

## **FUSARIUM POAE AND MYCOTOXINS: POTENTIAL RISK FOR CONSUMERS**

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**Resumen:** *Fusarium poae* y micotoxinas: el riesgo potencial para los consumidores. La fusariosis de la espiga es una enfermedad importante que afecta a los granos de los cereales. *Fusarium graminearum* es el principal agente causal de esta enfermedad en todo el mundo, pero algunos investigadores han documentado un incremento en importancia de *Fusarium poae*. Además, la presencia de *F. poae* está acompañada de la posible producción de micotoxinas, siendo capaz de producir tricotecenos de tipo A como diacetoxiscirpenol, monoacetoxiscirpenol, scirpentriol, toxina HT-2, toxina T-2 y neosolaniol, así como tricotecenos del tipo B como nivalenol y fusarenona-X. Fuera del grupo de los tricotecenos, *F. poae* se ha reportado como productor de eniatinas, beauvericina y moniliformina. Dado que *F. poae* puede estar presente en los granos de cereales utilizados para la alimentación, el objetivo de esta revisión es reconocer la importancia del riesgo existente por la posible presencia de micotoxinas producidas por *F. poae* para los consumidores humanos y animales, mediante una abreviada descripción de métodos que permitan determinar la presencia de micotoxinas y analizar los diferentes efectos causados por la exposición a estas micotoxinas.

**Palabras clave:** *Fusarium poae*, métodos, micotoxinas, efectos.

**Abstract:** *Fusarium head blight* is an important disease affecting cereal grains. *Fusarium graminearum* is the major causal agent of this disease around the world, but some researchers have documented the increased importance of *F. poae*. Moreover, *F. poae* presence may be accompanied of its mycotoxins production, being able to produce trichothecenes of type A diacetoxyscirpenol, monoacetoxyscirpenol, scirpentriol, HT-2 toxin, T-2 toxin and neosolaniol, as well as the type B nivalenol and fusarenone-X. Outside the trichothecenes group, *F. poae* has been reported to produce enniatins, beauvericin and moniliformin. Due to *F. poae* may be present in cereal grains used for food and processed products, the aims of this review is to recognize the importance of the hazard effects of the *F. poae* mycotoxins on animal and human consumers by a short description of the methods that allow determining the mycotoxin presence and analyse the different effects caused by the mycotoxin exposure.

**Key words:** *Fusarium poae*, methods, mycotoxins, effects.

## **INTRODUCTION**

*Fusarium head blight* (FHB), also known as scab, is an economically devastating fungal disease of small-grain cereals such as wheat, barley and

oat (Kulik *et al.*, 2007). *Fusarium graminearum* is the major causal agent of this disease in many areas of the world, while in Europe other species such as *F. culmorum*, *F. avenaceum* and *F. poae* have been found frequently (Nicholson *et al.*, 2003). Several researches have documented the increased importance of *F. poae* in some countries of the world like Argentina, France and Poland (Logrieco *et al.*, 2002a; Ios *et al.*, 2004; González *et al.*, 2008; Stenglein, 2009). Moreover, *F. poae* has been considered a major *Fusarium* component in England, Hungary, Ireland, Poland, Slovakia, Scotland and Wales (Logrieco *et al.*, 2002a; Lukanowski & Sadowski 2002; Roháček & Hudec, 2005; Xu *et al.*, 2005).

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This species was commonly isolated from glumes or grains affected by ear blight symptoms but some studies have demonstrated the presence of *F. poae* in asymptotically contaminated grains (Barreto *et al.*, 2004; Kulik & Jestoi, 2009; Stenglein *et al.*, 2012).

In the history of the humanity, several outbreaks related to the consumption of cereals contaminated with toxins have been experienced. In 1932, Russian scientists described a mysterious disease that caused nausea, vomiting, and diarrhea. In more chronic cases, the disease caused lesions of the gastrointestinal tract which were often fatal. This disease was called “alimentary toxic aleukia” and was associated with the presence of toxins in grains produced by *Fusarium poae* and *F. sporotrichioides* (Desjardins, 2006). A similar outbreak occurred in Japan in 1933 and was associated with the consumption of wheat, barley and other grains contaminated with *Fusarium* (Desjardins, 2006).

*Fusarium poae* infections on grains cause a serious problem due to its capacity to produce mycotoxins. Mycotoxins are secondary metabolites produced by filamentous fungi that in small concentrations can evoke an acute or chronic disease in vertebrate animals when introduced via a natural route (Gravesen *et al.*, 1994). This fungus may be present in food and processed products because the mycotoxins can be stable under normal processing conditions, causing concrete damages in consumers due to its neurotoxic, carcinogenic and cytotoxic activities (Gutleb *et al.*, 2002; Meca *et al.*, 2010a). Moreover, some researches have demonstrated that the type and amount of toxins produced vary substantially depending on the isolates and substrates (Jestoi *et al.*, 2008; Vogelgsang *et al.*, 2008b).

In conclusion, the presence of the fungus *Fusarium poae* in grains can cause a serious risk to consumers of foods derived from these grains accompanied by the consumption of mycotoxins with different negative effects on animal and human health.

## METHODS FOR THE ANALYSIS OF MYCOTOXINS

There are some methods that allow detecting and quantifying some mycotoxins. Nowadays, the

usual methods for chemotyping *Fusarium* isolates and for substrate mycotoxin analyses are high performance liquid chromatography (HPLC) or gas chromatography-mass spectroscopy (GS-MS) which allow analyzing and quantifying toxins present in diverse substrates. HPLC involves various methods with different normal-phase or reversed-phase columns, distinctive elution mixtures and gradients, detection methods, sample preparation and purification procedures where the mycotoxins are characterized by the retention time (Rahmani *et al.*, 2009).

