauret et al., 2002).
Lew et al. (1991), reported the corn contamination with fumonisin B_1 in Austria (Lew et al., 1991).
In oat, barley and wheat of United Kingdom (Patel et al., 1997) have not detected Fumonisins but (Preis and Vargas, 2000) declared the concentration of fumonisin B_1 in corn of UK (0.2 to 6 mg/kg).

1.4 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 (Zinedine et al., 2007).
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., 1992) and 8.514 in new literature by (Mngqawa et al., 2015).
Getachew et al. (2018), detected the fumonisin B_1, B_2, and B_3 in corn of Ethiopia (Getachew et al., 2018).
Evaluation of Fumonisins on corn products of Africa is low, and these investigations consisted of corn meal (Sydenham et al., 1991), corn kernel (Kedera et al., 1999), and corn grits (Sydenham et al., 1991).

2. 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. (1999), reported that fumonisin B obstruct sphingolipid biosynthesis by specifically inhibiting sphingosine (sphinganine) N-acyltransferase, *in vitro* and *situ* (D’mello et al., 1999).

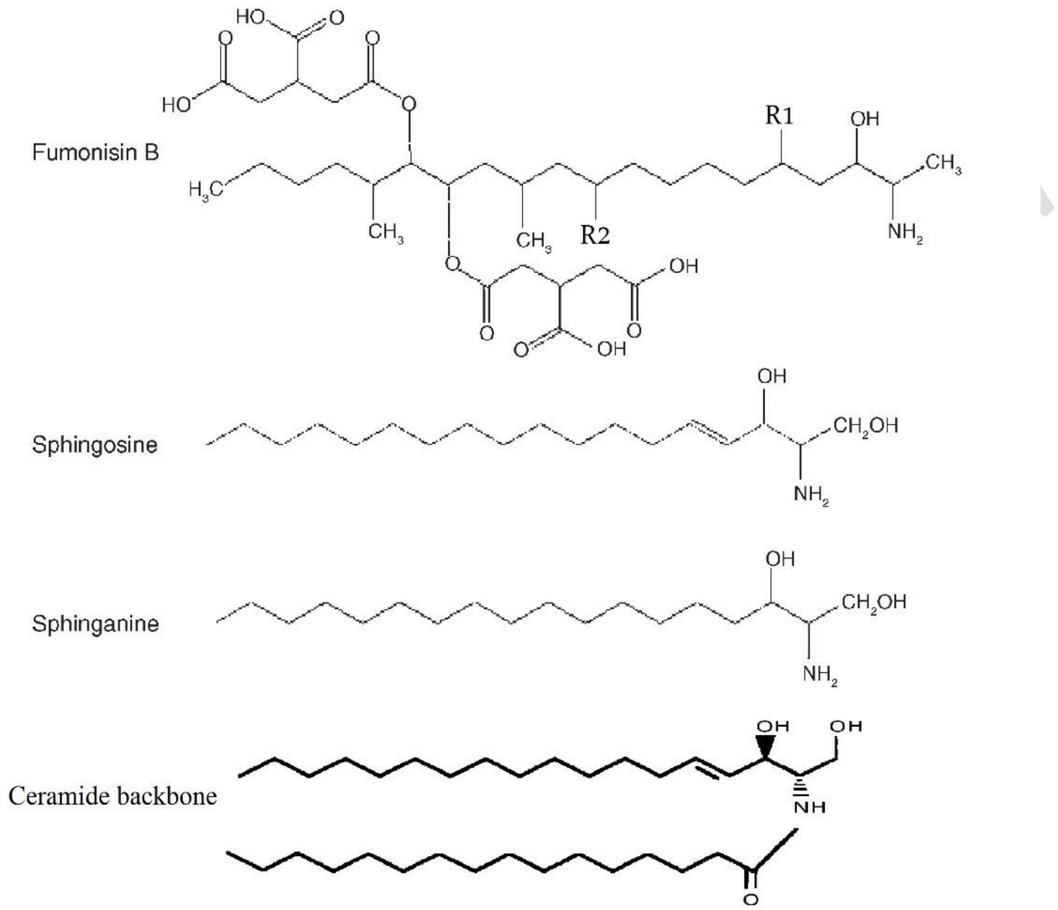

Fig. 2. Structures of fumonisin B, sphingosine, sphinganine and ceramide backbone(Jackson and Jablonski, 2004); (Merrill Jr et al., 2001)

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 (Merrill et al., 1997). In Fig. 3 presents location of working of fumonisin B-induced inhibition of the enzyme CER synthase, is presented.

