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Mycotoxins in Food

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1. General principles

The term mycotoxin was used for the first time in 1961 in the aftermath of a veterinary crisis in England, during which thousands of animals died. The disease was linked to a peanut meal, incorporated in the diet, contaminated with a toxin produced by the filamentous fungus *Aspergillus flavus* (Bennet & Klich, 2003; Richard, 2007).

In general, mycotoxins are low-molecular-weight compounds that are synthetized during secondary metabolism by filamentous fungi; their chemical structure may range from simple C4 compounds to complex substances (Paterson & Lima, 2010).

Mycotoxins are natural contaminants in raw materials, food and feeds. Mould species that produce mycotoxins are extremely common, and they can grow on a wide range of substrates under a wide range of environmental conditions; they occur in agricultural products all around the world (Bennet & Klich, 2003). Many mycotoxins may be toxic to vertebrates and other animal groups and, in low concentrations, some of them can cause autoimmune illnesses, and have allergenic properties, while others are teratogenic, carcinogenic, and mutagenic (Bennet & Klich, 2003; Council for Agricultural Science and Technology [CAST], 2003).

Apparently, mycotoxins have no biochemical significance on fungal growth; they may have developed to provide a defense system against insects, microorganisms, nematodes, animals and humans (Etzel, 2002).

Exposure to mycotoxins may occur through ingestion, inhalation, and dermal contact, and it is almost always accidental. Most cases of mycotoxicoses (animals and humans) result from eating contaminated food. Human exposure can be direct *via* cereals or indirect *via* animal products (e.g. meat, milk and eggs) (CAST, 2003).

Most mycotoxins are relatively heat-stable within the conventional food processing temperature range (80–121°C), therefore so little or no destruction occurs under normal cooking conditions, such as boiling and frying, or even following pasteurization (Milicevic et al., 2010). The stability of mycotoxins during food processing has been reviewed in the work by Bullerman & Bianchini (2007). In general, the application of a food process reduces mycotoxin concentrations significantly, but does not eliminate them completely. The food processes that have been examined include physical treatments (cleaning and milling) and thermal processing (e.g. cooking, baking, frying, roasting and extrusion). The different treatments have various effects on mycotoxins, and those that utilize the highest temperatures have the greatest effects: roasting or cooking at high temperatures (above 150 °C) appear to reduce mycotoxin concentrations significantly (Bullerman & Bianchini, 2007).

It has been estimated that 25% of the world's crops are affected by fungal growth, and commodities may be, both pre- and post-harvest, contaminated with mycotoxins. The mycotoxins that can be expected in food differ from country to country in relation to the different crops, agronomic practices and climatic conditions (Bryden, 2007). Since climate changes affect the growth of mycotoxigenic fungi, mycotoxin production is also influenced (Magan et al., 2003).

Currently, more than 400 mycotoxins are known. Scientific attention has mainly focused on those that have proven to be carcinogenic and/or toxic in humans and animals. Five classes of mycotoxins are considered the most significant in agriculture and in the food industry: aflatoxins (aflatoxin B1), ochratoxins (ochratoxin A), fumonisins (fumonisin B1), zearalenone, and patulin which are derived from polyketide (PK) metabolism, and trichothecenes (deoxynivalenol), whose biosynthetic pathway is of terpenoid origin. PKs are metabolites that are derived from the repetitive condensation of acetate units or other short carboxylic acids, via an enzymatic mechanism that is similar to that responsible for fatty acid synthesis (Huffman et al., 2010).

Aflatoxin, ochratoxin, fumonisin, trichothecene, zearalenone and patulin are the most widespread mycotoxins in animal feed and human food. The chemical structure, biosynthetic pathway, mycotoxigenic fungi, the influence of environmental factors and toxicology will be briefly described for each class. Zearalenone will not be dealth with in the present work as, because of its hormonal activity, there is considerable knowledge about ZEA and its derivatives which can be found in the literature on growth hormones.

1.1 Toxigenic fungi

Aspergillus, *Alternaria*, *Claviceps, Fusarium, Penicillium* and *Stachybotrys* are the recognized genera of mycotoxigenic fungi (Milicevic et al., 2010; Reddy et al., 2010). Many of these genera are ubiquitous and, in some cases, apparently have a strong ecological link with human food supplies. The natural fungal flora associated with food production is dominated by the *Aspergillus, Fusarium* and *Penicillium* genera (Sweeney & Dobson, 1998). *Fusarium* species are pathogens that are found on cereal crops and other commodities, and they produce mycotoxins before, or immediately after, the harvest. Some species of *Aspergillus* and *Penicillium* are also plant pathogens or commensals, but these genera are more commonly associated with commodities and food during drying and storage (Pitt, 2000).

Toxigenic moulds are known to produce one or more of these toxic secondary metabolites. However, not all moulds are toxigenic and not all secondary metabolites from moulds are toxic. Many fungi produce several mycotoxins simultaneously, especially *Fusarium* species.

Moreover, recent studies have demonstrated that the necrotrophic pathogens of wheat, *Stagonospora nodorum*, *Pyrenophora tritiirepentis* and *Alternaria alternata,* are also capable of synthesizing an array of mycotoxic compounds during disease development (Solomon, 2011).

Nowadays, the identification and quantification of mycotoginenic fungi are carried out by PCR. Diagnostic PCR-based systems are now available for all of the most relevant toxigenic fungi: producers of aflatoxins, trichotecenes, fumonisins and patulin (Niessen, 2007; Paterson, 2006). The primers for mycotoxin pathway sequences have been reviewed in the work by Paterson (2006).

1.2 Influence of environmental factors on mycototoxin production

The production of mycotoxins is highly susceptible to temperature, moisture, water activity (a_w), pH and oxygen concentration, the same environmental factors that affect the growth of

toxygenic fungi. Moisture and temperature are two factors that have a crucial effect on fungal proliferation and toxin biosynthesis (Bryden, 2007; Paterson & Lima, 2010). The incidence and level of mycotoxin contamination are closely related to the geographic position and to seasonal factors as well as to the cultivation, harvesting, stocking, and transport conditions (Milicevic et al., 2010).

Mycotoxin contaminations can be divided into the one that occurs in the developing crop (pre-harvest) and the one that develops after maturation (post-harvest). In the pre-harvest period, preventive measures are included in good agronomic practices, such as the careful use of insecticides and fungicides, irrigation to avoid moisture stress, harvesting at maturity and improvement by genetic resistance to fungal attack. During the post-harvest period, the control of the moisture and temperature of the stored commodity will largely determine the degree of fungal activity and consequently the mycotoxin synthesis (Bryden, 2007). Treatments with chemicals, including sodium bisulfite, ozone, and ammonia, acids and bases, represent an opportunity to control fungal growth and mycotoxin biosynthesis in stored grains (Bozoglu, 2009; Magan, 2006; Magan & Aldred, 2007). In recent years, a good control of mycotoxigenic fungi has been achieved using plant products (e.g. extracts and essential oils) as environmental friendly fungicides (Nguefacka et al., 2004; Reddy et al., 2010; Thembo et al., 2010).

Moreover, biological control represents a new opportunity in control strategies: there is evidence that *Bacillus* sp., propionic acid bacteria and lactic acid bacteria (LAB) are able to inhibit fungal growth and mycotoxin production (Bianchini & Bullerman, 2010).

1.3 Toxicology and health

Mycotoxins are toxic to vertebrates and humans at low concentrations. Mycotoxicoses in humans or animals have been characterized as food or feed related, non-contagious, non-transferable, and non-infectious (Zain, 2011).

Mycotoxins have various acute and chronic effects on humans and animals, depending on the species. Within a given species, the impact of mycotoxins on health is influenced by age, sex, weight, diet, exposure to infectious agents, and the presence of other mycotoxins (synergistic effects) and pharmacologically active substances (Milicevic et al., 2010; Zain, 2011).

The majority of mycotoxins currently known are grouped, according to their toxic activity, under chronic conditions as mutagenic, carcinogenic or teratogenic. Grouping according to their site of action results in hemo-, hepato-, nephron-, dermato-, neuro- or immunotoxins (Niessen, 2007).

