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Review

Fumonisins and fumonisin-producing *Fusarium* occurrence in wheat and wheat by products: A review

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A B S T R A C T

Cereals, including wheat, rice, barley, maize, rye, oats and millet, make up the majority of the production of the crop sector, being the most important food sources for human consumption. Cereals are commonly colonized by *Fusarium* species and often contaminated with mycotoxins that have a major impact on health, welfare and productivity. Among the mycotoxins produced by *Fusarium* species, fumonisins are usually present in maize and maize-based products, but in the last ten years natural occurrence of fumonisins in wheat in different regions have been observed. This review provides information on the occurrence of fumonisins in wheat and wheat by products around the world. Also, data on ecophysiology of *Fusarium proliferatum*, one of the main species associated to fumonisin presence in wheat are included. Some data on strategies to reduce the problem are included. The possible human exposure risk of these toxins through the wheat consumption in areas where this cereal represents the main staple food is discussed.

Contents

1. Introduction

Wheat, after rice, is the most important source of calories as well as source of protein for humans. World wheat production in 2015 and 2016 was at a record 734.2 and 760.3 million tons, respectively. Among wheat exporter countries, Argentina, Australia, Canada, the

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EU, Kazakhstan, Russian Federation, Ukraine and the United States are included (Food and Agriculture Organization of the United Nations (FAO), 2016). For consumption, this cereal is ground into flour and semolina, being the basic ingredients for bread and other bakery products, and pasta (Chandrika and Shahidi, 2006). Wheat flour per capita consumption varies widely by region; in countries like Egypt, Algeria, Israel, and many others in the Middle East and Eastern Europe, per capita consumption of wheat flour is high and often exceeds 150 kg per year. In other countries that rely more heavily on other cereals, per capita consumption is lower, averaging 35 kg in Central America, and 17 kg in Sub Saharan Africa. Developing countries use more than 80% of their wheat supply for food, compared to developed countries that use less than 50%. Even though global per capita food use of wheat has held relatively steady over the past 50 years or so, consumption in developing countries has increased significantly during this time, offsetting the overall declining consumption in the developed world. In many Asian countries, increase in wheat consumption has been partly at the expense of rice. This is attributed to diversification of diets as a result of growing economies and increased global trade (Awika, 2011).

Cereals are commonly colonized by *Fusarium* species and often contaminated with mycotoxins that have a major impact on health, welfare and productivity. Among the mycotoxins produced by *Fusarium* species, fumonisins (FBs) are usually present in maize and maize-based products, but also, natural occurrence of fumonisins in wheat in different regions have been observed. In 2005, since the finding of fumonisins in wheat and wheat-based products was questionable, Shephard et al.,(2005) reviewed several of the previous reports on fumonisins in wheat. They concluded that careful evaluation of the analytical method and possible source of contamination, as well as confirmation by appropriate and valid method is required in order to prevent the report of false positive results.

Fumonisins are a group of mycotoxins mainly produced by *F. verticillioides* and *F. proliferatum*. Fumonisin B_1 is the most significant fumonisin in terms of toxicity and occurrence. Fumonisin B_2, FB_3 and FB_4 are in order less prevalent and differ structurally from FB_1 in the number and placement of hydroxyl groups on the molecule's hydrocarbon “backbone” (Voss et al., 2007). The fumonisins consumption has been associated with leukoencephalomalacia in equine, hepatic and renal toxicity in rodents, pulmonary edema in pigs and esophageal cancer and neural tube defects in humans (Marasas, 2001; Marasas et al., 2004; Missmer et al., 2006; Sun et al., 2007). Recent studies suggest that the fumonisins exposure could also be related with stunting in children (Kimanya et al., 2010; Shirima et al., 2015). Due to the toxicological effect in animals and humans, FB_1 has been classified as a “2B” carcinogen by the International Agency of Research on Cancer (International Agency for Research on Cancer (IARC), 2002). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has determined a provisional maximum tolerable daily intake (PMTDI) of 2 μg/kg body weight per day for FB_1, FB_2 and FB_3 alone or in combination (World Health Organization (WHO), 2001). Maximum fumonisin limits for human consumption in cereals and cereal-based foods were established by the European Union in 2007 (EC N°1126/2007) but has not been specifically established for wheat or wheat-based foods yet.

Several studies using biomarkers to evaluate fumonisins exposure have been done in human populations but only a few have been carried out in Latin America. Sphinganine and sphingosine were measured in urine samples as FB_1 biomarker in populations with high maize consumption from North Argentina and South Brazil showing a mean Sa/So ratio significantly higher as compared to low or no maize consumption areas, mainly in South Brazil (Solfrizzo et al., 2004). In Mexico, urinary FB_1 (UFB_1) was also compared with dietary information on maize-based tortilla consumption and both the frequency of positive samples and the levels were associated with tortilla consumption (Gong et al., 2008). In Guatemala, UFB_1 reflected the estimated FB intake and showed that when the UFB_1 was between 0.1 and 0.5 ng/mL, the relative risk for exceeding the JECFA PMTDI increased in comparison to the group in which UFB_1 was not detected (Torres et al., 2014). The results obtained in these previous studies indicated that in areas where maize is contaminated with fumonisins, the populations have a higher exposure risk of this mycotoxin. Therefore, in those regions where the consumption of fumonisin-contaminated wheat is high, the same exposure risk could occur.