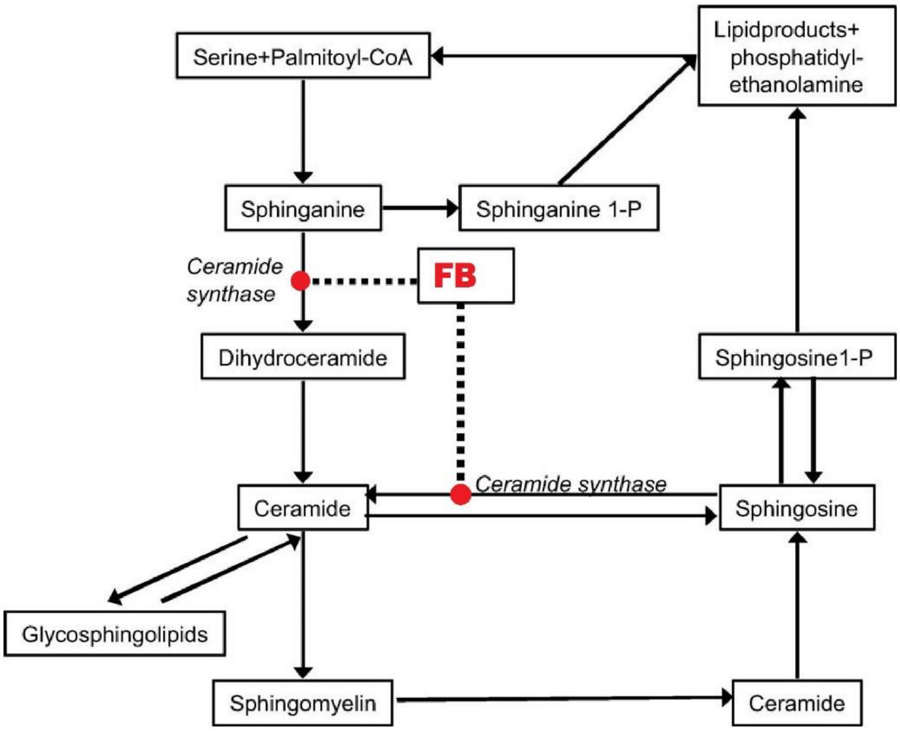

Fig. 3. A summarized scheme of the sites of action of fumonisin B-induced inhibition of the enzyme ceramide synthase on the pathway of de novo sphingolipid synthesis and turnover in mammalian cells and (Stockmann-Juvala and Savolainen, 2008).

2.1 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 (Riley et al., 2001).

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 (Stockmann-Juvala and Savolainen, 2008). Also, Yin et al. 1998 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 (Yin et al., 1998).

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, followed by sphinganine-induced cell proliferation, apoptosis and cancer incidence might be elevated (Jackson and Jablonski, 2004).

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 (Stockmann-Juvala and Savolainen, 2008).

Wang et al. (2014), 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 (Wang et al., 2014).