GS-MS is used for volatile mycotoxins at the column temperature that can be converted into volatile derivatives. By using MS, it can ionize molecules identified and sort them according to their mass-to-charge ratio (Rahmani *et al.*, 2009).

Enzyme-linked immunosorbent assays (ELISA) have been advocated for using as mycotoxin screening tests (Stratton *et al.*, 1993). The technique consists on the antigenic-antibody reaction which develops colour by adding enzyme substrates where the intensity of the solution colour is inversely proportional to the concentration of mycotoxin in the sample (Maragos *et al.*, 2001).

There are some methods based in membrane based immunoassay. One of them is the lateral flow test or strip test. It consists of a sample pad, a conjugate pad, a membrane, an absorbent pad and an adhesive backing. A sample extract is added into the sample pad and a positive result will show no visible line in the test zone (Zheng *et al.*, 2006).

Moreover, methods based on fluorometric assays have been described. For example, the immunoaffinity column clean-up technique, which uses immunoaffinity columns (IAC) with anti-mycotoxin antibody, immobilized into a solid support. The sample is added to an IAC containing specific antibodies to a specific mycotoxin. Then, by adding a solvent such as methanol, the mycotoxin is removed from IAC and the final solution is measured by a fluorometer (Zheng *et al.*, 2006).

Fluorescence polarization immunoassay (FP) is based on the competition between mycotoxin and a mycotoxin-fluorescein tracer for a mycotoxin specific antibody. Positive samples show lesser antibody bound to the tracer reducing polarization which is a measure of the orientation of the fluorescence emission from horizontal and vertical directions (Zheng *et al.*, 2006).

A new technique to detect mycotoxins is the Matrix-assisted laser/desorption ionization time of flight mass spectrometry (MALDI-TOF MS). This technique is based on the utilization of a matrix, which absorbs the energy emitted by the sample pulsed by a laser. The matrix is vaporized and the intact sample is analyzed into vapour phase, where the matrix exchanges ions with the analyte allowing the formation of charged analyte molecules. The resulting ions are detected by an analyzer. The most simple is TOF mass analyzer, where low mass ions arrive at the detector faster than high mass ions, considering that the mass of the generated ion corresponds to the mass of the analyte (Fuchs *et al.*, 2010). MALDI-TOF MS has the ability to analyze small samples and obtain results in few minutes. It offers a sensitive and rapid analysis at femtomole or attomole at organic or biomolecular levels without the destruction of the samples (Elosta *et al.*, 2007).

The discovery of specific restriction endonucleases made the isolation and synthesis *in vitro* of particular molecular fragments of the DNA possible (Mullis *et al.*, 1986). In the last years, several researches have used PCR assays using specific primers to amplify genes involved in the biosynthesis of toxins to detect and screen them. Moreover, real time PCR assay have been developed not only to detect but to quantify mycotoxin genotypes. This technique is based on the 5' nuclease activity of *Taq* polymerase and the use of probes in the extension phase that emits fluorescence, which is detected by a sequence fluorescence detector. The measured fluorescence allows following the amplification in real time (Heid *et al.*, 1996).

In conclusion, there are a lot of tools that allow screening and quantifying mycotoxins. In general, the use of techniques depends on the objectives to follow as well as the budget to invest in each tool.

### ***Fusarium poae* Mycotoxins**

*Fusarium poae* (Peck) Wollenweber has been reported to produce trichothecenes, a large group of sesquiterpenes epoxides whose chemical features allow designing them into four subclasses or types. *Fusarium* species can produce two of them (type A and type B trichothecenes) that can be characterized by the presence (type A trichothecenes) or absence

(type B trichothecenes) of a keto group at the C-8 position (Desjardins, 2006; Gutleb *et al.*, 2002; Jurado *et al.*, 2005). *F. poae* has been reported to produce the type A trichothecenes diacetoxyscirpenol (DAS), monoacetoxyscirpenol (MAS), scirpentriol (STO), HT-2 toxin, T-2 toxin and neosolaniol (NEO), as well as the type B trichothecenes nivalenol (NIV) and fusarenone-X (FX). Although *F. poae* has been reported to produce deoxynivalenol (DON) (Salas *et al.*, 1999), no recent investigations have confirmed this capacity.

Outside the trichothecenes, *F. poae* has been reported to produce enniatins (ENN), beauvericin (BEA) and moniliformin (MON) (Jestoi *et al.*, 2008; Thrane *et al.*, 2004).

#### *Diacetoxyscirpenol (DAS) toxin*

Diacetoxyscirpenol (C<sub>19</sub>H<sub>26</sub>O<sub>7</sub>), also named anguidine, is a type of A trichothecene mycotoxin produced by several *Fusarium* species (Omurtag *et al.*, 2007), including *F. poae*.

Numerous studies have been conducted to investigate the major effects of this compound. Lautraite *et al.* (1997) evaluated the response of granulo-monocystic progenitors from human umbilical cord blood, and rat bone marrow in the presence of DAS. They concluded that the human haematopoietic system appears to be extremely sensitive to DAS (Lautraite *et al.*, 1997). Moreover, Ayril *et al.* (1992) examined *in vitro* effects of DAS on some functions of murine peritoneal macrophages and determined, by using some different concentrations of DAS and DON, that DAS suppressed peritoneal macrophage functions *in vitro* (Ayril *et al.*, 1992). In 1997, some researches demonstrated that the toxicity of DAS is due to the apoptotic cell death, as well as cell cycle arrest in human Jurkat T cells (Jun *et al.*, 2007).