The most important mycotoxins worldwide are aflatoxins, fumonisins, ochratoxins, deoxinyvalenol and zearalenone. Carcinogenic properties have been recognized with regard to aflatoxin and fumonisins (Mazzoni et al., 2011; Wogan, 1992).

Aflatoxin B1 (AFB1) has been linked to human primary liver cancer, in which it acts synergistically with HBV infection and it has been classified as a carcinogen in humans (Group 1 carcinogen). Fumonisin B1, the most abundant of the numerous fumonisin analogues, was classified as a Group 2B carcinogen (possibly carcinogenic to humans) (Zain, 2011; Wild & Gong, 2010).

The potential role of dietary factors to counteract the toxic effects of mycotoxins has been reviewed by Galvano et al. (2001): the effect of antioxidants, food components and additives on reducing toxicity, by decreasing toxin formation and enhancing the metabolism, has been reported.

A mixture of mycotoxins may occur simultaneously, depending on the environmental conditions and substrate availability (Milicevic et al., 2010). Therefore it can be expected that

humans and animals are exposed to a mixture rather than to individual compounds. For example, the interactive (synergistic) cytotoxic effects of Ochratoxin A (OTA), Ochratoxin B (OTB), citrinin, and patulin, which are produced by a number of *Penicillium* and *Aspergillus* species, have recently been evaluated by Heussner et al. (2006).

2. Aflatoxins

Aflatoxins (AFs) are the best known and most widely studied mycotoxins. They were first isolated in the early 1960s when 100,000 turkey poults died after consuming aflatoxin-contaminated peanut meal in the UK (the so-called Turkey X disease); this event was followed by proliferation in research on fungal toxins contaminating food and feeds. AFs were found to be the most potent naturally formed carcinogen, and researchers started their investigating on factors that influence this production (Blount, 1960; CAST, 1989).

AFs are highly toxic, mutagenic, and carcinogenic compounds (Wogan, 1999). They are secondary metabolites that are produced mainly by *Aspergillus parasiticus* and *Aspergillus flavus*; in fact, the name ''aflatoxin" is derived from the first letter in Aspergillus, and the first three letters in flavus. These fungi are found in many countries, especially in tropical and subtropical regions, where the temperature and humidity conditions are optimal for the growth of moulds and the production of toxin (Rustom, 1997).

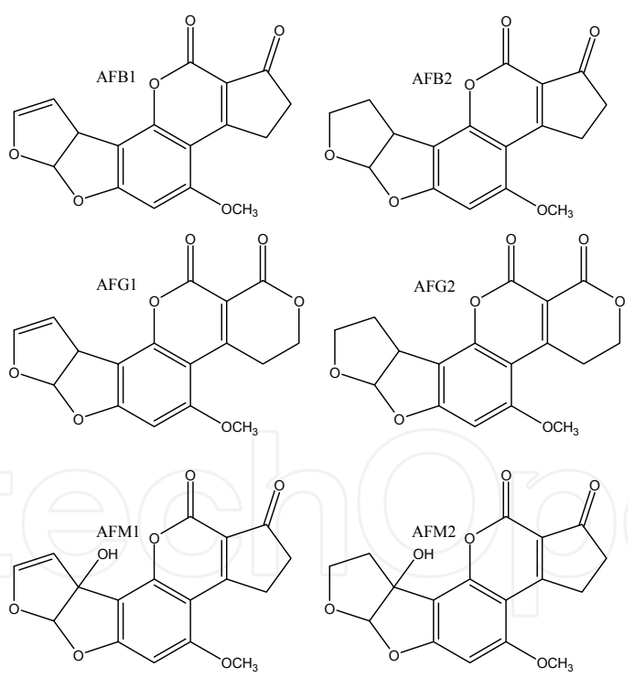


Fig. 1. Principal aflatoxins and metabolites.

AFs are natural contaminants of several agricultural products, such as: corn, peanuts, cottonseed, and other grain crops (Gourama & Bullerman, 1995). Diet is the major way through which humans as well as animals are exposed to these mycotoxins. AFM1 is transformed at the hepatic level by means of cytochrome P450 enzymes and excreted into the milk in the mammary glands of both humans and lactating animals after the animals have ingested feeds contaminated with AFB1 (Oveisi et al., 2007; Prandini et al., 2009).

Structurally, AFs are difurocoumarin derivatives that fluoresce under ultraviolet light. Depending upon colour of the fluorescence, AFs are divided into aflatoxin B1 and B2 (AFB1, AFB2) for blue, and G1 and G2 (AFG1, AFG2) for green (Dalvi, 1986) (Figure 1). Aflatoxin M1 and M2 (AFM1, AFM2), known as milk-AFs, are the metabolites of AFB1 and AFB2, respectively (Carnaghan et al., 1963). Other metabolites of AFB1 are aflatoxin Q1 (AFQ1) and aflatoxicol. Of the known AFs, AFB1 is the most common produced mycotoxin and the most potent; it has been reported to be the most powerful natural carcinogen in mammals (Creppy, 2002).

The biosynthesis of aflatoxins is a complex process, involving multi-enzymatic reactions. Genetic studies on the molecular mechanism of aflatoxin B1 biosynthesis have identified an aflatoxin pathway gene cluster of 70 kilobase pairs in length consisting of at least 24 identified structural genes including a positive regulatory gene as the transcription activator. The structural genes encode cytochrome P450 monooxygenases, dehydrogenases, oxidases, methyltransferases, a polyketide synthase and two unique fatty acid synthases (Yu et al., 2002).

2.1 Fungi

Aflatoxins are closely related to a group of aspergilli: *A. flavus*, *A. parasiticus*, and *A. nomius*; although one report also adds a sclerotium producing strain of *A. tamarii*, which is closely related to *A. flavus*, to the list (Goto et al., 1996). Earlier reports of the production of aflatoxins by other aspergilli, penicillia or even a species of *Rhizopus*, have not been adequately confirmed (Moss, 2002a).

A. flavus and *A. parasiticus*, which are found worldwide in the air and soil, usually infest both living and dead plants and animals, and as a consequence, aflatoxins in agricultural commodities are primarily produced by *A. flavus* and *A. parasiticus*. *A. flavus* produces only B aflatoxins, while *A. nomius* and *A. parasiticus* produce both B and G toxins (Rustom, 1997; Yu et al., 2002).

2.2 Food

Aflatoxin contamination of food and feeds is a serious problem worldwide. Studies focusing on AF contamination in foodstuffs have in fact been reported in many countries, especially those in tropical and subtropical regions, such as Asia and Africa (Bankole et al., 2010; Shundo et al., 2009; Soubra et al., 2009).

Aflatoxin contamination can develop both in the pre- and post-harvest periods, but the highest levels are usually associated with post-harvest spoilage of food commodities, stored under inappropriate high moisture content and high temperature conditions which facilitate the rapid growth of moulds; the level of contamination depends on the plant stress, temperature, water activity, genotype, culture and storage conditions, but appropriate post-harvest treatments, under dry cool settings, should control this source of contamination (Moss, 2002a; Wilson & Payne, 1994).

As far as pre-harvest, is concerned, aflatoxigenic fungi have a complex ecology. The spores of *A. flavus* and *A. parasiticus* can germinate on the stigma surfaces of plants, and the germ tube can penetrate the developing embryo in a manner which mimics pollen germ tubes. The mycelium can establish an endotrophic relationship, which is not harmful to a healthy plant, while if the plant is stressed (e.g. drought), significant levels of aflatoxin may be produced during field growth. Under these circumstances food commodities may already be contaminated at harvesting and, even though the concentrations are never as high as

those formed in stored commodities, they can be economically significant and this field contamination is much more difficult to control than post-harvest spoilage (Hill et al., 1983; Moss, 2002a).