Fumonisins contamination in food and feed chains depends on different factors such as agroclimatic conditions. Temperature and water availability are probably the most critical environmental factors that determine crops grown in a given region. Wheat is grown in a wide range of environments, from relatively limited water availability to high water availability. In addition, wheat can withstand a wide temperature range, and is thus widely produced in the temperate regions both in the winter and spring. The knowledge of the incidence of fumonisin-producer species on wheat and the agroecological condition that favour its production is essential to reduce the impact of fumonisins, not only to improve food and feed quality but also to maintain their safety.

This review focuses on *Fusarium* species FB-producers and fumonisin contamination on wheat worldwide and the factor that influence their accumulation.

2. Studies on natural occurrence *Fusarium* species and fumonisins in wheat and wheat based products

Natural occurrence of fumonisins in wheat and wheat-based products have been reported in many countries worldwide (Table 1). Differences in fumonisin contamination levels have been observed depending on the wheat variety and/or wheat by-product and their geographic origin. Moreover, fumonisin co-occurrence with other mycotoxins has also been evaluated in several studies. The information about the *Fusarium* species presence in wheat or wheat-based products is available in some reports. In the present review the information has been classified according to the different continents.

2.1. America

In Argentina, a survey was carried out to determine fumonisin contamination in 55 durum wheat (*Triticum turgidum* L. var. durum) samples collected during 2007 and 2008 harvest seasons. The analyses were performed using HPLC and further LC-MS/MS confirmation. In 2007, 97% of the samples showed total fumonisin ($FB_1 + FB_2$) levels ranging from 10 to 1246 μg/kg, while very low levels of fumonisins were detected in samples collected during 2008 harvest season. It was noticeable also that 5 samples showed higher levels of fumonisin B_2 (FB_2) than fumonisin B_1 (FB_1) (Palacios et al., 2011). A second survey was carried out by Cendoya et al. (2014b) to evaluate total fumonisin ($FB_1 + FB_2 + FB_3$) contamination in 135 common (*Triticum aestivum* L.) and 40 durum wheat samples collected during 2011 harvest season in the main wheat production area of Argentina using LC-MS/MS. A 93% of total samples showed fumonisin contamination, with levels ranging from 0.16 to 680 μg/kg and from 0.15 to 1304 μg/kg in common and durum wheat samples, respectively. These results show that the contamination levels with fumonisins in durum wheat were higher than those detected in common wheat and similar to those observed by Palacios et al. (2011) during the 2007 harvest season.

Table 1
Worldwide occurrence of fumonisins in wheat and wheat by products

Country	Year	Food	FB_1		FB_2		FBt		Method	Ref
			Occurrence[a]	Range[b]	Occurrence[a]	Range[b]	Occurrence[a]	Range[b]		
Argentina	2007	Durum wheat	29/30/97/193.7	10.5–987.2	25/30/83/66.15	15–258.5			HPLC-MS/MS	Palacios et al., 2011
Argentina	2008	Durum wheat	6/25/24/ND	<LOQ					HPLC-MS/MS	Palacios et al., 2011
Argentina	2012	Durum wheat	31/40/77.5/84.75	0.15–1304.4	17/40/42.5/10.47	0.43–47			HPLC-MS/MS	Cendoya et al., 2014b
Argentina	2012	Wheat	131/135/97/30.07	0.16–680.4	69/135/51/2.88	0.25–23.7			HPLC-MS/MS	Cendoya et al., 2014b
Brazil	2010/2011	Wheat cultivars	6/11/54/2814.33	958–4906					HPLC-FL	Mendes et al., 2015
Canada	1999–2001	Wheat					5/29/17/16	LOQ-51	HPLC	Roscoe et al., 2008
Canada	1999–2001	Buck wheat					1/1/100/5	5	HPLC	Roscoe et al., 2008
Central Europe	2009/2011	Wheat/wheat bran					3/9/33/268	LOQ-450	ELISA	Rodrigues and Naehrer, 2012
China	ND	Wheat flour					13/16/81/200	0–400	ELISA HPLC	Sun et al., 2011
China	ND	Wheat flour					2/30/7/0.1	ND	LC-MS/MS	Liu et al., 2012
China	2014	Wheat flour	23/369/6.2/ND	0.3–34.6					UPLC-MS-MS	Li et al., 2015
France	2011	Bread and dried bread products	ND/14/ND/1.4	ND	ND/14/ND/0.3	ND			LC-MS/MS	Sirot et al., 2013
France	2011	Sweet or savoury biscuits and bars	ND/8/ND/35	ND	ND/8/ND/75	ND			LC-MS/MS	Sirot et al., 2013
France	2009–2012	Organic Oat, rye and wheat flakes with maple syrup	3/27/11/ND	75.7–98.1	3/27/11/ND	62.1–81.1			HPLC-MS/MS	Rubert et al., 2013
France	2009–2012	Organic wheat flakes	9/63/14/ND	75.8–125.8	9/63/14/ND	63.8–101.1			HPLC-MS/MS	Rubert et al., 2013
France	2009–2012	Conventional corn and wheat squares	9/54/16/ND	29.5–48.7	9/54/16/ND	21.7–32.5			HPLC-MS/MS	Rubert et al., 2013
Germany	2009–2012	Organic wheat flakes	6/44/14/ND	20.2–59.8	5/44/11/ND	25.4–41.8			HPLC-MS/MS	Rubert et al., 2013
Iran	2011	Wheat flour used at bakeries					18/21/86/300	LOQ-4500	ELISA	Roohi et al., 2012
Iran	2011	Wheat flour used at confectioneries					17/21/81/290	LOQ-4100	ELISA	Roohi et al., 2012
Iran	ND	Stored wheat samples	56/82/68/ND	15–155	35/82/43/ND	12–86			HPLC	Chehri et al., 2010
Italy	2000	Farro	5/8/62/36.18	20.05–70	NQ[c]	<LOQ			HPLC-MS	Castoria et al., 2005
Italy	2001–2002	Cereals, whole meal flours	36/111/32/70	10–2870	34/111/31/60	10–420			LC-MS	Cirillo et al., 2003a
Italy	2001–2002	Bread and related products	7/24/29/50	30–150	8/24/33/118	56–400			LC-MS	Cirillo et al., 2003a
Italy	2001–2002	biscuits	2/24/8/ND	80–200	6/24/25/88	10–220			LC-MS	Cirillo et al., 2003a
Italy	2003	Wheat-based conventional foodstuff	14/44/31/97	40–2870	17/44/38/25	15–67			LC/MS	Cirillo et al., 2003b
Italy	2003	Wheat-based organic foodstuff	7/36/20/90	10–380	12/36/32/210	70–790			LC/MS	Cirillo et al., 2003b
Italy	2008	Durum wheat	4/4/100/6.2	2.8–9.6					HLPC-MS-MS	Amato et al., 2015
Italy	2009	Durum wheat	4/4/100/5.3	2.7–7.9					HLPC-MS-MS	Amato et al., 2015
Italy	2010	Durum wheat	4/4/100/33	15–51					HLPC-MS-MS	Amato et al., 2015
Japan		Wheat	1/47/2/ND	>10					LC-ESI-MS-MS	Kushiro et al., 2009
North Asia	2009–2011	Wheat/wheat bran					8/73/11/371	LOQ-874	ELISA-HPLC	Rodrigues and Naehrer, 2012
Oceania	2009–2011	Wheat/wheat bran					13/109/12/269	LOQ-1196	ELISA-HPLC	Rodrigues and Naehrer, 2012
Serbia	2005	Wheat	23/28/82/2079.45	750-5400					ELISA	Stanković et al., 2012
Serbia	2007	Wheat	69/75/92/918.76	750-4900					ELISA	Stanković et al., 2012
Serbia	2007–2009	Wheat	109/180/61/852.7	750-4900					ELISA	Stanković et al., 2011
Serbia	2010	Wheat					39/75/51/241	27–614	ELISA	Jakšić et al., 2012
South Africa	ND	Wheat and wheat based products	4/210/2/ND	1000–30,000					TLC, HPLC, Ms/MS	Mashinini and Dutton, 2006
South America	2009–2011	Wheat/wheat bran					2/40/5/1047	LOQ-1715	ELISA-HPLC	Rodrigues and Naehrer, 2012