The capacity of several *Fusarium* species to produce DAS in different substrates has been evaluated by using different available assays. A total of 85 samples of commercially available cereal and pulse products in Turkey collected from markets and street bazaars were analyzed by using HPLC and all of the samples were DAS free. All of them were reconfirmed by GC-MS, and showed the same results (Omurtag *et al.*, 2007). Lincy *et al.* (2008) determined the presence of toxigenic fungi and the quantification of trichothecenes levels in

food and feed materials from India. Initial screening using thin layer chromatography (TLC) showed four samples of sorghum positive for DAS that was later confirmed by HPLC assay (Lincy *et al.*, 2008). Recently, a GC-MS method for the simultaneous determination of some mycotoxins has been evaluated in 44 samples of barley from the 2007 harvest in Navarra, Spain. The results indicated the presence of DAS in 4.5% of the samples (Ibañez-Vea *et al.*, 2011). In our species of interest, Liu *et al.* (1998) verified the mycotoxin production on rice and two liquid media, in 22 Norwegian and two Polish isolates of *F. poae* by analyzing them with GS-MS. Eighty three percent of them were found to be producers of DAS, although in low quantities for most of the isolates (Ibañez-Vea *et al.*, 2011). More studies are necessary to study the capacity of *F. poae* to produce DAS, as well as their occurrence and quantification to know the probability to find it in cereals and food, and the hazard of the consumption of this mycotoxin.

All of these studies have demonstrated the presence of this important mycotoxin in different substrates and the consequences that it brings to human and animal consumers. Despite all, there is no regulation governing the consumption of food contaminated with DAS.

#### *Scirpentriol (SCR) toxin*

Scirpentriol (C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>) is a type of A trichothecene, that can be produced by *Fusarium poae*.

Ademoyero & Hamilton (1991a) evaluated the effects of SCR and other mycotoxins in male broiler chickens which were fed with different doses of mycotoxins for 21 days after hatching. The results showed that mouth lesions caused by each mycotoxin were dose-dependent and the most affected sites by SCR were angles, upper beak, lower beak and tongue. Moreover, a better description of the toxicity of dietary SCR in young broiler chickens was developed. Dietary SCR was given to four groups of 10 days old male broiler chickens for 3 weeks and the effects were evaluated depending on the doses. The minimum effective dose (MED) for reducing growth rate was 4 µg/g and the same dose increased serum alkaline phosphatase and relative weight of the gizzard. The relative sizes of the spleen and pancreas were not altered. Moreover, the enzymes alkaline phosphatase (AP), lactic

dehydrogenase (LDH), aspartase aminotransferase (AST), total protein, albumin, Cl<sup>-</sup>, Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>++</sup>, PO<sub>4</sub><sup>3-</sup>, uric acid and cholesterol showed variations in activity depending on dose (4 µg/g to 32 µg/g) (Ademoyero & Hamilton, 1991b).

Salas *et al.* (1999) tested the ability of some *Fusarium* species to produce mycotoxins in barley and by using GC-MS could confirm the capacity of *F. poae* isolates to produce SCR. According to this and after Torp & Nirenberg (2004) separated some previously determined species as *F. poae* to a related species called *F. langsethiae*; Thrane *et al.* (2004) compiled individual results of chemical analysis profiles of different laboratories and confirmed the capacity of *F. poae* to produce SCR.

Schollenberger *et al.* (2005) screened 219 food samples commercially available such as food stores, health food stores and gluten-free food collected in 2000 and 2001. A GC-MS was improved to determine 13 mycotoxins including SCR. The results showed that this toxin is absent in samples of cereal-based including gluten-free foods, but it is present in samples of vegetables and fruits (Schollenberger *et al.*, 2005). The presence of SCR and another 15 mycotoxins have been evaluated by using HPLC with fluorescence and UV-detection in 220 different samples such as cereals, corn plants, corn silages and non-cereal feedstuffs randomly collected in Germany. A high degree of SCR contamination was found in the first type of samples while that in non-cereal feedstuffs only detected 1-3% of incidence in 95 samples tested (Schollenberger *et al.*, 2006). Moreover, these authors evaluated some toxins in soy foods commercially available in Southwest Germany, and they found the presence of SCR in at least one sample of 45 samples tested (Schollenberger *et al.*, 2007). Recently, three wheat cultivars of the *Triticum aestivum*, *T. spelta* and *T. durum* species were screened by using GC-MS and the presence of SCR was detected (Wiwart *et al.*, 2011). However, in maize samples from Nigeria this mycotoxin was not found (Bankole *et al.*, 2010).

Schollenberger *et al.* (2011) inoculated autoclaved oats with *Fusarium poae* and other species of this genera, and by using GC-MS they could determine that the quantity of SCR increased with the age of the *F. poae* cultures while other mycotoxins such as 4,15-diacetoxyscirpenol and 15-monoacetoxyscirpenol decreased.

There are a lot of researches about the occurrence of SCR in different substrates but so much work is necessary to study the causes of the consumption of grains contaminated with mycotoxins. Moreover, there is no legislation about a maximum content in foods and feeds.