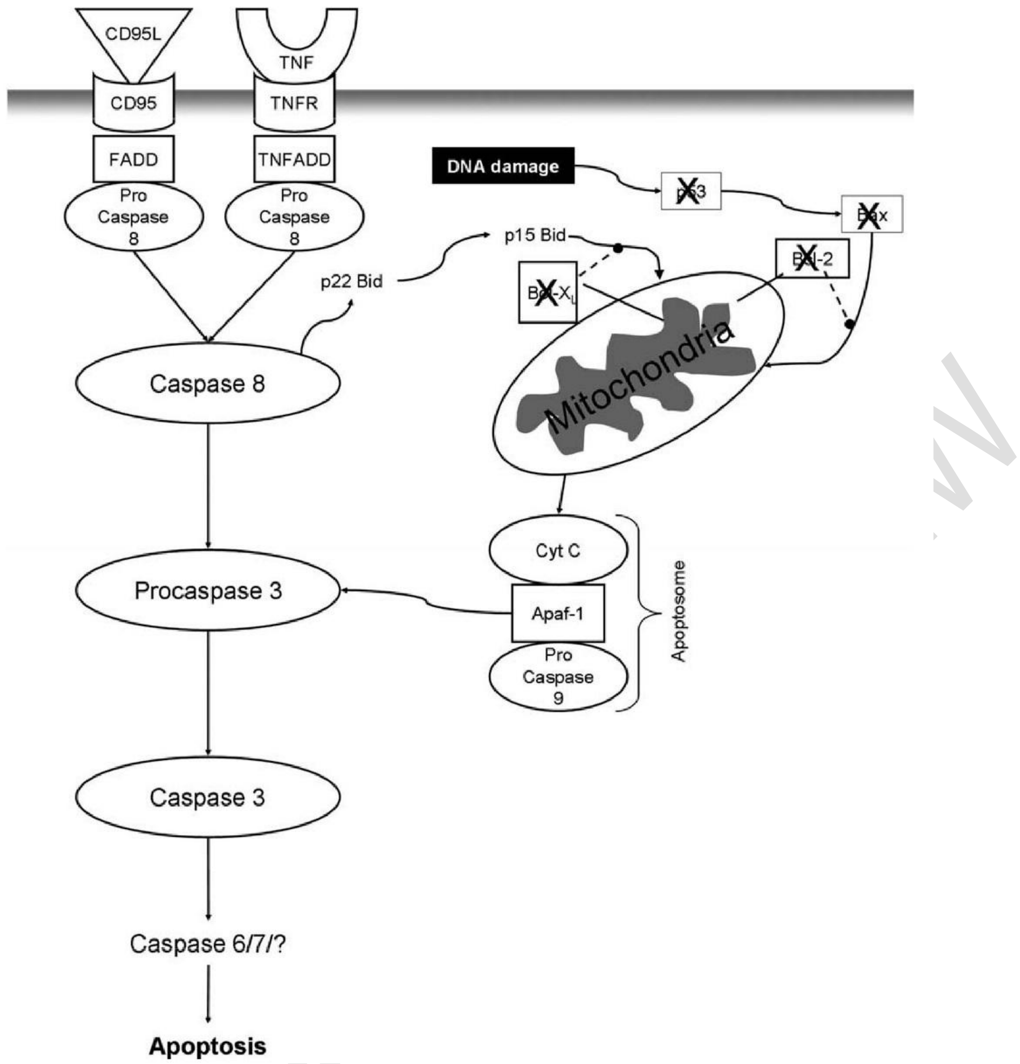

Fig. 4. A schematic landscape of the pathways conduct to apoptosis and the mechanisms probably consisted of fumonisin B1 -induced activation of caspase-3 resulted in apoptosis. X mark showed the mechanisms that do not consisted of the apoptosis caused by fumonisin B1 (Stockmann-Juvala and Savolainen, 2008).

2.2 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 (Sharma et al., 2000).

2.3 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 lipopolysaccharide expression of IL-1β, IL-6, and the chemokines CCL3 and CCL5 in human dendritic cells (Stockmann-Juvala and Savolainen, 2008).

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 (Halloy et al., 2005); (Taranu et al., 2005).

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 (Stockmann-Juvala and Savolainen, 2008).

2.4 Mechanism of Fumonisins in Some Disorder

Smith et al. (2002), 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 (Smith et al., 2002).

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 (Marasas et al., 2004); (Cornell et al., 1983).

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 (Constable et al., 2000); (Smith et al., 2000).

3. 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. (1997), rats are more sensitive to fumonisin B_1 than mice (Bondy et al., 1997). We summarized disorder effects, dosage, duration and source of fumonisin in Table 2.

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	(Stockmann-Juvala and Savolainen, 2008)
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	(Sun et al., 2007)
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	(Minervini et al., 2014)
Human cells	Medicine with FB1 for 24, 48, 72 and 96 h		The proliferation of human esophageal epithelial cells (HEECs)	(Wang et al., 2014)
Women	Exposure to FB1 corn tortilla intake during the first trimester and before the pregnancy.	case–control study	Raise the risk of NTD	(Missmer et al., 2006)
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	(Edrington et al., 1995)
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	(Osweiler et al., 1993)
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	(Mathur et al., 2001)