Table 1 (*continued*)

Country	Year	Food	FB_1		FB_2		FBt		Method	Ref
			Occurrence[a]	Range[b]	Occurrence[a]	Range[b]	Occurrence[a]	Range[b]		
South-East Asia	2009–2011	Wheat/wheat bran					2/40/5/172	LOQ-292	ELISA-HPLC	Rodrigues and Naehrer, 2012
Southern Europe	2009–2011	Wheat/wheat bran					3/10/30/386	LOQ-925	ELISA-HPLC	Rodrigues and Naehrer, 2012
Spain	1994,1995,1996	Wheat	8/17/47/2900	200- 8800	1/17/6/200	200	8/17/47/2900	200-8800	LC-MS	Castellá et al., 1999
Spain	2009–2012	Organic Gofio of wheat[c]	27/35/77/ND	787.5 –1001.4	27/35/77/ND	645.2 –952.1			HPLC-MS/MS	Rubert et al., 2013
Syria	2009–2010	Durum wheat	4/40/10/5	5–6	1/40/2/12	12			HPLC-MS/MS	Alkadri et al., 2014
Tunisia	2010	Wheat-based products (1 pasta-1 soup)	2/65/3/ND	<LOQ (88.33)-184					LC-MS/MS	Serrano et al., 2012
Tunisia	2010	Wheat			2/21/9/ND	121 –158			LC-MS/MS	Serrano et al., 2012
United States	2006–2007 -2008	Wheat	9/43/21/464.11	5-2210	4/43/9.3/121.25	2–249			LC-MS	Busman et al., 2012
Zimbabwe	1995–1997	Wheat	5/5/100/4200	2500–6000					HPLC	Gamanya and Sibanda, 2001

NQ Not quantifiable.
ND No Data.
[a] Positive samples/total samples/incidence %/mean (μg/kg).
[b] μg/kg.
[c] Flour obtained from toasted wheat.

Therefore, the wheat variety and the differences in the meteorological conditions registered in the different seasons could be factors that affect the fumonisin contamination.

In Brazil, Mendes et al. (2015) evaluated the presence of FB_1 in 11 common wheat cultivars grown in the North-Eastern and North-Western areas of Rio Grande do Sul during 2010/2011 harvest season. Of the total samples analyzed, 54% were contaminated with FB_1 at levels ranging from 958 to 4906 μg/kg and Quartzo and OR Marfim cultivars presented the highest contamination. These levels were similar to those observed in common wheat varieties from Argentina but the percentage of contaminated samples was lower.

In Canada, Roscoe et al. (2008) studied the mycotoxin incidence in 166 samples of breakfast cereals (maize-, oat-, wheat- and rice-based cereals, as well as mixed-grain cereals) collected from the Canadian retail marketplace over a 3-year period. Fumonisins were found in 17% (5/29) of the wheat-based samples with a mean level of 3 μg/kg. Only one sample of buckwheat cereal was analyzed and FBs were detected (5 μg/kg). Although the fumonisins levels detected in wheat based breakfast products obtained from the Canadian retail market were low, the authors concluded that the risk of exposure of these mycotoxins is present.