#### *T-2 and HT-2 toxins*

The A trichothecenes T-2 ( $C_{24}H_{34}O_9$ ) and its deacetylated form known as HT-2 ( $C_{22}H_{32}O_8$ ) were found frequently in cereals. Some studies were made to evaluate the effects of these dangerous toxins in different animals. To probe the neurotoxic events of T-2, Chaudhary & Rao (2010) evaluated the comparative toxicity of percutaneous and subcutaneous exposure of T-2 toxin on brain oxidative damage in mice. They demonstrated that T-2 could cause damage in the brain through the depletion of hepatic glutathione, increased lipid peroxidation, alterations in the activity of antioxidant enzymes and oxidation of proteins. Moreover, T-2 and T-2 toxin combined with a low diet were evaluated in rat epiphyseal plates and metaphysic to determine possible pathogenic factors of an osteoarthropathy disease known as Kashin-Beck disease (KBD) (Yao *et al.*, 2010). The results confirmed that T-2 could induce chondrocytes necrosis which was aggravated by low nutrition. Tornyoos *et al.* (2011) evaluated the effects of T-2 toxin on feed consumption and sperm quality of rabbit bucks. They exposed animals to different doses for 73 days and demonstrated that adult male rabbits may tolerate low concentration of T-2 (0.1 mg/animal/day), but in high dosages (0.2 mg/animal/day) the toxin caused alterations in Leydig cells, and as the dosages increased to 0.2 mg, the animals had a marked feed refusal effect and showed proliferation and hyperplasia in the Leydig cells. Wu *et al.* (2011) evaluated the effects of T-2 on apoptosis of ovarian granulosa cells and the possibility that this toxin could be an inductor of apoptosis. The results yielded that the toxin induced inhibition of cellular proliferation and apoptosis in this kind of cells. These works demonstrated different effects of the exposure to these potent toxins.

Other effects of T-2 were evaluated in beer malt, where it is showed that the toxin interfered with the correct function of amylases in the stage of malting which caused serious problems in the quality of the

production of beer (Garda-Buffon *et al.*, 2010).

Some assays have been tested to screen T-2 and HT-2. In 2010, Wang *et al.* (2010) developed a polyclonal antibody with high affinity and specificity of T-2 to detect it in different cereals and feedstuff. The results were validated by HPLC in tandem MS (MS/MS) and they showed a good correlation. Moreover, a gel-based immunoassay has been developed as a visual qualitative test to screen T-2 and other mycotoxins only 15 minutes after the chromogenic substrate application (Basova *et al.*, 2010). A fast method was developed to detect HT-2 and T-2 toxins in cultures grown *in vitro* in oats with different extraction solvents, diverse extraction times and extract drying procedures using LC. The method proposed was able to detect T-2 and HT-2 toxin in cultures of *Fusarium langsethiae* grown on oat based media (Medina *et al.*, 2010). De Baere *et al.* (2011) examined the quantity of T-2, HT-2 and other trichothecenes in plasma and bile of chickens and pigs, by using liquid chromatography (LC) combined with electrospray ionization (ESI) tandem MS (LC-ESI-MS/MS) and could develop a quantitative and semiquantitative determination of these toxins in animal plasma and bile, respectively, due to the fact that there was not enough blank matrix in the bile to use in this study (De Baere *et al.*, 2011).

An interesting work related to the frequency of appearance was made by Sun *et al.* (2011) where they collected 40 air samples in one hen house feeder with more than five thousand layer chickens in Dalian, a marine climate city in the northeast of China. HPLC was used for the detection of T-2 and HT-2 and the results showed that HT-2 was higher than T-2 toxin, and some T-2 toxin could be decomposed to HT-2 toxin. Other researchers have evaluated the presence of these toxins in feed. This is the case of Vulić *et al.* (2011) who tested 50 commodities and feed in Croatia by using ELISA to screen T-2 and HT-2 toxins and were able to detect these toxins in 19 of 25 samples tested. Moreover, the content of T-2 and other mycotoxins were evaluated in 75 samples of bread and pasta from bakeries and supermarkets in Spain. A GC-MS was used to screen these toxins and it determined the presence of T-2 in 2.7% of bread and 9.3% of pasta samples (González-Osnaya *et al.*, 2011). Moreover, cereals sold in markets in South Korea were tested by using HPLC to screen the presence

of T-2 and HT-2 toxins. The results showed that 13 of 25 samples tested were found to be contaminated with T-2 and HT-2 and 4 samples presented both mycotoxins (Kassim *et al.*, 2011). Recently, an analytical method using two solid phase extractions and ultra-high-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) to detect and quantify 14 mycotoxins (patulin, deoxynivalenol, aflatoxins B1, B2, G1, G2, M1, T-2 toxin, HT-2 toxin, zearalenone, fumonisins B1, B2, B3 and ochratoxin A) was developed. Twenty-seven domestic and imported wines in Japan were tested and no T-2 toxin and HT-2 toxin were found in none of the samples (Tamura *et al.*, 2012). Recently, a rapid competitive immunoassay has been developed for the simultaneous determination of the sum of T-2/HT-2 and DON in cereals and cereal-based products. It is based on the employment of a monoclonal antibody raised against HT-2 with cross reactivity to T-2 and a polyclonal antibody raised against DON, allowing the detection of type A and B trichothecenes. The technique showed the presence of T-2/HT-2 in oat, barley, baby food, breakfast cereal and wheat samples tested (4 µg/kg to 528 µg/kg). Moreover, the results showed correlation with LC-MS/MS and no false negatives or positives were found (Meneely *et al.*, 2012).

Several studies have determined the capacity of *Fusarium poae* to produce T-2 and HT-2 toxins (Thrane *et al.*, 2004; Vogelgsang *et al.*, 2008a) which represent a potential hazard to consumers, all which generate the need to develop and validate methods for the rapid and sensitive determination of the presence of this important pathogen and the probability to produce these hard toxins. Conversely, there is no available legislation about the maximum acceptable levels for T-2 and HT-2 in the world, but there is not doubt that these should be potential candidates for future legislation.

#### *Neosolaniol (NEO) toxin*

Other type of A trichothecene produced by *Fusarium poae* is neosolaniol (C<sub>19</sub>H<sub>26</sub>O<sub>8</sub>).

The effects of this toxin were evaluated in plants and animals which were exposed to NEO in different concentrations. In plants, this toxin showed cytotoxic effects when they were exposed to high concentrations (5000 ng/g) while in animals, it caused the death of all the birds tested within

mean times of 7 days or less with different levels of NEO ranging from 310 to 2060 ng/g (Lamprecht *et al.*, 1989).