Although a wide variety of foods are susceptible to aflatoxin contamination, it has most commonly been associated with peanuts, maize, pistachio, dried fruit, nuts, spices, figs, vegetable oils, cocoa beans, corn, rice and cotton seeds (JECFA, 1998; Reports on Carcinogens [ROC], 2003). Among the agricultural commodities usually infected by aflatoxigenic fungi (Table 1) some are food sources while others are used as animal feeds: the greatest difficulty is that aflatoxin affects the health of the humans and the livestock that consume these commodities and the related products. Speijers & Speijers (2004) reported that AFB1 and OTA are amongst the most frequently observed combinations of mycotoxins in different plant products. According to several other authors, cereals, olives and dried vines are other commodities which could support aflatoxigenic and ochratoxigenic mould growth and OTA and AFB1 production (Molinié et al., 2005; Zinedine et al., 2006).

While aflatoxin B1 is frequently found in contaminated feeds, aflatoxin M1, its hydroxylated metabolite, is normally not present in food, except though carry-over from animal feeds (Fallah, 2010; Kamkar, 2008): following the ingestion of contaminated feedstuffs by lactating dairy cows, AFB1 is biotransformed, by hepatic microsomal cytochrome P450 into AFM1, and is then excreted into the milk (Frobish et al., 1986). Moreover, the AFM1 content in milk is closely correlated to the level of AFB1 in the raw feedstuffs (Bakirci, 2001). AFM1 can be detected in milk 12–24 h after the first ingestion of AFB1; generally, it is deemed that approximately 1–3% of the aflatoxin B1 present in animal feeds appears as AFM1 in milk, depending on the animal, time of milking and many other factors. When the intake of the contaminated source is stopped, the concentration of the toxin in the milk decreases to an undetectable level within 72 h (Gurbay et al., 2006). Additionally, when specific conditions during feed storage are prevalent for the growth of aflatoxigenic species, an additional production and accumulation of AFB1 may occur; this in turn leads to the accumulation of additional AFM1 in the milk. Aflatoxin M1 can survive pasteurization and has even been reported in UHT milk (Unusan, 2006).

AFM1 binds to casein, has a high stability and concentrates in curd during cheese production, in different proportions according to the applied technology (Barbiroli et al., 2007; Brackett & Marth, 1982). In this way, it can also be present in dairy products, manufactured with contaminated milk, at higher concentrations than in the milk (Govaris et al., 2001; Lopez et al., 2001; Oruc et al., 2006). Cheese-making and the ripening period do not result in a reduction in the toxin (Dragacci et al., 1995; Yousef & Marth, 1985). This is why the risk remains, not only in commercially available milk, but also in other derived dairy products. The concentration of AFM1 in cheese varies according to the type of cheese, water content and production technologies (Bakirci, 2001; Lopez et al., 2001). Since the sources of aflatoxin contamination in animal feeds differ because they are location dependent and the incidence and occurrence of AFM1 contamination in animal feeds from different countries varies, there are many reports on AFM1 contamination in cheese and other dairy products from different countries: Slovenia, North Africa, Turkey, Brazil and Portugal (Bakirci, 2001; Elgerbi et al., 2004; Oliveira et al., 2006; Martins & Martins, 2000; Torkar & Vengus, 2008).

Food commodity	Country
Soy beans	Argentina
Almonds; Brazil nuts	USA
Dried figs	Austria, Switzerland
Nutmeg	Japan
Chilli	Pakistan
Herbs, spices	UK
Spices	Sweden
Peanuts	India, Sudan, Brazil, Egypt, South Africa
Maize	Argentina, India, China, Uganda, Nigeria, USA
Pistachio nuts	Netherlands, USA, Turkey,
Wheat	Uruguay, China, Russia
Rice	Ecuador, China, India
Millet	India
Sunflower oil	China, Russia
Coconut	India
Mustard seed	India

Table 1. Presence of aflatoxins in food commodities (Moss, 2002a; Rustom, 1997).

2.3 Toxicity

Aflatoxins can be both acute and chronic toxins; acute poisoning is usually rare and exceptional, while chronic toxicity is of serious concern and it drives international concern about the occurrence of aflatoxins in food (Moss, 2002a).

AFB1 is toxic for a wide range of animal species. AFB1 is principally a hepatotoxin and hepatocarcinogen (JECFA, 1998), but it can cause a myriad of other effects: immunosuppresion, reduced growth rate, lowered milk and egg production, reduced reproductivity, reduced feed utilization and efficiency and anemia. AFB1 has been shown to induce hepatocellular carcinoma in many animal species including fish, poultry, non-human primates, and rodents (Wogan, 1992).

Species susceptibility to various acute toxic manifestations, as measured by TD50, is also variable (Gold et al., 1984). A wide variation exists in species susceptibility to AFB1 hepatocarcinogenesis.

In humans, acute aflatoxicosis is manifested by vomiting, abdominal pain, pulmonary edema, coma, convulsions, and death with cerebral edema and fatty involvement of the liver, kidneys, and heart (Mwanda et al., 2005). Epidemiological studies have consistently demonstrated that AFB1 is a liver carcinogen in humans (Groopman et al., 1988; Van Rensburg et al., 1985). The International Agency for Research on Cancer has concluded that there is sufficient evidence for the carcinogenicity of AFB1 in humans and hence placed this mycotoxin in group I.

AFB1 is not mutagenically active itself. It is primarily metabolized in the liver and has several metabolites, such as aflatoxicol and AFQ1. AFB1 is mainly activated by cytochrome P450 dependent monooxygenase; most of the metabolic products, such as AFM1 and AFQ1, are less toxic than the parent AFB1, but aflatoxin B1-8-9-expoxide (AFBO) is the most toxic metabolite (Hwan Do & Choi, 2007). The carcinogenic and mutagenic action of AFB1 might be the result of the affinity of the electrophilic and highly reactive AFBO for cellular nucleophiles, such as DNA (Coulombe, 1993). Thus, epoxidation is generally considered in metabolite activation, while hydroxylation, hydration, and demethylation are considered

metabolic detoxications. The toxic and carcinogenic effects of aflatoxin B1 are intimately linked to both the rate of activation and the rate of detoxification at the primary and secondary levels of metabolism, in a similar way to chlorinated hydrocarbon (Olaniran et al., 2006).

3. Ochratoxin A

Mycotoxin ochratoxin A (OTA) was discovered in 1965 in South Africa (Van der Merwe et al., 1965): it was isolated as a toxic metabolite of *Aspergillus ochraceus* from corn meal artificially inoculated with the fungus. In 1969, naturally occurring OTA was isolated from a commercial corn sample in the United States (Shotwell et al., 1969). Later, it was recognized as a secondary metabolite of several *Aspergillus* and *Penicillium* spp. which are characterized by widespread occurrence and different behavior which depends on the ecological niches, the products affected and the environment (Duarte et al., 2010).

OTA is one of the most relevant mycotoxins, with great public health and agroeconomic significance, due to the confirmed nephrotoxic, genotoxic, neurotoxic, imunotoxic, embriotoxic and teratogenic effects and its suspected carcinogenicity (JECFA, 2008). OTA has been documented as a global contaminant of a wide variety of commodities and staple food. Humans are directly and indirectly exposed to OTA: it can enter the food chain, through contamination of the ingredients or foodstuffs consumed by humans, or the feed chain, through contamination of the feeds for animals destined for human consumption (Cark & Snedeker, 2006).

The chemical name of OTA is N-[(3R)-(5-Chloro-8-hydroxy-3-methyl-1-oxo-7-isochromanyl)carbonyl]-L-phenylalanine; OTA belongs to a group of metabolites with a similar chemical structure, as shown in Figure 2 and Table 2.

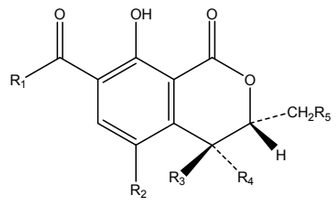


Fig. 2. General structure of OTA and its metabolites (El Khoury & Atoui, 2010).

The biosynthetic pathway for OTA has not yet been completely established; however, the isocoumarin group is a pentaketide skeleton formed from acetate and malonate via a polyketide synthesis pathway with the L-phenylalanine being derived from the shikimic acid pathway (O'Callaghan et al., 2003).