In the United States, Busman el at. (2012) analyzed 43 wheat samples with symptoms of kernel black point disease, and detected low levels of fumonisins in 9 of them ranging from 5 to 2,210, from 2 to 249 and from 2 to 163 μg/kg for FB_1, FB_2 and FB_3, respectively.

Natural occurrence of FBs (FB_1 and FB_2), deoxynivalenol (DON), nivalenol (NIV), HT-2 toxin, zearalenone (ZEA) and ochratoxin A (OTA), in wheat samples was evaluated. In Argentina, twenty-five wheat samples (15 common and 10 durum wheat cultivars) were selected for DON analysis among all the samples analyzed for fumonisin content. Deoxynivalenol contamination was present in 24 out of 25 wheat samples, the levels ranging from 50.60 to 28,650 μg/kg. Nine out of 25 wheat samples reached values higher than 1000 μg/kg. However, there was no correlation between fumonisin and DON contamination levels (Cendoya et al., 2014b). In wheat by-products from Canada commonly used for breakfast, DON was frequently detected (72%) and the mean level was 110 μg/kg. Zearalenone and OTA were each found in 38% and the mean levels of were 0.9 and 0.11 μg/kg, respectively (Roscoe et al., 2008). However, this study does not specify the occurrence of mycotoxins in the same sample. In studies where natural incidence of fumonisins on durum wheat samples was analyzed, *Fusarium* genera was isolated being *F. proliferatum* the most frequent species (Palacios et al., 2011). The capability to produce fumonisins of *F. proliferatum* strains (n = 88) isolated from durum wheat on autoclavated durum wheat grains was demonstrated by Palacios et al. (2015). The study revealed that 97% of the strains were able to produce fumonisin in variable levels. Interestingly, there were 18 strains that produced more FB_2 than FB_1, 13 strains that produced more FB_3 than FB_2 and 5 strains that produced more FB_3 than FB_1. *Fusarium proliferatum* was also isolated from wheat samples with symptoms of kernel black point disease in the United States and Nepal contaminated with fumonisins, and pure cultures of the fungus from both sources caused black point symptoms when inoculated into healthy wheat (Busman et al., 2012; Desjardins et al., 2007).

2.2. Europe

In Spain, in only one study performed by Castellá et al. (1999) the natural occurrence of FB_1 and FB_2 was evaluated in 17 wheat samples by HPLC analysis and confirmed by LC/MS. The results showed that 47% of the samples were contaminated with FB_1 in levels ranging from 200 to 8800 μg/kg. Rubert et al. (2013) analyzed the occurrence of FB_1 and FB_2 in 1250 cereal-based conventional and organic products from local stores and supermarkets in France, Germany and Spain. As a result they found that both fumonisins could contaminate cereal-based products, but the highest incidence was observed in organic maize and wheat. Fumonisin B_1 in organic wheat flakes ranged from 20.2 to 125.8 μg/kg, while FB_2 ranged from 25.4 to 101.1 μg/kg. In Italy, a survey on natural occurrence of FB_1 and FB_2 was carried out by Cirillo et al. (2003b) in two lots of human foodstuffs from conventional and organic brand foods from super-markets using LC-MS. Wheat-based foodstuffs consisted of raw material and processed cereal foods (biscuits, flour, bran, bread, and pasta): 44 batches of conventional and 36 of organic products. Data showed that FB_1 was present in 20% and 31% of organic and conventional foods, respectively, while FB_2 was detected in more than 32% of the food samples from both types of agricultural practices. The highest median concentration of FB_1 was detected in conventional maize-based foods (345 μg/kg), and FB_2 highest median concentration was observed in organic wheat-based foods (210 μg/kg). The levels of FB_1 were significantly higher in conventional wheat-based foodstuff than in the corresponding organics. Cirillo et al. (2003a) performed a second survey in order to obtain the frequency and levels of contamination FB_1 and FB_2 in Italian marketed foods. Out of 202 samples including raw material and processed cereal foods (bread, pasta, breakfast cereals, biscuits, baby and infant foods) 26% were contaminated with FB_1 in levels ranging from 10 to 2870 μg/kg and 35% with FB_2 levels ranging from 10 to 790 μg/kg. The highest levels of FB_1 were detected in raw cereals and wholemeal flours while highest levels of FB_2 were detected in durum wheat pasta, but no FB_1 was detected in those samples. Interestingly, FB_2 was detected at higher levels in wheat-based products than in the rest of the products. In general, when fumonisins content is analyze, FB_1 concentrations usually exceed those of FB_2 and FB_3 of about 3 or more times, although, as many researchers have shown higher concentrations of FB_2 or FB_3 can also be observed in natural contaminated wheat samples (Voss et al., 2011). Also in Italy, Castoria et al. (2005) confirmed, by HPLC-MS, the presence of natural occurrence of FB_1 and FB_2 in Farro samples (*Triticum monococcum* L., *Triticum dicoccon* Schrank and *Triticum spelta* L.) collected from Italy. Sixty-two percent (5 out of 8) of the samples were contaminated with both toxins in low concentrations: up to 70 μg/kg for FB_1 and levels below the quantification limit (LOQ) for FB_2.