In 2008, several *Fusarium poae* isolates were investigated for their capacity to produce some toxins. First of all, rice was inoculated with three isolates of *F. poae* and by using LC-MS/MS, confirmed that *F. poae* isolates were able to produce NEO. Then, the same isolates were tested in wheat, rice, and oat grains and cracked maize kernels by using the latest method, and the presence of NEO with 21.8 mg/kg mean concentration was found (Vogelgsang *et al.*, 2008a). In contrast, Bankole *et al.* (2010) analyzed 32 maize samples destined to human consumption in Nigeria, by using GC-MS, and no NEO was present. Recently, the presence of some toxins, including NEO, was tested in 19 silage maize. They could not found these toxins in the samples tested by using LC-MS/MS (Eckard *et al.*, 2011).

The finding and availability of new information will help to understand the biology and effects of NEO as well as the pathogens able to produce it such as *Fusarium poae*. NEO is another mycotoxin which lacks legislation.

#### *Nivalenol (NIV) toxin*

Nivalenol (C<sub>15</sub>H<sub>20</sub>O<sub>7</sub>) is one of the most studied types of B trichothecene mycotoxins that can be produced by *Fusarium poae*. NIV is known to be lymphotoxic inhibiting B and T cells (Forsell & Petska, 1985). Choi *et al.* (2000) demonstrated that NIV could inhibit total and antigen-specific IgE (antibody effectors in allergy) in serum in mice. Moreover, it was a problem in the cell proliferation and was able to induce the apoptosis in human promyelocytic leukaemia cell line HL60 (Nagashima *et al.*, 2006). The effect of this toxin was evaluated in the murine monocyte macrophage cell line which was exposed to NIV. The results determined that this toxin exhibited a stronger cytotoxic effect on the cell line tested, which could be ascribed to an acceleration of apoptotic pathway (Marzocco *et al.*, 2009).

Some researchers have evaluated the occurrence of NIV in different substrates. Sugiura *et al.* (1993) evaluated 13 wheat samples in Hokkaido, Japan and obtained 48 isolates of *F. poae*. By using GC-MS, the occurrence of NIV was determined and high quantities of these mycotoxins were found

in 12 of the total isolates tested. The authors suggested that this species was responsible for the natural wheat contamination with NIV. *In vitro* and *in vivo* mycotoxin production was evaluated in some different Finnish *Fusarium* species. The analysis of inoculated rice using MS determined that NIV was produced in high concentrations by *F. poae*. Its production was corroborated by analysis of artificially contaminated samples with *F. poae* isolates (Jestoi *et al.*, 2008). Vogelgsang *et al.* (2008b) investigated the ability of *F. poae* to produce NIV on rice kernels and determined the effect of different substrates and isolates on the type and amount of mycotoxins production. The results showed that NIV was synthesized in rice, but no NIV production was found in other substrates. In summary, the NIV production would depend on both the isolates and the substrates used (Vogelgsang *et al.*, 2008b).

A real time quantitative PCR method for *F. poae* was developed in order to determine if the presence of DNA of *F. poae* was correlated with NIV contents in Finnish barley, wheat and oat grains. *F. poae* isolates were found in all samples tested and high levels of NIV were found. A significant correlation between *F. poae* DNA and NIV was found considering this specie as the most NIV producer of *Fusarium* species (Yli-Mattila *et al.*, 2008).

Some genes linked in the *TRI* gene cluster are involved in the trichothecene biosynthetic pathway (Desjardins, 2006). The *tri7* and *tri13* genes are required for acetylation and oxygenation of the oxygen at C-4 to produce NIV and 4 acetyl nivalenol, respectively (Lee *et al.*, 2009). Some researchers have developed specific primers to screen the potential NIV production of *Fusarium* species. Ward *et al.* (2002) developed a primer set specific to detect NIV producer *F. graminearum* complex based on polymorphism on the *tri12* gene that play an important role in trichothecene biosynthesis. Later, Quarta *et al.* (2005) designed specific based primers on polymorphism on the *tri7* gene considered to be the sequences of *F. graminearum* described by Lee *et al.* (2001) and Ward *et al.* (2002). Moreover, in 2008 a specific primer set based on the *tri13* gene was developed to identify three different mycotoxin chemotypes and NIV producers of *F. graminearum* isolates (Wang *et al.*, 2008). Recently, Pasquali *et al.*

(2011) compared the three methods above cited and determined that these were not able to discriminate between different NIV producers of *F. poae* isolates. Recently, Dinolfo *et al.* (2012) developed a specific primer pair based on *tri7* gene that allows the detection of *F. poae* NIV producers.

NIV is a toxin whose effects and occurrence have been well studied. Moreover, several sets of primers have been developed to detect NIV producer of *Fusarium* species but despite the consequences of its consumption, there is not legislation about the limits of NIV.

#### *Fusarenon X (FUS-X) toxin*

The type B trichothecene Fusarenon X (C<sub>17</sub>H<sub>22</sub>O<sub>8</sub>) is a 4-acetylnivalenol produced by *Fusarium poae* (Thrane *et al.*, 2004). In order to investigate the effects of FUS-X mycotoxin, Miura *et al.* (1998) injected FUS-X intraperitoneally on mice and by analyzing the thymus and T-cells subpopulations, it was observed that FUS-X caused severe atrophy and disappearance of thymocytes in the thymic cortex. Moreover, CD<sub>4</sub><sup>+</sup> and CD<sub>8</sub><sup>+</sup> thymocytes were depleted by the exposure to FUS-X. In 2003, Poapolathep *et al.* (2003) evaluated the excretion and tissue distribution of H<sup>3</sup>-NIV and H<sup>3</sup>-FUS-X in mice. By analyzing the radioactivity, they could determine that FUS-X is more toxic than NIV due to the fact that FUS-X is easily absorbed by the gastrointestinal tract in comparison with NIV, followed by a rapid NIV to FUS-X conversion by the mice liver and kidney.