			ductular cells, vacuolar change, proliferation of proximal renal tubular cells, apoptosis, and karyomegaly.	
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	(Albonico et al., 2017)
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	(Ledoux et al., 1992)
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	(Weibking et al., 1993a)
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.	(Henry et al., 2000)
Broiler chicken	Dietary; 0, 50, 100 or 200 mg fumonisin B1/kg b.w	21 days	Cell proliferation in response to mitogens, immunosuppress	(Li et al., 1999)
Broiler chicken	Dietary; 300 mg fumonisin B1/kg b.w	21 days	Increase activities of AST, LDH, GGT	(Kubena et al., 1997)
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	(Poersch et al., 2014)
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	(Antonissen et al., 2015)
Broiler chicken	Purified FB (0 or 10 ppm)	34 days	Higher feed-to-gain ratio than control, Serum nitric oxide (NO) levels were elevated	(Lee et al., 2017)
Chicken Embryos	Injection in air cell of chicken eggs; 0, 2, 4, 8, 16,	In 72h of incubation	Not microscopic abnormalities but	(Henry and Wyatt, 2001)

	32, and 64 µg fumonisin/egg		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	(Weibking et al., 1993b)
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	(Bailly et al., 2001)
Mouse embryos	Exposure of FB1	Long term Short-term	NTD; 65% in continuing experimentation and by almost 50% in temporary experimentation	(Sadler et al., 2002)
Mice	Subcutaneous; 2.25 mg fumonisin B1/kg b.w	5 days	Hepatotoxic effects, increase in AST and liver enzymes in circulation	(Sharma et al., 2000)
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.	(Howard et al., 2002)
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	(Bondy et al., 1997)
Mice	Dietary; 0, 1, 3, 9, 27, or 81 ppm FB1	13 weeks	Hepatopathy	(Voss et al., 1995)
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,	(Alizadeh et al., 2015)

			proliferative activity of gastric glands lower than the control	
Female B6C3F1 mice	Fed 50 or 80 ppm FB1	2-year feeding	Hepatocellular adenomas and carcinomas	(Howard et al., 2001)
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	(Dassi et al., 2018)
Rat	Dietary; 0, 1, 3, 9, 27, or 81 ppm FB1	13 weeks	Nephrosis	(Voss et al., 1995)
Male BD IX rats	Intake of 50 ppm FB1	Up to 2 years	Culminated in the appearance of hepatocellular carcinomas and cholangiocarcinomas	(Gelderblom et al., 2001a)
Male F344 rats	FB1	2-year feeding	No hepatocarcinogenic effects ,but FB1 caused renal tubule tumors	(Howard et al., 2001)
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	(Gelderblom et al., 2001b)
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	(Orsi et al., 2009)
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	(Bucci et al., 1996)
Rabbit	10 mg/kg fumonisin B1	4 weeks	Increasing in liver weight dramatically, change in active monovalent cation	(Szabó et al., 2014)
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,	(Kellerman et al., 1990)
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.	(Thiel et al., 1991)

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	(Thiel et al., 1991)
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	(Giannitti et al., 2011)
Pony	Feeding; 1-88 ppm fumonisin B1, B2, B3	120 days	Leukoencephalomalacia and hepatic necrosis	(Ross et al., 1993)
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	(Reisinger et al., 2016)
Pigs	Intravenously; 4.6-7.9 mg fumonisin B1/kg b.w Orally; 48-166 ppm FB1	15 days	Pulmonary edema and hepatic necrosis	(Haschek et al., 1992)
Pigs	Dietary; 16 mg fumonisin B1/kg b.w		Hydrothorax, variably severe pulmonary edema, icterus and hepatocellular necrosis	(Colvin et al., 1993)
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	(Pósa et al., 2016)
Pigs	Feeding; 10 mg/kg fumonisin B_1	4 weeks	Higher sphinganine/sphingosine ratio and gained less weight	(Régnier et al., 2017)
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	(Stan et al., 1993)
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	(Dilkin et al., 2010)

3.1 Carcinogenicity

Contamination of wheat, corn and rice with Fumonisin B can increase the risk of esophageal cancer in human (Stockmann-Juvala and Savolainen, 2008), (Alizadeh et al., 2012),(Sun et al., 2007) by stimulating the proliferation of human esophageal epithelial cells (HEECs) (Wang et al., 2014).

Furthermore, Mathur et al. (2001) 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 (Mathur et al., 2001).

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 (Gelderblom et al., 2001a; Howard et al., 2001).