In France, Sirot et al. (2013) performed the second French total diet study (TDS), analysing mycotoxins in 577 food samples collected in mainland to be representative of the population diet and prepared as consumed. As a result they found FBs contamination in biscuits (35 μg/kg FB_1 and 75 μg/kg FB_2), and bread, dried bread products and breakfast cereals where both FB_1 and FB_2 were simultaneously present, as well as in sweet or savoury biscuits and bars. The authors also, estimated the exposure of adult and child populations to different mycotoxins by combining national consumption data with analytical results. The authors concluded that in adults as in children, bread and bread products appears to be the main contributor to the mean exposure to OTA, DON, NIV, ZEA, and FB_1 for adults only (36%). Interestingly, the adults exposure to FBs decreased since the first TDS in 2005. But, for children, the estimation was equivalent to the first one.

In Serbia, two studies were conducted in order to compare the fumonisins occurrence found in different cereals, mainly wheat and maize. Stanković et al. (2011) evaluated FB_1 contamination in maize, wheat and barley grains by ELISA assay. Samples were obtained from different local warehouses between 2007 and 2009 harvest seasons: 203 maize, 180 wheat and 120 barley samples. Positive results were found in 70.7%, 60.6% and 34.1% in the maize, wheat and barley samples, respectively. The mean levels were 1225.7 μg/kg in maize, 852.7 μg/kg in wheat, and 768.2 μg/kg in barley, while concentrations ranged from: 750–4900 μg/kg, 750–4300 μg/kg, and 750–1225 μg/kg, for wheat, maize and barley samples, respectively. Jakšić et al. (2012) also performed a survey in Serbia where evaluated FBs contamination in wheat and maize samples collected during 2010 season using also ELISA analysis. They analyzed different wheat cultivars and three different locations which represent a broad range of environmental conditions. Out of 75 wheat samples analyzed, 57% were contaminated with FBs in levels ranging from 27 to 614 μg/kg. FBs were present in 100% of maize samples in levels ranging from 60 to 12,800 μg/kg. The occurrence of fumonisins contamination in wheat was the same on all locations with similar average levels but differences were observed between cultivars. Data obtained of both studies showed that although there is a higher FBs incidence in maize samples than in wheat, the FBs presence in wheat is relevant and it is necessary to control their occurrence in this cereal. Moreover, the authors postulated that agricultural conditions in Serbia seem to affect the natural contamination of FB_1 not only in maize, but also in wheat and barley grains. However, neither Stanković et al. (2011), nor Jakšić et al. (2012) confirmed their results by using a chromatographic method. In other study, Stanković et al. (2012) analyzed FB_1 occurrence in 103 winter wheat samples collected after four to six months storage in family barns from different locations by ELISA. FB_1 was present in 82.1% and 92% of all samples with ranges of 750–5400 μg/kg (mean 2079 μg/kg) and 750–4900 μg/kg (mean 918 μg/kg) in 2005 and 2007, respectively. A large number of samples (53.1% in 2005 and 64.0% in 2007) contained FB_1 levels higher than 1000 μg/kg. These FBs levels were higher than those obtained in other studies, this fact could be attributed to the analytical method and/or the harvest season evaluated.

Co-occurrence of FB_1 with DON in Italian marketed foods, mainly in raw cereals and whole meal, was detected by Cirillo et al. (2003a), out of 202 samples 84% were contaminated with DON (at levels ranging from 7 to 930 μg/kg), 26% with FB_1 (at levels ranging from 10 to 2870 μg/kg) and 35% with FB_2 (at levels ranging from 10 to 790 μg/kg). On durum wheat samples from Italy, low FB_1 levels also occur with relevant levels of DON (1500–13,000 μg/kg) and NIV (500–1000 μg/kg) and lower concentrations of enniantins (<LOQ) and beauvericin (BEA) (<LOQ - 48 μg/kg) (Amato et al., 2015). The authors hypothesized that low levels of fumonisins commonly occur in wheat grains, but that they may remain undetected as long as mycotoxin monitoring programs for wheat not included fumonisins. In France, wheat and cereal-based products appeared to be also contaminated with other mycotoxins; for example, biscuits with ZEA (3 μg/kg) and FBs (35 μg/kg FB_1 and 75 μg/kg FB_2), bread and bread products with OTA (0.13 μg/kg) and DON (132 μg/kg), pasta with OTA (0.10 μg/kg), pizza/savoury pastries and hamburgers with DON (101 and 83 μg/kg, respectively) (Sirot et al., 2013). Moreover, in wheat samples collected from Serbia DON, T-2 and ZEA were observed besides FB_1 during 2005 and 2007 harvest season: in 78.6 and 86.7% for DON, 60.7 and 52% for T-2, and 67.9 and 88% for ZEA, respectively (Stanković et al., 2012).

Rodrigues and Naehrer (2012) conducted a worldwide survey analyzing the presence of several mycotoxins in a total number of 7049 samples including maize, soybean/soybean meal, wheat, dried distiller grains with soluble (DDGS) and finished feed samples between 2009 and 2011. Samples were sourced in the Americas (North and South), Europe and Asia. According to the results in wheat samples the major contaminant throughout all regions was DON, but ZEA was also detected. Regarding fumonisin presence in wheat in North America there were no positive samples out of 7 analyzed samples, while in South America 2 out of 40 samples were contaminated with fumonisin (average: 1407 μg/kg). Also, no fumonisin was detected in the only sample analyzed from Northern Europe, while 33 and 30% of wheat samples from Central and Southern Europe, respectively, were contaminated with this toxin. Also, 11, 5 and 12% of wheat samples were contaminated in North Asia, South-East Asia and Oceania, respectively. Highest fumonisin levels in wheat were found in South America samples.