According to this result, Poapolathep *et al.* (2008) incubated FUS-X with liver and kidney postmitochondrial fractions, red blood cells and plasma of broilers and ducks. The results showed that the livers and kidneys of the ducks tested were capable of converting FUS-X in NIV in high amounts (98.95% and 94.32%, respectively) while the same organs tested in broiler chickens showed a FUS-X to NIV conversion in 70.12% and 94.39%, respectively (Poapolathep *et al.*, 2008).

In 2006, 220 samples of German cereals, cereal by-products, corn plants, corn silages and non-cereal feedstuffs were analyzed and a low degree of contamination was found for FUS-X in the first. In non-cereal feedstuffs FUS-X was not detected (Schollenberger *et al.*, 2006). More works were developed to screen some toxins, including FUS-X, but in these cases no production of this mycotoxin

was detected (Müller *et al.*, 1997; Monbaliu *et al.*, 2010; Skrbic *et al.*, 2011). Recently, a validated method for simultaneous determination of eight trichothecenes was tested in 44 barley samples collected in Navarra, Spain. By using GC-MS analysis they found only one sample contaminated with FUS-X (Ibañez-Vea *et al.*, 2011). Major works are needed to understand the biology and effects of this acetylated toxin.

#### *Enniatin (ENN) toxin*

Outside trichothecenes, *Fusarium poae* is able to produce enniatins and this was confirmed by Thrane *et al.* (2004), who detected it at trace levels in some of the isolates tested. The ENN (C<sub>33</sub>H<sub>57</sub>N<sub>3</sub>O<sub>9</sub>) contains three residues of  $\alpha$ -hydroxyisovaleric acid alternating with three N-methylated branched chained amino acids (Desjardins, 2006).

Different studies have been developed to analyze the effects of ENN and some different kinds of this, such as ENN A, A1, B, B1, B2, B3, B4, J3 among others. Ivanova *et al.* (2006) purified A, A1, B, B1 B2 and B3 ENN from *Fusarium avenaceum* rice cultures and their toxicity were tested in well-known cell lines of human origin. By using the BrdU and Alamar Blue assays, it was determined that the toxicity of ENN is similar to the one of deoxynivalenol (trichothecene with strong effects in the cell) in one of the two cell lines tested. Moreover, ENN B was tested in V79 cells which are lung fibroblasts from male Chinese hamster cells, and the results determined that this toxin was able to increase in mutation rates and produce genotoxicity effects (Föllmann *et al.*, 2009). What is more, the effects of ENN were evaluated on mitochondrial functions in isolated mitochondria and in intact cells and the results indicated that the ENN mycotoxins target the mitochondrion and the homeostasis of potassium ions (Tonshin *et al.*, 2010). Recently, the cytotoxicity of ENN A, A1, A2, B, B1, B4 and J3 were compared in three tumour cells such as the human epithelial colorectal adenocarcinoma (Caco-2), the human colon carcinoma (HT-29), and the human liver carcinoma (Hep-G2) and the results showed that the ENN can exert cytotoxic cell effects (Meca *et al.*, 2011).

The antifungal effect of ENN was studied by using fractions of purified ENN of *Fusarium tricinctum* against other fungi such as *F.*

*verticillioides*, *F. sporotrichioides*, *F. oxysporum*, *F. poae*, *F. tricinctum*, *F. proliferatum*, *Beauveria bassiana*, *Trichoderma harzianum*, *Aspergillus flavus*, *A. parasiticus*, *A. fumigatus*, *A. ochraceus* and *Penicillium expansum* and the results showed that ENN B promoted the inhibition of some genera tested while ENN B1, A and A1 were non-toxic on the isolates proved (Meca *et al.*, 2010a).

In 2008, a fast method for the detection of ENN A, A1, B and B1 was developed to screen fresh and ensiled maize. By using HPLC without using solid-phase extraction cleanup procedures, the presences of ENN were determined and the prevalence of ENN B was demonstrated to be stable during ensiling of maize (Sorensen *et al.*, 2008). Rasmussen *et al.* (2010) arrived at the same conclusion when they analyzed 27 maize silage samples.

Finnish egg samples collected in 2004-2005 were evaluated to study the presence and contamination levels of ENN and beauvericin. The results indicated that ENN B and ENN B1 are very common in Finnish eggs while ENN A and ENN A1 were not found in any samples tested (Jestoi *et al.*, 2009).

The presences of different ENN have been screened in cereals available in supermarkets in Spain by using LC with diode array detector (DAD). High incidence of ENN, especially ENN A1, was found in corn, wheat and barley (Meca *et al.*, 2010b). According to this, Mahnine *et al.* (2011) found the prevalence of ENN A1 in breakfast cereals and infant cereals from Morocco.

Kulik *et al.* (2007) developed a specific primer based on an *esn1* gene encoding multifunctional enzyme ENN synthetase for the detection of potential ENN-producing FHB species such as *F. poae*. Recently, a specific genotype probe was developed on the basis of *esn1* gene to detect ENN levels in asymptomatic wheat grain samples by using real time PCR. The results demonstrated that this assay would be a tool to detect *F. poae* ENN genotypes in the grains (Kulik *et al.*, 2011). These studies showed genotyping advances that allow the detection of potential ENN producing *Fusarium* isolates in a short time.

The behaviour of ENN has been extensively studied and several tools are available to analyze its presence in different substrates. However there is no regulation to control the ENN presence in foods.