OTA is a weak organic acid (the pKa is 7.1 and the molar mass is 403.8 g mol^{-1}). In acidic conditions, OTA is soluble in polar organic solvents, slightly soluble in water and insoluble in petroleum ethers and saturated hydrocarbons. In alkaline conditions, OTA is soluble in aqueous sodium bicarbonate solutions and in all alkaline ones. It has a melting point of about 90 °C, when crystallized from benzene as a solvate (El Khoury & Atoui, 2010; Keeper-Goodman & Scott, 1989). Due to its resistance to acidic conditions and high temperatures, OTA is characterized by high stability. Thus, it is very difficult to eliminate the molecule: OTA is only partially degraded at normal cooking conditions and after three hours of high pressure steam sterilization at 121 °C, or even at 250 °C, its destruction is not complete (Boudra et al., 1995).

Name	R1	R2	R3	R4	R5
OTA	Phe*	Cl	H	H	H
OTB	Phe	H	H	H	H
OTC	Ethyl-ester, Phe	Cl	H	H	H
OTA methyl-ester	Methyl-ester, Phe	Cl	H	H	H
OTB methyl-ester	Methyl-ester, Phe	H	H	H	H
OTB-ethyl-ester	Ethyl-ester, Phe	H	H	H	H
OTα	OH	Cl	H	H	H
OTβ	OH	H	H	H	H
4-R-hydroxy OTA	Phe	Cl	H	OH	H
4-s-hydroxy OTA	Phe	Cl	OH	H	H
10-hydroxy OTA	Phe	Cl	H	H	OH
Tyr* analog of OTA	Tyr	Cl	H	H	H
Ser* analog of OTA	Ser	Cl	H	H	H
Hyp* analog of OTA	Hyp	Cl	H	H	H
Lys* analog of OTA	Lys	Cl	H	H	H

Table 2. Radicals in OTA metabolites *(Phenylalanine; Tyrosine; Serine; Hydroxyproline; Lysine) (El Khoury & Atoui, 2010).

3.1 Fungi

Ochratoxin A is produced by *Aspergillus* and *Penicillium* species listed in Table 3. These microorganisms differ according to the ecological conditions and commodities that characterize different geographical regions. In general, *Penicillium verrucosum* is responsible for OTA contamination in cool-temperate conditions, whereas *Aspergillus ochraceus* is particularly relevant in hot-tropical regions (Battaccone et al., 2010; Scudamore, 2005).

The major *Aspergillus* producers in food and feeds are *A. alliaceus*, *A. carbonarius*, *A. ochraceus*, *A. steynii* and *A. westerdijkiae*. *A. melleus*, *A. ostianus*, *A. persii* and *A. petrakii* may produce trace amounts of OTA, but since the publication by Ciegler (1972) and Hesseltine et al. (1972) no further confirmation has been found.

In the genus *Penicillium*, *P. verrucosum* and *P. nordicum* are the only species that are able to produce OTA (Abruhnosa et al., 2010; El Khoury & Atoui, 2010). *P. chrysogenum*, *P. brevicompactum*, *P. crustosum*, *P. olsonii* and *P. oxalicum* have been claimed as OTA producers, but a confirmation of these findings is required (Paterson, 2006).

Aspergillus section Circumdati
A. cretensis; A. flocculosus; A. ochraceus ; A. pseudoelegans; A. roseoglobulosus; A. sclerotiorum ; A. steynii; A. sulphureus ; A. westerdijkiae; Neopetromyces muricatus
Aspergillus section Flavi
A. alliaceus; Petromyces albertensis
Aspergillus section Nigri
A. carbonarius; A. lacticoffeatus; A. niger; A. sclerotioniger; A. citricus ; A. fonsecaeus
Penicillium
P. nordicum; P. verrucosum

Table 3. OTA producing fungi (Abrunhosa et al., 2010; El Khoury & Atoui, 2010; Moss, 2002b).

3.2 Food

OTA has a widespread diffusion, and it has in fact been detected in agricultural commodities, livestock products and processed food (Abrunhosa et al., 2010).

The main OTA contamination concerns cereals and their products, listed in Table 4, which include food and beverages for human consumption, but also by-products that are usually utilized as animal feeds. Ochratoxin contamination can occur from temperate to tropical climates, from hot and wet climatic conditions to low temperature environments, and affects numerous countries: Northern America, Northern and Western Europe, African countries, South Asia and South America (Battaccone et al., 2010; Cabanes et al., 2010; El Khoury & Atoui, 2010; Moss, 2002b). Vega et al. (2009) suggests that cereals should be considered a major source of OTA contamination, as 50% of human daily intake of this mycotoxin is due to the consumption of different cereal derived products.

cereals
Corn (grains, gluten); Rice; Wheat; Barley; Oats; Rye; Sorghum; Millet
cereal products for human consumption
Beer; Baby food; Breakfast cereals; Bread
cereal feed products
Cracked grains; Cereal cleanings; Wheat bran; Corn bran; Rice bran

Table 4. Cereals contaminated by OTA (Abrunhosa et al., 2010; Scudamore et al., 2003).

Cereals may be colonized by both *Aspergillus* and *Penicillium*. The two fungal species do not invade the crop in the field, but mainly do in the post-harvest phase. Considering that the main abiotic factors that influence mould growth and OTA production are water availability and temperature, cereals should be dried quickly after harvesting and maintained at a lower moisture content than 14.5% during storage to avoid OTA contamination (Magan & Aldred, 2005). OTA is mainly concentrated in the seed coat, which is often used for animal feeding. Moreover, on-farm production and the storage of barley and wheat with a high moisture content increases the risk of mould growth and toxin production (Scudamore et al., 2003). Some cereal processing, like malting, malt fermentation, bread production and feed extrusion, can contribute significantly to reduce OTA concentration in the final food products (Baxter et al., 2001; Scott et al., 1995; Scudamore et al., 2003). Other practices can increase OTA values; for example, cracked grains and cereal cleanings are often the most contaminated fractions and are usually directed for feed proposes (Scudamore et al., 2003).

Wine is considered the second source of the human consumption of OTA. Many works have highlighted the presence of considerable levels of this toxin in wines, musts and grape juices. This occurrence has been explained by the fact that grapes are contaminated in the vineyard by various ochratoxigenic species, belonging above all to the *Aspergillus* section *Nigri* genus (*A. carbonarius* and *A. niger* aggregates) and that OTA production increases rapidly with the maturation stage. Thus, the date of the grape harvest would have an important effect on the OTA content in grapes and their derived products (Cabanes et al., 2002; El Khoury et al., 2006).

OTA contamination of many other raw agricultural products has been well documented; such a contamination occurs in a variety of food and feeds, such as coffee beans, pulses, spices, meat and cheese products (Wolff et al., 2000).

3.3 Toxicity

OTA can have several effects, such as nephrotoxic, hepatotoxic, neurotoxic, teratogenic and immunotoxic effects on several species of animals, and can cause kidney and liver tumours in mice and rats; OTA toxicity varies depending on the sex, the species and the cellular type of the tested animal (El Khoury & Atoui, 2010).

Nephropathy is the main toxic effect of OTA; it is potentially nephrotoxic in all non-ruminant mammals (Ribelin et al., 1978). OTA plays an important role in the etiology of porcine nephropathy (Elling et al., 1985). This mycotoxin was also associated with human nephropathy and it is suspected to be the cause of the human Balkan Endemic Nephropathy (BEN) and the Tunisian Nephropathy (TCIN) (Hassen et al., 2004; Pfohl-Leszkowicz, 2009).

The administration of OTA at gestation period in rats induced many malformations in the central nervous system. OTA can be regarded as a possible cause of certain lesions as well as damage at the cerebral level. OTA seems to be highly toxic for the nervous cells and able to reach the neural tissue (Soleas et al., 2001).