In analogy to maize, the origin of fumonisins in wheat has been generally attributed to *F. proliferatum* and *F. verticillioides* species. The results reported by Infantino et al. (2012) indicated that *F. verticillioides* could be the major source of fumonisins in durum and common wheat in Italy. However recently, Amato et al. (2015) evaluated durum wheat samples collected in Italy between 2008 and 2010 period for colonization with *Fusarium* species and they found that *F. proliferatum* appeared to be the only relevant source of fumonisins in wheat grains. Unlike the previous study, fungal biomass was determined using species-specific qPCR. No *F. verticillioides* DNA was detected in the samples evaluated. The detection of *F. proliferatum* DNA in the total DNA extracted from wheat kernels motivated the authors to extend the analysis of mycotoxin content to fumonisins and BEA, being both toxins produced by this species.

2.3. Asia

In Japan, only one study was done in order to evaluate the natural occurrence of fumonisins in brown rice and wheat using LC-ESI-MS-MS. Forty-seven and 48 wheat and rice samples respectively were screened for FB_1 and FB_2, just one sample was positive for FB_1 at a level higher than the detection limit (10 μg/kg) and no fumonisins were found in any of the rice samples (Kushiro et al., 2009).

In China, Sun et al. (2011) analyzed natural incidence of FBs in 209 food samples, consisting of maize, rice, plant oil (soybean and peanut), peanut and wheat flour collected from individual households. The mycotoxin analyses were done by ELISA and the authors confirmed the contamination of some samples by HPLC. High contamination rates with FB_1 were observed in cereal grain samples, including maize, rice and wheat flour with mean levels of 0.3, 0.3 and 0.2 mg/kg, respectively. Later on, Liu et al. (2012) carried out another survey to evaluate FBs (FB_1+FB_2+FB_3) contamination in maize and wheat flour samples purchased from different supermarkets by LC-MS/MS. Fumonisins were detected in 95% of maize samples and in 7% of wheat flour samples, with mean levels of 441 μg/kg and 0.09 μg/kg, respectively. Recently Li et al. (2015) analyzed the occurrence of FB_1, FB_2 and FB_3 in 522 maize products and wheat flour samples collected from Shandong province during 2014 harvest season. Fumonisins were detected in 98.1% of maize samples with average values of 268.3, 53.7 and 47.2 μg/kg of FB_1, FB_2 and FB_3, respectively while 6.2% of wheat flour samples were contaminated with FB_1 at concentrations ranging from 0.3 to 34.6 μg/kg.

In Iran, 82 stored wheat samples were collected from several supermarkets and tested for the presence of fumonisins by HPLC. Natural occurrence of FB_1 was detected in 56 (68.2%) samples with levels ranging from 15 to 155 μg/kg, FB_2 was detected in 35 (42.6%) samples ranging from 12 to 86 μg/kg, and FB_3 in 26 (31.7%) samples ranging from 13 to 64 μg/kg (Chehri et al., 2010). Also, Roohi et al. (2012) evaluated fumonisin contamination in 21 wheat flour samples used in bakeries and 21 wheat flour samples used at confectioneries in Iran. As a result, they found that the bakeries samples were more contaminated and 3 out of 42 samples contained more than 4000 μg/kg fumonisins (FB_1 + FB_2), above the limit recommended by US-FDA (2000–4000 μg/kg).

In Syria, Alkadri et al. (2014) applied an analytical method for the detection of FB_1 and FB_2 in wheat grains based on simultaneous extraction using matrix solid-phase dispersion (MSPD) followed by LC-MS/MS. They analyzed 40 durum and common wheat samples and detected that the 10% of them were contaminated with both FB_1 and FB_2.

Fumonisins co-occurrence with AFs was observed in wheat flour samples from China. Sun et al. (2011) detected a high co-occurrence rate between AFB_1 and FB_1 (89 and 71% in Huantai and Huaian regions, respectively) at similar concentrations, while Liu et al. (2012) found a low co-occurrence rate (12%) between the same mycotoxins, and also the levels of both toxins were low.

Regardless fumonisin-producer species, both *F. verticillioides* and *F. proliferatum,* were isolated from stored wheat samples produced in Iran (Chehri et al., 2010).

2.4. Africa

In Zimbabwe, Gamanya and Sibanda (2001) analyzed FB_1 levels in cereals and oilseeds. They found out that the metabolites exhibited a substrate preference: maize followed by wheat, rapoko and sorghum. In wheat samples, the FB_1 levels ranged from 2500 to 6000 μg/kg.

In South Africa, a study has been undertaken to survey FB_1 contamination of wheat grains obtained from the field and of processed wheat products purchased from supermarkets and outlets. Thin layer chromatography (TLC), HPLC and LS-MS methods were used to detect this toxin. Fumonisin levels, ranged from 1000 to 30,000 μg/kg for field samples and from 1000 to 2000 μg/kg for retail samples, being those levels not insubstantial and in some cases approached levels found in maize. An interesting observation was that samples of wheat taken from the field with high *Fusarium* levels were contaminated with FB_1 (Mashinini and Dutton, 2006).

In Mediterranean regions, Serrano et al. (2012) studied the contents of mycotoxins in cereals and cereals products in different countries, including Tunisia. Forty-one samples (pasta, soup and grains) were collected in 2010, and FB_1 was detected in 2 wheat pasta and soup samples from Tunisia, while FB_2 was detected in 2 wheat grain samples. The maximum FB_1 value (184 μg/kg) was found in a wheat pasta sample.