*Beauvericin (BEA) toxin*

The capacity of *Fusarium poae* to produce beauvericin has been confirmed by several studies. Beauvericin (C<sub>45</sub>H<sub>57</sub>N<sub>3</sub>O<sub>9</sub>) consists of three residues of  $\alpha$ -hydroxyisovaleric acid alternating with three N-methylated phenylalanine (Desjardins, 2006).

Wu *et al.* (2002) examined the ion mechanisms by which BEA interacts with ion channels on NG 108-15 neuronal cells. The results showed that BEA inhibited the L-type voltage dependent Ca<sup>2+</sup> in the cell lines used (Wu *et al.*, 2002). In 2003, by using the Trypan Blue assays, Caló *et al.* (2004) evaluated the BEA cytotoxic effects on mammalian cells. Two cell lines, the monocytic lymphoma cells U-937 and the promyelocytic leukaemia cells HL-60 were used. The results showed that cell lines declined in viability after an exposure time of 24 hours confirming their cytotoxic effects (Caló *et al.*, 2004). Turkey peripheral blood lymphocyte was exposed to some mycotoxins such as BEA. After 72 hours, a decrease in cell proliferation was observed. Moreover, internucleosomal DNA fragmentation and morphological features characteristic of apoptosis were seen, suggesting that BEA may affect immune functions by suppression proliferation and by inducing apoptosis of lymphocytes (Dombrink-Kurtzman, 2003). BEA is known to have ionophoric properties. To study this, Kouri *et al.* (2003) evaluated channel-forming activity of BEA in ventricular myocytes and synthetic membranes and observed that BEA formed cation channels in lipid membranes which could affect the ionic homeostasis (Kouri *et al.*, 2003).

*Fusarium* species were tested for having the capacity to produce BEA. The analysis was carried by high performance thin layer chromatography (HPTLC) and HPLC, and the results showed that BEA is produced by some species such as *F. poae* (Logrieco *et al.*, 1998). Logrieco *et al.* (2002b) isolated some *Fusarium* species in 13 wheat samples affected by FHB and determined the production of some mycotoxins of 773 isolates obtained, within which 2% of the total were *F. poae*. One of the *F. poae* isolates was tested to produce BEA by using HPLC and the result was positive for this toxin (9.4  $\mu$ g/g). Norwegian oats, barley and wheat were analyzed by LS-MS and BEA was found in 73 of the 228 samples analyzed, finding the highest concentrations of BEA in oat samples (120000  $\mu$ g/g). The regression models showed that

the probability of detecting BEA was significant related to the presence of *F. poae* (Uhlig *et al.*, 2006).

In 2007, *Fusarium poae* isolates were inoculated on maize ear samples collected in 1998 and 1999 in Poland. By using HPLC-MS, BEA and other mycotoxins were screened and the results showed that 18 of 27 samples tested were able to produce BEA. All of that confirmed the capacity of this species to produce this toxin (Chelkowski *et al.*, 2007).

Kokkonen *et al.* (2010) evaluated seven different *Fusarium* isolates such as *F. langsethiae*, *F. sporotrichioides*, *F. poae*, *F. avenaceum*, *F. tricinctum*, *F. graminearum* and *F. culmorum* frequently found in Finland. They were cultivated on a grain mixture and exposed under different environmental conditions. The production of BEA was analyzed by LC-MS/MS, and concluded that it was the only toxin able to be produced by *F. poae*.

The production of some mycotoxins in 81 *Fusarium poae* isolated from durum wheat kernels were analyzed and the results showed, using HPLC, that most of the isolates tested had the ability to produce this mycotoxin (Somma *et al.*, 2010).

Recently, 68 samples of breakfast cereals and infant cereals were collected in supermarkets and pharmacies in Morocco. All samples were tested by BEA and it was present in four of the total samples: two samples of muesli and two samples of infant cereals. All of these results were confirmed by using LC-MS/MS (Mahnine *et al.*, 2011). There are some works that show the presence and effects of BEA in some samples like food, wheat, oat and barley among others. Despite all, this mycotoxin does not have a consumption regulation as the others.

*Moniliformin (MON) toxin*

The capacity of *Fusarium poae* to produce MON have been cited only by Jestoi *et al.* (2008) whose work shows the presence of MON in one *F. poae* isolate tested.

MON (C<sub>4</sub>H<sub>2</sub>O<sub>3</sub>) is a high acute toxic mycotoxin. Its structure is characterized as the sodium or potassium salt of 3-hydroxycyclobut-3-ene-1, 2-dione (Chung *et al.*, 2005).

The effects of the exposure to this mycotoxin have been widely studied. The genotoxic effects of MON have been studied in bacterial tests and in micronucleus and chromosomal aberration assays

with primary rat hepatocytes (Knasmüller *et al.*, 1997). The cell lines exposure to MON showed strong effect on chromosomal aberration, deletion of both the chromosome and chromatid type and the presence of dicentric and ring chromosomes were observed (Knasmüller *et al.*, 1997). In 2005, Javed *et al.* (2005) compared pathologic changes in broiler chicks which had been fed with food contaminated with fumonisin and MON. The results showed that MON produces ascites, but all the characteristics and severity of lesions were dose, toxin and age dependent (Javed *et al.*, 2005). The electromechanical and electrophysiological effects of MON and MON combined with ENN and BEA were evaluated on ventricular myocytes, Caco-2-cells and in papillary muscles and terminal ilea of the guinea pig. Moreover, the influence of MON on cell homeostasis in absence or presence of ENN and BEA was also studied (Kamyar *et al.*, 2006). The results showed that MON does not change rates of activity or cardiac action potentials. This mycotoxin had no effect on intracellular concentrations of ions and did not affect pH. Reduced contractility in papillary muscle, terminal ileum, the aorta and the venous artery has been observed. Moreover, there is no synergistic relationship between MON and other metabolites tested, and between BEA and ENN (Kamyar *et al.*, 2006). In 2008, Sharma *et al.* (2008) investigated clinical signs, growth response, serum biochemical changes and cell-mediated immune response in chicks fed with some mycotoxins such as MON. A total of 105 birds fed with MON showed 20% of mortality. Moreover, all the blood components analyzed like serum aspartate transaminase (AST), alanine transaminase (ALT), total serum proteins (TSP), albumin, cholesterol and creatinine showed values higher than the correspondent to the control group which was composed of birds fed with no contaminated food. The cell-mediated immune response was similar to the control group response (Sharma *et al.*, 2008). Recently, inhibitory effects of MON on the proliferation of progenitor white blood cells, progenitor platelets and progenitor red blood cells have been evaluated and the results showed that MON produced cytotoxic effects on progenitor red blood cells while no cytotoxic effects were produced in the other cell lines tested (Ficheux *et al.*, 2012).