3.2 Hepatotoxic Effect

Fumonisins could create a mild hepatopathy in lambs (Edrington et al., 1995). 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 (Osweiler et al., 1993). Hepatic lesions were distinguished by the different severity of disorganized hepatic cords and hepatocyte apoptosis (Mathur et al., 2001). 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 (Ledoux et al., 1992). In researches of Kubena et al. (1997) and Weibking et al. (1993), 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 (Kubena et al., 1997; Weibking et al., 1993a). Also, TBARS (Thiobarbituric acid reactive substance) levels, catalase activity, and Vit C content increased (Poersch et al., 2014). 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.

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 (Weibking et al., 1993b).

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 (Bailly et al., 2001). 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 (Dassi et al., 2018) and liver enzymes like AST and ALT in circulation (Sharma et al., 2000). 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 (Bondy et al., 1997; Howard et al., 2002)

Effects of FB_1 on rabbits are a significant increase in liver weight (Szabó et al., 2014), 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 (Bucci et al., 1996; Orsi et al., 2009).

Because of fumonisin B_1, B_2, and B_3, hepatic necrosis in ponies occurred (Ross et al., 1993).

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 (Colvin et al., 1993; Dilkin et al., 2010; Haschek et al., 2001; Stan et al., 1993). The hepatic changes especially disorganization in piglet by Fumonisins is probably because of an acute pathway of this mycotoxin.

3.3 Kidney Toxicity

Fumonisin in the kidney of lambs revealed with tubular nephrosis (Edrington et al., 1995).

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 (Mathur et al., 2001).

Effect of fumonisin in the kidney of turkeys and broiler chicken was increasing in kidney weight (Henry et al., 2000; Weibking et al., 1993a; Weibking et al., 1993b).

In both sexes of rats, Fumonisins caused decrease in the weight of the kidney, nephrosis in outer medulla (especially in female rats) (Voss et al., 1995). Ferric reducing antioxidant power (FRAP) content in the kidney of mice was decreased (Dassi et al., 2018).

Bucci et al. (1996) and Orsi et al. (2009), 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 (Bucci et al., 1996; Orsi et al., 2009).

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 (Dilkin et al., 2010; Pósa et al., 2016).

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.

3.4 Leukoencephalomalacia

Fumonisins (especially fumonisin B_1) are the causal factor in the development of LEM in horses (Thiel et al., 1991). The lethality rates, mortality, and morbidity in horses were 85.7%, 10%, and 11.6% respectively (Giannitti et al., 2011).

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 (Giannitti et al., 2011; Kellerman et al., 1990; Thiel et al., 1991). 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 (Giannitti et al., 2011; Kellerman et al., 1990; Thiel et al., 1991).

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 (Bucci et al., 1996). 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.

3.5 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 (Haschek et al., 2001; Pósa et al., 2016).

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(Colvin et al., 1993; Haschek et al., 2001).

3.6 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) (Haschek et al., 1992; Missmer et al., 2006). Also, Fumonisins in human colon cells caused to main and early induction of lipid peroxidation, assessing IL-8 secretion, and increasing in membrane microviscosity (Minervini et al., 2014).

Feeding by fumonisin in calves has some effects such as; impairing the lymphocyte blastogenesis (Osweiler et al., 1993), decreasing in serum-induced granulosa cell (GC) proliferation (Albonico et al., 2017), 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 (Mathur et al., 2001), and have no effects on cell proliferation, progesterone production, CYP11A1 and CYP19A1 gene expression of bovine granulosa cell (Albonico et al., 2017).

Diarrhea and lethargy detected in fumonisin administrated lambs (Edrington et al., 1995).

In broiler chicks, FB_1 had an adverse effect on weight, water consumption, feed efficiency, and body (Henry et al., 2000). Also, Fumonisins reduced villus height and crypt depth of the ileum, the abundance of Candidatus Savella and Lactobacilus spp (Antonissen et al., 2015), 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 (Henry et al., 2000; Ledoux et al., 1992), slightly inhibition in estradiol production(Antonissen et al., 2015), and elevation in the level of serum nitric oxide (NO) (Lee et al., 2017).
Henry and Wyatt (2001), reported that fumonisin in the egg could cause extreme hemorrhages of the thoracic area, head, and neck of the dead embryos in the egg (Henry and Wyatt, 2001).

Fumonisin B_1 in turkey appeared thymic cortical atrophy, and moderate enlarging of the proliferation and degeneration of hypertrophied zones of tibial physis (Weibking et al., 1993b).