Concerning the co-occurrence of mycotoxins, DON and/or NIV were present in wheat samples from South Africa and Tunisia besides FBs (Mashinini and Dutton, 2006; Serrano et al., 2012).

Within *Fusarium* species, only *F. verticillioides* was isolated from wheat samples collected from Zimbabwe, but an interesting observation was that this species had a much lower incidence in this cereal than in maize (Gamanya and Sibanda, 2001).

3. Pathosystem wheat-*Fusarium proliferatum*

Due to the increased number of reports about the occurrence of fumonisin and also the presence of *F. proliferatum* on wheat around the world, field pathologist and mycologist showed interest in understanding this pathosystem. Guo et al. (2016) reported that *F. proliferatum* strains originating from different host were able to infect wheat via seeds (systemic colonization), causing accumulation of fumonisin and BEA in kernels. However, the amounts of FB_1 in infected kernels were much lower than the levels commonly found in maize. A tight correlation between *F. proliferatum* DNA amount and FB_1 concentration in wheat kernels was observed. These results indicated that the mycotoxins were produced in kernels rather than being transported to kernels from the stem. In order to prove this hypothesis, the fumonisin and BEA contents in stems of wheat plants should be further analyzed. It is important to remark that the authors have not detected any symptom in the inoculated plants.

As *Fusarium* species, may be present on a substrate for long periods during which a_W may change, it is important to know both the optimal a_W range for growth and that permitting sub-optimal growth. Under field conditions, temperature fluctuations, changes in relative humidity, and rainfall all influence colonization of developing grain by *F. proliferatum*. Cendoya et al. (2014a) compared for the first time the impact of both a_W (0.995–0.90) and temperature (15, 25 and 30 °C) on growth and fumonisin production on a wheat-based medium by 3 *F. proliferatum* strains isolated from wheat in Argentina. All the conditions evaluated were those which usually occurred during wheat grain development, especially at milk and dough stages in the field. Maximum growth rates were obtained at the highest a_W (0.995) and 30 °C, with growth decreasing as the a_W of the medium was reduced. Maximum amounts of total fumonisins (FB_1, FB_2 and FB_3) were produced at 0.99 a_W and 25 °C for 2 strains, and at 15 °C and 0.98 a_W for the third strain. It was also observed that 2 out of 3 *F. proliferatum* evaluated strains produced almost exclusively FB_2 and negligible amounts of FB_1 on a wheat based-media at 25 °C. This pattern of production, more FB_2 than FB_1, has been observed previously on naturally contaminated wheat grain in Argentina (Palacios et al., 2011). The other strain showed a normal fumonisin profile ($FB_1 > FB_2 > FB_3$) but the production was higher at 15 °C in comparison to the other temperatures evaluated. The results indicate that the production of different types of fumonisin by *F. proliferatum* seems to be favoured by different temperatures. Also, it has been established that this species seems better adapted to low temperatures and may produce greater amounts of FB_1 than *F. verticillioides* at these temperatures (Ryu et al., 1999). This is important if we consider that wheat is a winter crop and the optimal temperature for cultivation of this cereal ranged between 10 and 24 °C. Moreover, recently Cendoya et al. (2017) compared the impact of a_W and temperature on growth, fumonisin production, and *FUM8* and *FUM19* gene expression on a wheat-based medium, for three strains of *F. proliferatum* isolated from wheat in Argentina, and found out that although no fumonisin was detected after five days of incubation at 15 °C in the absence of osmotic stress, no inhibition of the expression of *FUM8* and *FUM19* genes compared to the conditions at 25 °C ($a_W = 1$) was highlighted. The authors suggested that one possible explanation could be that the biochemical process of fumonisin biosynthesis is slower at this temperature, leading to a delay in the accumulation of fumonisins in wheat–based media and consequently to the lack of detectable levels of the toxin after five days of incubation. Indeed, significant amounts of fumonisins were quantified in wheat-based media inoculated by the same set of *F. proliferatum* strains and incubated for 28 days at 15 °C (Cendoya et al., 2014a). It is well known that unlike *F. verticillioides, F. proliferatum* colonizes a wide range of host plants other than maize, such as wheat and barley among others, with no host preference. A phylogenetic study of a large number of *F. proliferatum* strains from wheat has revealed a high genetic variability and has also shown that the ability to produce fumonisins was widely distributed indicating that this species can represent a health risk similar to *F. verticillioides*. This high genetic diversity can be explained due to sexual reproduction which will be favoured by the presence of both mating alleles (MAT-1 and MAT-2) in a ratio close to 1:1 in the population analyzed (Palacios et al., 2015).

4. Management of *Fusarium* species fumonisin producers in wheat grains

As fumonisins in wheat have been described in the recent past years, there is limited data about how to manage this problem. The presence of *F. verticillioides* and *F. proliferatum* in wheat kernels implies that fumonisins could be present on wheat. Presuming that the fungicides used for FHB management are active against all *Fusarium* species, they could be effective against the accumulation of various *Fusarium* mycotoxins by reducing fungal presence and activity in wheat spikes. In Croatia, Ivic et al. (2009) conducted a study to evaluate the efficacy of 9 commercial products with different fungicides combination mainly based on triazole groups used to control *Fusarium* head blight severity. The researchers assumption was that these fungicides could also control the fumonisin producers *Fusarium* species and fumonisin accumulation. It was observed that all the fungicides combinations were able to reduce Fusarium head blight severity in comparison with untreated plots but were unable to reduce fumonisin B_1 content. Another study was carried out by Sumalan et al. (2013) who evaluated the effect of some essential oil as inhibitory of *Fusarium* growth and fumonisin accumulation on natural contaminated wheat samples. As a result, all essential oils showed inhibitory effect on fungal contamination of wheat grains, and this ability was dose-dependent. The highest inhibitory effect on *Fusarium* and *Aspergillus* fungi was recorded after 5 days of treatment. The best control of fumonisin production, expressed by a reduction over 90% related to the control, was observed for all levels of *Cinnamomum zeylanicum*, *Mentha piperita*, and *Thymus vulgaris* essential oils.