OTA is a potent teratogen for laboratory animals. It can cross the placenta and accumulate in fetal tissue, causing various morphological anomalies. It has been reported to elicit prenatal dysmorphogenesis in rats, mice, hamsters and chick embryos (El Khoury & Atoui, 2010).

OTA also has an immunosuppressor effect. Necroses of lymphoid tissues has been reported, and humoral and cellular immunity affections have also been described (Creppy et al., 1991; Holmberg et al., 1988). OTA seems to play a role in the inhibition of proliferation of the peripheral T and B lymphocytes and stops the production of interleukin 2 (IL2) and its receptors (Lea et al., 1989). Moreover, it blocks the activity of killer cells as well as the production of interferon (Pfohl-Leszkowicz & Castegnaro, 1999). OTA is taken as an important immunosupressor agent, in fact it is considered to be the cause of lymphopenia, regression of the thymus, and suppression of the immunity response (Petzinger & Weidenbach, 2002).

OTA is anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. Hepatocellular tumors, renal cell tumors, hepatomas, and hyperplastic hepatic nodules have been observed in male mice (Huff et al., 1992). OTA has been correlated with hepatocellular and renal-cell carcinomas and adenomas in mice and rats (El Khoury & Atoui, 2010). On the other hand there are no adequate studies of the relationship between exposure to OTA and human cancer; incidence and mortality from urothelial urinary tract tumours have been correlated with the geographical distribution of Balkan endemic nephropathy in Bulgaria and Yugoslavia (Feier & Tofana, 2009).

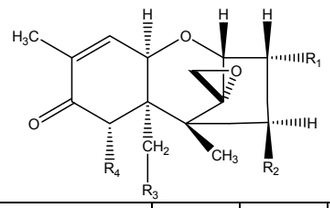
4. Trichothecenes

Trichothecin was first isolated from *Trichothecium roseum* and described by Freeman and Morrison in 1949. The discovery of trichothecin was followed by the isolation and description of other trichothecenes (TCTs), such as diacetoxyscirpenol (DAS), T-2 toxin (T-2), nivalenol (NIV) and deoxynivalenol (DON) (Yazar & Omurtag, 2008).

The Alimentary Toxic Aleukia (ATA) that occurred in Russia during World War II was caused by T-2 toxin and its derivatives; *F. sporotrichioides* was isolated from contaminated grains (Yazar & Omurtag, 2008). DON is the most prevalent toxin associated with Fusarium Head Blight (FHB), and it belongs to the phytotoxic type B trichothecene (Foroud & Eudes, 2009).

TCTs are the most important group of mycotoxins and they are produced above all by various *Fusarium* plant pathogen species (Kimura et al., 2007). They are non-volatile, low-

molecular-weight tricyclic sesquiterpenes with a basic 12,13-epoxy-trichothec-9-ene ring system (Figure 3) and are further classified as macrocyclic, or non macrocyclic depending on the presence of a macrocyclic ester or an ester–ether bridge between C-4 and C-15 (Bennett & Klich, 2003; Merhej et al., 2011). Trichothecenes are a family of more than 200 related compounds which are divided into four subclasses (Types A–D), according to their characteristic functional groups. Type A has a functional group other than a ketone at position C-8; Type B has a ketone at position C-8; Type C has a second epoxy group at C-7,8 or C-9,10 and Type D contains a macrocyclic ring between C-4 and C-5 with two ester linkages (Sweeney & Dobson, 1998). The major Type A trichothecenes in *Fusarium* species include T-2 toxin (T-2) and HT-2 toxin (HT-2), both of which have an isovalerate function in C-8. Type B TCTs include Fusarenone-X, deoxynivalenol (DON) and nivalenol.



Trichothecene	R1	R2	R3	R4
Deoxynivalenol (DON)	-OH	-H	-OH	-OH
Nivalenol (NIV)	-OH	-OH	-OH	-OH

Fig. 3. Chemical structure of trichothecens.

The trichothecene biosynthetic pathway in *Fusarium* has been reported extensively by Sweeney & Dobson (1998) and Desjardins & Proctor (2007); it begins with the cyclization of the isoprenioid intermediate farnesyl pyrophosphate to trichodiene by the enzyme trichodiene synthase. After this a number of oxygenation, isomeritation, cyclization, and esterification leading from trichodiene to dyacetoxyscirpenol, T-2 toxin and 3-acetyldeoxynivalenol (Huffman et al., 2010). The recent advances concerning the regulation of trichothecene biosynthesis in *Fusarium* and the potential implication of various general regulatory circuits has been reported in the work of Merhej et al. (2011); the knowledge of the role of these regulatory systems might be useful in designing new strategies to reduce mycotoxin accumulation.

Deoxynivalenol (DON) is the most studied mycotoxin produced by *Fusarium*. DON, also known as vomitotoxin, is a polar organic compound, which is soluble in water and polar organic solvents (e.g. aqueous methanol, ethanol, chloroform, acetonitrile and ethyl acetate); it is optically active. The chemical name of DON is 12,13-epoxy-3α,7α,15-trihydroxytrichothec-9-en-8-one, and the molar mass is 296,32 g mol^{-1}. DON is very stable at temperatures within the 170°C to 350°C interval with no reduction in DON concentration after 30 min at 170°C (Sobrova et al., 2010). DON shows great stability during storage/milling and in the processing and cooking of food.

4.1 Fungi

The *Fusarium* genus includes a number of important plant pathogens that produce a wide range of mycotoxins (TCTs, fumonisine and zearalenone) which are mainly found in cereal grains (Vesonder & Golinski, 1989). *Fusarium* is the main genus implicated in the production of the non-macrocyclic TCTs. Many toxigenic *Fusarium* species have been associated with

infected grain, and the predominant pathogens are *F. graminearum* and *F. culmorum*. During infection, *F. graminearum* produces various mycotoxins in grains, in particular deoxynivalenol (DON), a type B trichothecene. *F. graminearum* is the most important DON producer, followed by *Fusarium culmorum*, but other species such as *Fusarium sporotrichioides* or *Fusarium langsethiae* have also been reported. The geographical distribution of the species is probably related to temperature requirements (Merhej et al., 2011). From an economic point of view, the most important TCT producers are *Fusarium* species that cause Fusarium Head Blight (FHB) in small-grain cereals and Gibberella Ear Rot (GER) in maize (Bottalico & Perrone, 2002). The first documented FHB-outbreak occurred in England in 1884, where the disease was named "wheat scab". Outbreaks have since been reported in the Americas, Asia, Australia, Europe, and South Africa (Foroud & Eudes, 2009). These diseases are associated with the temperature in the grain growing region: *F. graminearum* (optimal growth range between 24 and 26°C, minimum a_w value 0.90) is more dominant in warmer regions (North America and China), while *F. culmorum* (psychrotrophic strain, optimal temperature growth 21°C) is more dominant in cooler regions (northern Europe) (Sweeney & Dobson, 1998).

The main species responsible for the production of T-2 toxin is *F. sporotrichioides.* The natural occurrence of this species has been reported in Asia, Africa, South America, Europe and North America (CAST, 2003).

Apart from *Fusarium*, several other fungal genera are capable of producing TCTs: *Myrothecium*, *Phomopsis, Stachybotrys*, *Trichoderma*, *Trichothecium*. Macrocyclic TCTs are produced largely by *Myrothecium*, *Stachybotrys* and *Trichothecium* (Bennett & Klich, 2003).

Fusarium species are pathogens that are found on cereal crops and they produce mycotoxins before, or immediately after, harvesting. Consequently, strategies for the prevention of TCTs from entering human and animal food chain include the elimination of TCTs in grains in the field, detoxification of TCTs that are already present in food and feeds, and inhibition of TCTs absorption in the gastrointestinal tract (He et al., 2010).

To date, the control of *Fusarium* proliferation in the field is not ensured, therefore, generation of resistant varieties of crop plants still remain the best way to reduce grain contamination by *Fusarium* without using chemical fungicides. The discovery of biological or chemical molecules which would be able to specifically block the biosynthetic pathway in order to limit the residual synthesis of toxins is a new challenge (Merhej et al., 2011).