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 (Bondy et al., 1997). Also, Fumonisins decreased the number of parietal cells, proliferative activity of gastric glands, gastric mucosa height and mitotic index in the gastric glands (Alizadeh et al., 2015). In contrast, Dassi et al. (2018), 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 (Dassi et al., 2018).
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 (Haschek et al., 2001; Régnier et al., 2017; Stan et al., 1993).
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 (Reisinger et al., 2016).

4. DIETARY INTAKE

In the European diet, the total intake of FB_1 has been evaluated at 1.4 µg/kg of body weight/week (Soriano and Dragacci, 2004a). Daily intake of Fumonisins in different countries and foods, are summarized in Table 3.
In Soriano and Dragacci, (2004) and Creppy, (2002) 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 (Soriano and Dragacci, 2004a); (Creppy, 2002).
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 (Coffey et al., 2009).
Orsi et al. (2009), 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 (Orsi et al., 2009).

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	(Hlywka and Bullerman, 1999)
Cereal commodities	France	22.8	All children in france	(Soriano and Dragacci, 2004a)
Cereal commodities	France	4.6	All female adults in france	(Soriano and Dragacci, 2004a)
Cereal commodities	France	3.2	All male adults in france	(Soriano and Dragacci, 2004a)
Cereal	France	9.96	All people in france	(Soriano and Dragacci,

commodities				2004a)
Cereal commodities	Germany	31.8	Users >14 years	(Soriano and Dragacci, 2004a)
Cereal commodities	Norway	430	6 month babies	(Soriano and Dragacci, 2004a)
Corn	Brazil	392	Camputed on the base of the 70 kg body weight from urban area	(Mac Jr and Valente Soares, 2000)
Corn	Brazil	1276	Camputed on the base of the 70 kg body weight from rural area people	(Mac Jr and Valente Soares, 2000)
Corn	Brazil	4.1 3.4 3.8	Conventional corn Organic corn Total	(Ariño et al., 2007)
Corn	France	45.6	All children in france	(Soriano and Dragacci, 2004a)
Corn	France	12.4	All female adults in france	(Soriano and Dragacci, 2004a)
Corn	France	7.4	All male adults in france	(Soriano and Dragacci, 2004a)
Corn	France	9.96	All people in france	(Soriano and Dragacci, 2004a)
Corn	Germany	8.7	Users >14 years	(Soriano and Dragacci, 2004a)
Corn	Switzerland	30		(Zoller et al., 1994)
Corn	The Netherlands	3.1	Adults	(Soriano and Dragacci, 2004a)
Corn	USA	80		(Humphreys et al., 2001)
Corn	USA	600000 to 2100000	Natural outbreak of LEM in horses	(Thiel et al., 1992)
Corn	Zimbabwe	140 and 5760	Shamva district	(Murashiki et al., 2017)
Corn	Zimbabwe	180 and 8092	Makoni district	(Murashiki et al., 2017)
Corn commodity	Brazil	63.3	São Paulo population	(Bordin et al., 2014)
Food with corn based	Argentina	0.73 to 2.29	Camputed on the base of the 70 kg body weight	(Torres et al., 2001)
Food with corn based	Brazil	maximum probable daily intake (MPDI): 256.07 average probable daily intake (APDI): 120.58		(Martins et al., 2012)
Food with corn based	Canada	89	All children	(Kuiper-Goodman et al., 1996)
Food with corn based	Canada	190	Child users	(Kuiper-Goodman et al., 1996)
Food with corn based	Denmark	400		(Petersen and Thorup, 2001)
Food with corn based	South Africa	14,000 to 440,000	A group of people exhibiting a high prevalence of human esophageal	(Thiel et al., 1992)
Food with corn based	South Africa	5,000 to 59,000	A group of people exhibiting a less prevalence of human esophageal	(Thiel et al., 1992)
Food with corn based	UK	30		(Gregory et al., 1990)