In 2002, Tomczak *et al.* (2002) evaluated the

presence of MON and other mycotoxins in wheat which suffered an epidemic case of FHB in Zulawy (Northern Poland) during 1998 and in Wielkopolska (West) and in Southern regions of Poland in 1999. One hundred seventy four wheat samples were analyzed by using HPLC and the presence of MON was confirmed in each subsequent year with a higher amount in 1999 (1.72 mg/kg) (Tomczak *et al.*, 2002). In 2007, a novel technique based on hydrophilic interaction chromatography (HILIC) for highly polar substances coupled MS was developed. The new tools allowed quantifying MON on maize samples infected by MON *Fusarium* producers (Sorensen *et al.*, 2007). Moreover, Kokkonen & Jestoi (2009) developed a method which comprises a multi compound LC-MS/MS technique that enabled the simultaneous determination of chemically diverse compounds at relatively low concentration levels. By using this novel method, MON was quantified in wheat and oat samples and showed high limits of detection and quantification (Kokkonen & Jestoi, 2009). MON seems to be a strong toxin whose effects do not have discussion as they have been studied extensively, but like the other mycotoxins produced by *F. poae*, it does not have a regulation.

#### *Other minor mycotoxins*

Butenolide (C<sub>4</sub>H<sub>4</sub>O<sub>2</sub>), culmorin (C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>), cyclonerodiol (C<sub>15</sub>H<sub>28</sub>O<sub>2</sub>) and fusarin C (C<sub>23</sub>H<sub>29</sub>NO<sub>7</sub>) are other mycotoxins able to be produced by *Fusarium poae* (Desjardins, 2006).

Butenolide is a 4-acetamido-4-hydroxy-2-butenic acid lactone that has been associated with a noninfectious condition of cattle called fescue foot, which is characterized by edema, lameness and gangrenous loss of extremities (Desjardins, 2006; Desjardins & Proctor, 2007). Moreover, butenolide has been reported as moderately toxic to mice, with a 50% lethal dose of 44 mg per kilogram of body weight by intraperitoneal injection and an oral toxicity of 275 mg per kilogram (Yates *et al.*, 1969).

De Nijs *et al.* (1996) mentioned the mycotoxins produced by *Fusarium poae* within which mentioned a sesquiterpene diol named culmorin (Desjardins, 2006). In field tests, culmorin inhibited the elongation of coleoptiles of different wheat cultivars, but only at concentrations of 100 µM to 1 mM (Wang & Miller, 1988).

The capacity of *Fusarium poae* to produce cyclonerodiol was described by Desjardins (2006). Cyclonerodiol is a sesquiterpene diol whose toxicity is unknown (Desjardins, 2006).

Fusarin C is other mycotoxin produced by *Fusarium poae* that are 2-pyrrolidones with a methylated, polyunsaturated side chain, but differ in the structure and substitution of the 2-pyrrolidone moiety. In fusarin C, the pyrrolidone contains a C-13,14 epoxide and an ethanolic side chain (Desjardins & Proctor, 2007). The consumption of grain infected with fusarin-producing *Fusarium* species has been associated epidemiologically with human diseases (Desjardins, 2006). Several studies showed that fusarin C is a mutagenic metabolite whose potency was comparable with other mutagens such as aflatoxin B1 and sterigmatocystin (Gelderblom *et al.*, 1984).

In the present, these mycotoxins have been little studied so most studies are needed to assess the frequency of occurrence and toxicity of these mycotoxins in cereals used for animals and human foods products.

## CONCLUSIONS

The prevalence of *Fusarium poae* has changed in course of time. Recently, a lot of works have demonstrated the high frequency of appearance of this species which allows considering *F. poae* as an important fungus with the capacity to produce a lot of mycotoxins whose effects, in general, have been well studied.

The available chemical methods to detect and quantify some toxins have led to learn the ability of *Fusarium poae* isolates to produce some important toxins whose hazard effects are not discussed.

Several researches have elucidated the presence of important mycotoxins in diverse substrates, most of them eaten by humans; so that the risk of the consumption of these mycotoxins is constant. Moreover, studies concerning the effects of exposure to mycotoxins have showed the hazard consequences on human beings and animals who consume them. The lack of a *Fusarium*-produced mycotoxin legislation that regulates the maximum content of these toxins in consumers products is notable. There is no doubt that these mycotoxins should be considered for future legislation.

The variable mycotoxin production which has been shown to depend on several factors should be a topic to be considered in future studies to try to understand the behaviour of *Fusarium poae*.

Some efforts are necessary to have tools to identify and quantify *Fusarium poae* mycotoxins. A lot of work related to specific primers design will be developed to have the possibility to screen mycotoxins in a short time. All those allow us to have available sequences in the database related to mycotoxin *F. poae* and the possibility to design mycotoxin specific probes to realize real time PCR to allow us to screen and quantify mycotoxins in several substrates.

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