At harvest and during the storage of cereals, the key factor for TCT formation is the presence of conidia and humidity combined with temperature. Minimizing or avoiding conidia contaminated materials, cleaning at an early stage during the harvest and drying the grain at low temperatures will allow cereals to be stored for more than 12 months without increasing TCTs levels (Yazar & Omurtag, 2008).

4.2 Food

TCTs are mainly associated with cereals grown in the temperate regions of Europe, America and Asia: wheat, barley, oats, rye, maize and rice (Yazar & Omurtag, 2008). Their presence has also been reported in soybeans, potatoes, sunflower seeds, peanuts and bananas. TCTs have also been found in processed foods, especially those produced from cereals (bread, breakfast cereals, noodles, and beer). The TCTs that are dominant in grains are deoxynivalenol (DON), nivalenol, and their acetylated derivatives (Foroud & Eudes 2009; Karlovsky, 2011). Corn, wheat, barley, oats, rice, rye and other crops have been reported to

contain T-2 toxin (CAST, 2003). Moreover, TCTs can enter the food chain through milk, meat and eggs from livestock and poultry that are fed with contaminated feeds, although the exposure risk to human through the consumption of animal tissue is much less than the direct consumption of contaminated grains (He et al., 2010).

Food and feed contamination by TCT have been associated with chronic and fatal toxicoses of humans and animals, including Alimentary Toxic Aleukia in Russia and Central Asia, Akakabi-byo (red mould disease) in Japan, and swine feed refusal in the central United States (Karlovsky, 2011). The epidemy that occurred in Russia between 1942 and 1948, where at least 100,000 people died, was caused by the ingestion of grain contaminated with T-2 produced by *F. sporotrichoides* or *F. poae* (Foroud & Eudes, 2009) .

4.3 Toxicity

At the cellular level, the main mechanism of TCT mycotoxins appears to be a primary inhibition of ribosomal protein synthesis, which is followed by a secondary disruption of DNA and RNA synthesis (Desjardins & Proctor, 2007; Richard, 2007; Zain, 2011), cytotoxicity, and apoptosis (Rocha et al., 2005; Rotter et al., 1996).

TCTs affect dividing cells, such as those coating the gastrointestinal tract, the skin, and lymphoid and erythroid cells. The toxic action of TCTs results in extensive necrosis of the oral mucous and skin in contact with the toxin, an acute effect on the digestive tract and decreased bone marrow and immune functions (Richard, 2007; Rocha et al., 2005).

In general, acute exposure of animals to DON resultes in decreased feed consumption (anorexia) and vomiting (emesis), while longer exposure causes reduced growth, and adverse effects on the thymus, spleen, heart, and liver (Sobrova et al., 2010).

Nowadays, the real concern is not related to acute exposure, but to a prolonged daily exposure, which leads to chronic toxicity, since it has been demonstrated that DON deregulates the immune response and induces cytokine up regulation (Merhej et al., 2011; Pestka & Smolinskj, 2005). It has been demonstrated that the ingestion of DON with contaminated feeds and food leads to growth retardation, and reproductive disorders in animals (Pestka, 2010; Rocha et al., 2005; Sobrova et al., 2010). To date, all the animal species evaluated have shown a differential level of susceptibility to DON with the pigs being the most susceptible (Pestka & Smolinski, 2005).

Human exposure to DON-contaminated grains has been reported to cause acute temporary nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, and fever (Sobrova et al., 2010).

In general, TCTs are heat-stable molecules and are not fully eliminated during the processes currently used in cereal-based food manufacturing (Hazel & Patel 2004). They are also stable at neutral and acidic pH and consequently, they are not hydrolyzed in the stomach after ingestion (Yazar & Omurtag 2008). Since DON is water soluble, its level is reduced in cooked pasta (Sobrova et al., 2010).

The chemical detoxification of DON by ozone (Young et al., 2006), ammonia, chlorine, hydrogen peroxide (He et al., 2010), sodium bisulfite (Young et al. 1986), sodium carbonate (Abramson et al. 2005), and chlorine dioxide (Wilson et al., 2005) has been demonstrated. Therefore, the best way to prevent contamination would be to limit TCT biosynthesis at the field level during crop cultivation (Merhej et al., 2011).

The enzymes involved in biological detoxification of DON and their application to genetically engineered crops and feed additives have been reviewed in the work by

Karlovsky (2011). Bacterial enzymes that catalyze oxidation, epimerization, and, but to a lesser extent, de-epoxidation of DON as well as of the application of acetylation in plant biotechnology have been described (He et al., 2010).

5. Fumonisins

Fumonisins are a group of non-fluorescent mycotoxins. They were discovered and characterized in 1988 (Bezuidenhout et al., 1988). The predominant fungus isolated from fumonisin contaminated corn, associated with the outbreak of Equine Leukoencephalomalacia (ELEM) in South Africa in 1970 and Porcine Pulmonary Edema (PPE) in Iowa, Illinois, and Georgia in 1989, was *F. verticillioides* (Yazar & Omurtag, 2008).
To date, twenty-eight fumonisins have been isolated and they can be divided into four series (A, B, C and P). FB1, FB2 and FB3 are the principal fumonisins analyzed as natural contaminants of cereals (CAST, 2003; Yazar & Omurtag, 2008). Fumonisin B1 is generally the most abundant member of this mycotoxin family; it comprises about 70 % of the total fumonisin content of *Fusarium* cultures (Reddy et al., 2010). Fumonisins have a similar structure to sphingosine, which forms the backbone of sphingolipids within the cell membrane (Sweeney & Dobson, 1998).
Fumonisins are polyketide metabolites, derived from the repetitive condensation of acetate units or other short carboxylic acids, via a similar enzymatic mechanism to that responsible for fatty acid synthesis (Huffman et al., 2010). The fumonisin biosynthetic pathway in *Fusarium* species begins with the formation of a linear dimethylatedpolyketide and condensation of the polyketide with alanine, followed by a carbonyl reduction, oxygenations, and esterification with two propane-1,2,3-tricarboxylic acids (Desjardins & Proctor, 2007).
Fumonisin biosynthetic genes have been mapped to one locus in the *F. verticillioides* genome (Desjardins & Proctor, 2007).

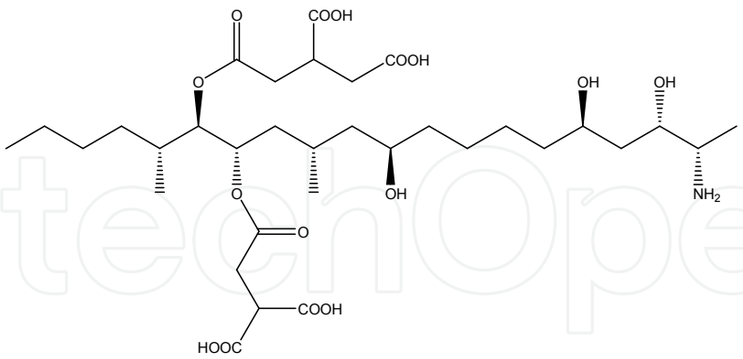


Fig. 4. Chemical structure of fumonisin B1.

The basic chemical structure of fumonisins is a C-20 aliphatic chain with two ester linked hydrophilic side chains (Richard, 2007). The chemical structure of FB1 is 1,2,3-Propanetricarboxylic acid, 1,1N-[1- (12 amino-4,9,11-trihydroxy-2-methyltridecyl)- 2-(1-methylpentyl)-1,2-ethanediyl] Ester (Figure 4). FB2 is the C-10-deoxy analogue of FB1 and FB3 is the C-5-deoxy analogue of FB1(Yazar & Omurtag, 2008). The molecular mass of FB1 is 721 g/mol, while FB2 and FB3 have the same value of molecular mass (705g/mol). FB1 is soluble in water to at least to 20 mg/ml, and in methanol and acetonitrile-water. FB1 and

FB2 are stable in methanol at −18 °C and degrade at 25 °C. However, in a mixture of acetonitrile/water (1:1) and at −25 °C, all fumonisins result to be stable (Wan Norashima et al., 2009).