Corn inferred commodities	Belgium	16.7		(Soriano and Dragacci, 2004a)
Corn inferred commodities	China	450 to 15,810 (Mean=3020)	Camputed on the base of the 50 kg body weight	(Li et al., 2001)
Corn inferred commodities	Germany	10.4	Users >14 years	(Soriano and Dragacci, 2004a)
Corn inferred commodities	Italy	185.6	Italian users	(Soriano and Dragacci, 2004a)
Corn inferred commodities	Italy	24.6	All people in Italy	(Soriano and Dragacci, 2004a)
Corn inferred commodities	Norway	0.24	Adult male and female population	(Soriano and Dragacci, 2004a)
Corn inferred commodities	Norway	0.50	Adult male and female users	(Soriano and Dragacci, 2004a)
Corn powder	Argentina	79 to 198	For samples during 1996/1997 and January 1998	(Hennigen et al., 2000)
Corn pieces	Germany	69.8	Users >14 years	(Soriano and Dragacci, 2004a)
Corn pieces	Italy	283.6	Italian users	(Soriano and Dragacci, 2004a)
Corn pieces	Italy	15.9	All people in Italy	(Soriano and Dragacci, 2004a)
Food	Mexico	0.4 (0-23.2)	User in state of Morelos	(Wild and Gong, 2009)
Food	Burkina Faso	0.8 (0-2.4)	All users	(Wild and Gong, 2009)
Food	South Africa	3.8	User in Transkei	(Wild and Gong, 2009)
Food	South Africa	0	User in KwaZulu-Natal	(Wild and Gong, 2009)
Food	Guatemala	3.5	Urban area	(Wild and Gong, 2009)
Food	Guatemala	15.6	Rural area	(Wild and Gong, 2009)
Food	Guatemala	0.2-23	All users	(Torres et al., 2013)
Rice	France	12.1	All children in france	(Soriano and Dragacci, 2004a)
Rice	France	5.6	All female adults in france	(Soriano and Dragacci, 2004a)
Rice	France	5.6	All male adults in france	(Soriano and Dragacci, 2004a)
Rice	France	5.7	All people in france	(Soriano and Dragacci, 2004a)
Rice	Germany	0.6	Users >14 years	(Soriano and Dragacci, 2004a)
Wheat commodities	France	345.1	All children in france	(Soriano and Dragacci, 2004a)
Wheat commodities	France	230.8	All female adults in france	(Soriano and Dragacci, 2004a)
Wheat commodities	France	256	All male adults in france	(Soriano and Dragacci, 2004a)
Wheat commodities	France	240.08	All people in france	(Soriano and Dragacci, 2004a)
Wheat commodities	Italy	62.1	Italian users	(Soriano and Dragacci, 2004a)
Wheat commodities	Italy	10.6	All people in Italy	(Soriano and Dragacci, 2004a)
Food and feeds	Germany	bad case scenario: 21,000 mean case scenario: 1,100	German users	(Zimmer et al., 2008)

5. 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 (Van Egmond, 1993). 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 (AC04318739, 2004); (Abdallah et al., 2015).

Table 4. Maximum limits for Fumonisins in feeds and foods in different countries (AC04318739, 2004); (Abdallah et al., 2015)

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	30	Animal feeds except Equines
	5	Feed of Equines

(FB1, FB2, FB3)

6. 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.

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	(Scott, 2012)
Sphingopyxis sp.	Hydrolysis of FB1 to HFB1	(Scott, 2012)
Saccharomyces	Decrase in FB1 and FB2	(Scott et al., 1995).
Lactobacillus strains (L. plantarum B7 and L. pentosus X8)	Removing Fumonisins (FB1 and FB2)	(Zhao et al., 2016)
Black yeasts Rhinoclodiella atrovirensa and Exophiala spinifera	Ester bonds was hydrolyzed of FB1	(Volcani Center, 2004)
Candida parapsilosis	Mycelial growth inhibition	(Fallah et al., 2016)
Physical process		
150–200 °C	87–100 % destruction of fumonisin B1 in corn cultures	(Volcani Center, 2004)
Extrusion and roasting	60–70 % loss of FB1 and FB2	(Scudamore, 2004)
Extrusion	30 % loss of FB1 and FB2	(Scudamore, 2004)
Extrusion	92 % loss of fumonisin B1	(Scudamore, 2004)
Extrusion	34-95% reduction of Fumonisins	(Shanakhat et al., 2018)
Extrusion of drymilled products	Decrease in fumonisin accumulation by 30–90 % for mixing-type extruders and 20–50 % for non-mixing extruders	(Meister, 2001)
Baking corn	16 and 28 % loss of FB1	(Shapira and Paster, 2004)
Frying corn chips	loss of 67 % of the fumonisin	(Shapira and Paster, 2004)
Cooking and canning	Small influence on fumonisin measure (23%)	(Shephard et al., 2002)
Ethanol–water extraction solvent at 80 °C	The most environmentally friendly, least toxic, and cheapest	(Lawrence et al., 2000)
Cholestyramine	Adsorption 85% of FB1	(Solfrizzo et al., 2001b)
Activated carbon	Adsorption 62% of FB1	(Solfrizzo et al., 2001b)
Ammonia process	Reduce FB1levels 30-45% No mutagenic potentials were apparent	(Norred et al., 1991)
Fructose	Obstruct the amine group of FB1, that is important for its toxicity	(Lu et al., 1997)
Chlorophorin	Reduced FB1 levels by 90–91%	(Beekrum et al., 2003)
Oxidizing agents	Little effects in FB1, but applicable because of the minimal cost and the minimal destruction of important nutrients	(Leibetseder, 2006)