5. Risk analysis

Advance in mycotoxin determination have shown that in addition to parent mycotoxins, cereals also contain mycotoxin conjugates. These compounds are commonly known as “modified mycotoxins”, since they originally escape routine methods on account of their different chemical properties compared to parent forms (Rychlik et al., 2014). Mycotoxin burden in cereals could be significantly higher if the “modified” forms are considered. Thus, Dall’Asta and Battilani (2016) concluded that modified FBs should be included in the monitoring plans to have an overview of the possible contribution to human exposure.

Szabó-Fodor et al. (2016) studied the hidden FB_1 in maize and wheat, which were inoculated with *F. verticillioides* (MRC 826). The study compared a routine extraction procedure with *in vitro* digestion sample pre-treatment. All samples showed a higher content of FB_1 after digestion, compared to the free fumonisin obtained only by extraction. The percentage of the hidden form was 38.6% (±18.5) in maize and 28.3% (±17.8) in wheat, expressed as the proportion of total FB_1. These results indicate that the toxin exposure of the experimental animals determined by the routine fumonisin analysis was underestimated, generally by 40%, as bioaccessibility was not taken into consideration. This is crucial in interpretation (and maybe in re-evaluation) of the results obtained from animal experiments. Conventional analytical methods used for the analysis of fumonisin content in foods and feeds fail to take into account the mycotoxin content bound to the matrix, which is otherwise bio-accessible and can be absorbed from the gastrointestinal tract (Versantvoort et al., 2005). Moreover, underestimation of fumonisin content using routine analytical methods can affect animal experiments using cereals contaminated by fungal culture.

Bakker et al. (2003) estimated the intake of FB_1 by the population in the Netherlands in an exposure assessment using data on concentrations of FB_1 in different food products combined with the consumption rate of these products. Wheat was found to be the main contributor (73%) to the total FB_1 intake. Although, the 99th percentile of the lifelong average intake (0.38 μg/kg bw/day as estimated in a worst-case scenario) was considerably lower than the tolerable daily intake set by World Health Organization (WHO) (2001) (2 μg/kg bw/day), the current dietary intake of FB_1 in the Netherlands was concluded as posing no appreciable health risk. Thus, Bakker et al. (2003) concluded that the intake of fumonisins occurs mainly via wheat and wheat products. So, although the concentration of FB_1 in maize was higher than that in wheat, it appears that wheat and not maize was the main source of fumonisin intake in the Netherlands.

The simultaneous exposure to more than one toxin is of concern and requires more study. Synergistic effects may explain why animals sometimes respond negatively to mycotoxin levels much lower than those reported in scientific studies as able to cause mycotoxicoses. In the study conducted by Rodrigues and Naehrer (2012) from the 7049 analyzed samples, only 19% of them tested negative for the presence of the five analyzed mycotoxins. 33%

showed the presence of one of them and two or more of the tested mycotoxins were present in 48% of the commodities.

Health risks associated with the consumption of cereal products, contaminated with *Fusarium* mycotoxins are worldwide recognized. Trichothecenes, zearalenone and fumonisins are distributed widely in cereals, including wheat. The problem of co-occurrence of *Fusarium* mycotoxins in wheat is a recurring feature, raising the question of possible interactions, synergistic or antagonistic actions in the manifestation of toxicity, which can be the future in this field of research (Stanciu et al., 2015).

Although there is currently no legislation about fumonisin levels in wheat and wheat-based products, the Joint FAO/WHO Expert Committee on Food Additives have indicate the need to analyze fumonisins in food samples using analytical methods with appropriate sensitivity to reduce the uncertainty in the exposure assessment for wheat. Also the Committee highlight the need to carryout studies on bound mycotoxins, specially the fate of these toxins during processing and their bioavailability for consumers (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2017).

6. Conclusions and future perspectives

- The present review showed the worldwide occurrence of fumonisin in wheat and wheat products.
- Evidences showed that *F. proliferatum* could be one of the main species responsible for fumonisin contamination on wheat around the world.
- The ecophysiology of *F. proliferatum* needs to be considered in a climate change scenario.
- In some studies, FB_2 was detected in higher levels than FB_1. Also, some *F. proliferatum* strains were able to produce more FB_2 than FB_1.
- The wheat-based products will be the main source of fumonisins intake in countries were wheat based foods are the main staple foods.
- Although low levels of fumonisins commonly occur on wheat they may remain undetected as long as mycotoxin monitoring programs for wheat do not include these mycotoxins.
- The low levels of fumonisins detected around the world could be the consequence of the routinary methodology used for toxin detection that failed to consider the fumonisin bound to the matrix (hidden fumonisin) which is otherwise bio accessible and can be absorbed by the gastrointestinal tract. The percentage of hidden fumonisins in wheat has been estimated as 28.3 expressed as the proportion of total FB_1.
- At present there is limited data on management of fumonisin accumulation on wheat. More studies are needed to understand the possible interactions among the *Fusarium* species in wheat.
- The co-occurrence of fumonisins in wheat with other mycotoxins such DON, ZEA need to be considered due the possible synergist effects of mycotoxins.

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