5.1 Fungi

Fumonisins are produced by a number of *Fusarium* species, notably *F. verticillioides* (formerly *Fusarium moniliforme=Gibberella fujikuroi), F. proliferatum, F. anthophilum, F. nygamai* as well as *Alternaria alternata* f. sp. *lycopersici* (Kumar et al., 2008; Sweeney & Dobson, 1998; Yazar & Omurtag, 2008). Recently, *Aspergillus niger* has also been found to produce fumonisins (i.e., fumonisins B2 and B4), and a new B-series fumonisin (FB6) has been identified from this fungus (Huffman et al., 2010).

Fumonisins found in food are produced mainly in the field; temperature and moisture conditions are important factors that affect *Fusarium* infection and toxin synthesis as is insect damage of corn ears and kernels (Richard, 2007; Yazar & Omurtag, 2008).

At a field level, two approaches are known to reduce infections and mycotoxin accumulation: pre-harvesting control strategies, which consist of crop practices designed to reduce the infection and the development of toxinogenic fungi (Nicholson et al., 2004; Wan Norashima et al., 2009;) and the utilization of genetically resistant hybrids (Munkvold, 2003; Blandino & Rejneri, 2008). Direct fungal control with chemical or biological products (e.g. microbial antagonist or competitor) has only recently been considered (Mazzoni et al., 2011).

Mycotoxin risk can be reduced by enhancing the resistence of insect attack, by inducing the process of detoxification pathway that inhibits the production of mycotoxins and increasing the resistance of the plant to infection by means of genetic engineering. A recent approach to the search for hybrids that are resistant to mycotoxin contamination consists in the obtaining of genetically modified hybrids which create the resistance action through transgenes (Blandino & Rejneri, 2008; Wan Norashima et al., 2009).

An increase in concentrations of fumonisins during storage does not appear to be a major problem. However, grains should be harvested without additional kernel damage, screened to remove broken kernels, dry stored and maintained at moisture concentrations < 14% (Richard, 2007).

5.2 Food

Fumonisins have been found to be a very common contaminant of corn-based food and feeds in Africa, China, France, Indonesia, Italy, the Philippines, South America, Thailand and the USA (Kumar et al., 2008).

In addition to corn or corn-based food and feeds, the occurrence of fumonisins has also been reported in other products, such as: rice and sorghum (CAST, 2003), wheat noodles, curry, beer and corn-based brewing adjuncts (Yazar & Omurtag, 2008).

Fumonisins B1 and B2 have been reported in "black oat" feeds from Brazil and forage grass in New Zealand. FB1 and FB2 have been found in rural areas of South Africa, in home-grown corn produced and consumed by the people living in those areas. Commercial corn based human foodstuff from retail outlets in several countries contains fumonisins (Wan Norashima et al., 2009).

Castelo et al. (1998) have reported that fumonisins found in artificially contaminated cornmeal samples are unstable under roasting conditions, but remain fairly stable during the canning and baking of corn-based foods because the canned and baked products reach

lower temperatures than the roasted products. Jackson et al. (1996) indicated that foods that reach greater temperatures than 150 ºC during processing may have lower fumonisin levels.

5.3 Toxicity

At a cellular level, the structural similarity between sphinganine and FB1 suggests that the action mechanism of this mycotoxin is mainly via the disruption of the sphingolipid metabolism. This mechanism is reflected in effects on cell growth and differentiation, in cell death (apoptosis) and carcinogenicity (Yazar & Omurtag, 2008). Fumonisins have often been found to be involved in liver and kidney toxicity; they have been shown to be hepatocarcinogenic in male rats and female mice and nephrocarcinogenic in male rats (Mazzoni et al., 2011). Purified FB1 has been shown to cause Equine Leukoencephalomalacia (ELEM) and Porcine Pulmunary Edema (PPE). In most animal species, the main target organs for FB1 are the liver and kidneys (Richard, 2007; Yazar & Omurtag, 2008; Wan Norashima et al., 2009). There is no carryover of fumonisins into milk in cattle and there appears to be little absorption of them in tissues (Richard et al., 2007). The high incidences of esophageal cancer in the Transkei region of South Africa, in northern Italy and in China have been linked to the ingestion of fumonisin contaminated maize; recent findings suggest that fumonisins might increase the risk of neural tube defects in populations that consume large amounts of contaminated maize (Mazzoni et al., 2011; Yazar & Omurtag, 2008).

6. Patulin

Patulin (PAT) was discovered in 1943 in relation to *P. griseofulvum* and *P. expansum*. The molecule was first studied as a potential antibiotic, but the subsequent research demonstrated its toxicological properties (Baert et al., 2007; Birkinshaw et al., 1943). PAT is produced by several species of *Aspergillus*, *Penicillium*, among these, *P. expansum* is the most relevant. In fact, almost all *P. expansum* isolates are PAT producers (Puel et al., 2010). This mycotoxins can be found in different food products and raw materials, but apples and apple by-products are of greatest concern regarding PAT accumulation: the frequency of contamination in other food resources and products is much lower than in apple processing (Moake et al., 2005).

PAT has been reported to be mutagenic and to cause neurotoxic, immunotoxic, genotoxic and gastrointestinal effects in rodents; therefore, there is some concern that similar effects may occur in humans as a consequence of the long-term consumption of contaminated food or beverages (Hopkins, 1993).

PAT, 4-Hydroxy-4H-furo[3,2-c]pyran-2(6H)-one, is a water-soluble unsaturated heterocyclic lactone (Figure 5). The biosynthesis involves a series of condensation and redox reactions. The pathway consists of approximately 10 steps, as suggested from several biochemical studies and from the identification of several mutants that are blocked at various steps in the PAT biosynthetic pathway. A cluster of 15 genes involved in PAT biosynthesis, containing characterized enzymes, a regulation factor and transporter genes, has recently been reported (Puel et al., 2010).

PAT is a colourless and crystalline low-molecular weight compound, which is relatively heat resistant , with a melting point of 110 °C and a maximum UV absorption at 276 nm. It is soluble in water, ethanol, ethyl acetate, chloroform and acetone, while it is weakly soluble in ethyl ether and benzene and insoluble in petroleum ether, pentane and hexane (Pohland et al., 1982). PAT is unstable in a basic solution and stable in acidic media; in sulfurous

compound solutions, the instability is accompanied by the loss of biological activity (Harrison, 1989). It is stable at pH values ranging between 3,0 and 6,5: if the pH is higher, the lactone ring is opened and the toxic effect is lost (Janotovà et al., 2011).

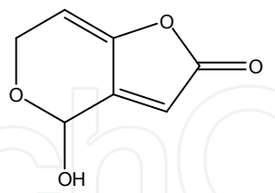


Fig. 5. Chemical structure of patulin.

6.1 Fungi

PAT has been isolated from several species of *Penicillium*, *Aspergillus*, *Paecilomyces* and *Byssochlamys* (Puel et al., 2010). Recent studies based on HPLC-DAD (High Pressure Liquid Chromatography-Diode Array Detector) or LC-MS (Liquid Chromatography-Mass Spectometry) analysis of secondary metabolites, have established the reliable PAT producing species, which are listed in Table 5.

Aspergillus, Clavati group (Varga et al., 2007)
A. clavatus; A. giganteus; A. longivesica
Penicillium (Frisvad et al., 2004)
P. carneum; P. clavigerum; P. concentricum; P. coprobium; P. dipodomyicola; P. expansum; P. glandicola; P. gladioli; P. griseofulvum; P. marinum; P. paneum; P. sclerotigenum; P. vulpinum
Paecylomyces (Samson et al., 2009)
Paecylomyces saturatus
Byssochlamys (Samson et al., 2009)
B. nivea

Table 5. Patulin producing fungi.