Bentonite	Adsorbed only 12% of the toxin FB1	(Solfrizzo et al., 2001b)
Celite	Not effective	(Solfrizzo et al., 2001b)
Chemical process		
Solution of SO2 at 60 °C for 6 h	Most impressive treatment to decline the measure of fumonisin B1	(Pujol et al., 1999)
Acidic aqueous solution by the addition of NaNO2	Fumonisin B1 was significantly deaminated	(Lemke et al., 2001)
NaCl solution	Fumonisin B1 had a little mass and that 86 % of the toxin could be eliminated	(Shetty and Bhat, 1999)
Ozone (O3)	No significant difference in FB1	(McKenzie et al., 1997)
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	(Leibetseder, 2006)

5.1 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 (Scott, 2012).

L. plantarum MYS6 is having potential probiotic attributes and antifungal activity against Fumonisin producing F. proliferatum MYS9 (Deepthi et al., 2016).

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 (Zhao et al., 2016).

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 (Scott et al., 1995).

Hydrolyzing ester bonds of fumonisin B_1 by black yeasts (*Exophiala spinifera* and *Rhinoclodiella atrovirensa*) reported by (Volcani Center, 2004).

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 (Fallah et al., 2016). 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.

5.2 Physical and Chemical Methods

Fumonisin B_1 needs a massive temperature (150–200 °C) to gain 87–100 % demolition in corn cultivation (Volcani Center, 2004).

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 (Saunders et al., 2001). 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 % (Scudamore, 2004). Destruction of Fumonisin B_1 in extrusion process of grits, was 92% (Scudamore, 2004). The economic, lowest toxic and most biodegradable solvent for Fumonisin extraction is ethanol-water (Lawrence et al., 2000).

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 (Jackson et al., 1997),(Shapira and Paster, 2004).

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 (Pujol et al., 1999). Nevertheless, canning and cooking had a small influence on fumonisin measure (Shephard et al., 2002).

In paper of Solfrizzo et al. (2001), the adsorption capacity of cholestyramine for fumonisin B_1 was 85% from a solution including 200 µg/ml FB_1 (Solfrizzo et al., 2001b).
Detoxification of corn with ammonia process reduced fumonisin levels (30 to 45 %), and no mutagenic potentials were found in the managed corn (Norred et al., 1991).
Obstruction in the amine group of fumonisin B1 by reaction with fructose is another way to the detoxification of fumonisin B_1 (Lu et al., 1997).
The percentage of reduction in FB_1 in corn by single $Ca(OH)_2$ (nixtamalization) or with Na-HCO_3 + H_2O_2 (modified nixtamalization), was 100% (Leibetseder, 2006).
Chlorophorin gets from vanillic acid, ferulic acid, caffeic acid, and iroko decreased FB_1 levels by 90–91% (Beekrum et al., 2003).
Although treatment with oxidizing agents is an economical method for detoxification of Fumonisin B_1, this method isn't demonstrated in bioassays (Leibetseder, 2006).
The acidic aqueous solution such as $NaNO_2$ can create deamination in fumonisin B_1, significantly (Lemke et al., 2001).
In the floating section after treatment with NaCl solution, 86% of FB_1 were removed (Shetty and Bhat, 1999).
Celite and O3 couldn't make any significant difference in the level of FB_1, but bentonite adsorbed only 12% of the FB_1 (McKenzie et al., 1997; Solfrizzo et al., 2001b).
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.

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.

Ethical Approval: NA

Consent: NA

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