6.2 Food

Patulin-producing strains have been isolated from a variety of fruit and vegetables and both pastorized and unpastorized related products, but within the food industry, apples and apple products are of predominant concern as far as PAT contamination (Moake et al., 2005; Sant'Ana et al., 2008). PAT occurs mostly in apples evidently mould-damaged fruit, but sometimes fungal growth can occur internally, as a consequence of various kinds of damage, and can result in the occurrence of PAT in externally undamaged fruit. Therefore, apples must be handled adequately before and during processing to avoid all kinds of damage. It is also fundamental to reduce the possibility of contamination by eliminating mouldy fruit and taking particular care when cleaning containers (Codex, 2003b; Food and Agriculture Organisation of the United Nations [FAO], 2003). In terms of apple storage conditions, in general *P. expansum* shows psychrotrophic characteristics, in fact it is able to growth and produce PAT under refrigerated storage, but different strains show different capacities to produce PAT in different storage conditions (refrigeration and or controlled atmosphere) (Lovett et al., 1975; Paster et al., 1995; Taniwaki et al., 1989). The elimination of mouldy fruit is fundamental during storage because the greater the percentage of damaged

fruit in a stored batch, the greater the amount of PAT in the derived products. It has also been shown that the concentration of PAT in deck stored apples increases with storage time (FAO, 2003; Sydenham et al., 1997). In order to improve storage under refrigeration and in a controlled atmosphere against fungal growth and PAT production, additive treatments can be employed, including the use of sanitizers, natural or biological agents or a combination of the two (Chen et al., 2004). Another alternative is the use of polyethylene (PE) packages, with or without a controlled atmosphere, during storage and transport (Moodley et al., 2002). PAT can be reduced in stored apples through a washing stage with tap water, or tap water with active chlorine, or with highly pressurized water; the decrease percent depends on the initial amount of mycotoxin. The use of pressurized water makes it possible to remove the rotten parts of the fruit and also to reduce the fungal population, but it can also suspend and disperse PAT and spores in the washing water because it disturbs the rotten areas (Acar et al., 1998; Marin et al., 2006; Sydenham et al., 1997). Of all the apple products, apple juice is the most important source of PAT in the human diet throughout the world (World Health Organisation [WHO], 1995); the main steps of this production are summarized in Figure 6.

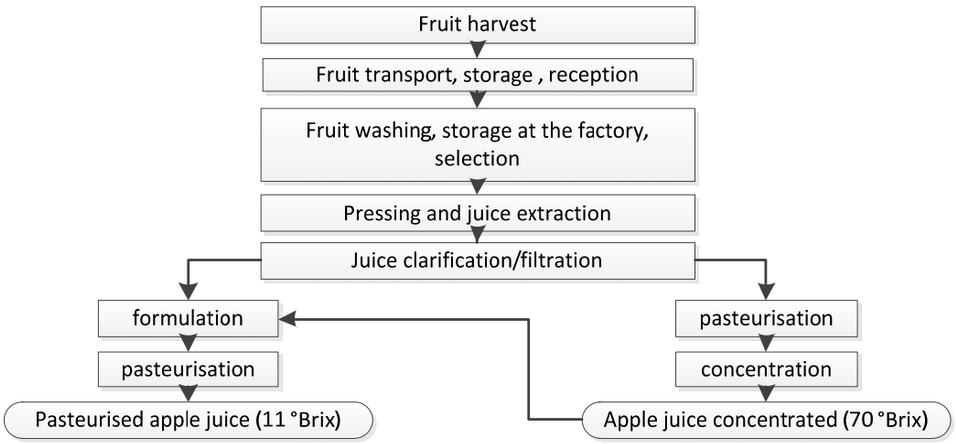


Fig. 6. Apple juice processing steps (modified from Sant'Ana et al., 2008)

PAT can be removed from juice by means of stirring or filtering through granulated activated carbon (Kadakal & Nas, 2002); the obtained percent of PAT reduction depends on the type of carbon, type of activation (physical or chemical), the solid content of the juice and the contact time (Leggott et al., 2001). As far as the heat treatments of juice, it is known that PAT is heat stable in acidic environments; nowadays various research and controversial results exist concerning the effect of the first pasteurization of the juice on the toxin (Kadakal & Nas, 2003). Experimental studies, on various combinations of temperature/time, generally demonstrate the heat stability of PAT to various time/temperature binomials (e.g. 80°C for 30 min, 100°C for 15 min at pH 2.0). Moreover, these studies show that if the contamination is high in the initial processing stages, it will be practically impossible to obtain significant reductions in the level of PAT. On the other hand, despite the studies showing no significant reduction in PAT in apple juice after pasteurization, the destruction of the spores of *P. expansum* reduces the risk of the subsequent production of this mycotoxin (FAO, 2003). Vacuum distillation is usually adopted for the concentration step of the juice and it can allow a reduction in the PAT level because of the time and temperature

exposition. Possibly PAT transformation occurs, while PAT removal to volatile phase is unprobable. As regard that, the results obtained in various studies are controversial, and in some cases show a certain reduction while in other no changes are observed (Kadakal & Nas, 2003; Leggott et al., 2000). The PAT levels in formulated juices may be affected by adding ingredients such as ascorbic acid, thiamine hydrochloride, pyridoxine hydrochloride and calcium pantothenate (Yazici & Velioglu, 2002). Nevertheless, the use of these additives has some limitations; as regard ascorbic acid, its use is influenced by the storage conditions and if it is oxidized, no further degradation of PAT is observable (Drusch et al., 2007). Other possible additives are sulphur dioxide, sodium benzoate and potassium sorbate (Lennox & McElroy, 1984; Roland et al., 1984), but the current demand for healthy food, free of additives, could result in an impediment to the use of such techniques. Thus, it is preferable to use treatments that guarantee the elimination/inactivation of the ascospores of the heat resistant fungi (such as filtration with diatomaceous earth) than to apply these additives.
It can be said that, although the juice manufacturing process stages are capable of reducing the amount of PAT in the final products to a certain extent, the incidence of this mycotoxin throughout the World confirms its stability to some degree; when faced with the techniques currently in use, only the adoption of adequate controls to reduce the incidence of fruit damage and rot, during pre-harvest, harvest and post-harvest, can lead to an important reduction in the final product, whether it is fruit for direct consumption or one of the various fruit products (Sant'Ana et al., 2008).

6.3 Toxicity

The health risks of PAT for humans include acute and chronic symptom and effects at a cellular level.
Some of the acute toxic signs that have consistently been reported are agitation, convulsions, dyspnea, pulmonary congestion, edema, and ulceration, hyperemia and distension of the gastro intestinal tract (WHO, 1995). Sub-acute toxicity has also been indicated: PAT is recognized to mainly induce gastrointestinal disorders; it has mainly been studied in rats, where it has been shown to induce weight loss, gastric and intestinal changes and alterations in the renal function (Puel et al., 2010).
PAT is genotoxic; most assays carried out with mammalian cells have been positive while those with bacteria have mainly been negative. Some studies have indicated that PAT impairs DNA synthesis. These effects might be related to the ability PAT to react with sulphydryl groups and to induce oxidative damage (Liu et al., 2007). The IARC has placed PAT in group 3, as "not classifiable as to its carcinogenicity to humans" (IARC, 1986). PAT can also alter the immune response of the host (Oswald & Comera, 1998). Several in vitro studies have demonstrated that PAT inhibits various macrophage functions. PAT has also been found to reduce the cytokine secretion of IFN-γ and IL-4 by human macrophages and of IL-4, IL-13, IFN-γ, and IL-10 by human peripheral blood mononuclear cells and human T cells (Luft et al., 2008; Wichmann et al., 2002). In vivo studies using mice have indicated variable effects of PAT on the immune system, such as an increased number of splenic T lymphocytes and depressed serum immunoglobulin concentrations (Escoula et al., 1988; Paucod et al., 1990). As regard humans, exposure to PAT, at levels that are consistent with potential human exposure in food, would not be likely to alter immune responses (Llewellyn et al., 1998). When injected into the air cell of chick eggs, PAT is found embryotoxic, depending on the age of the embryo, and teratogenic (Ciegler et al., 1976). PAT can induce a reduction in the protein and DNA content, in the yolk sac diameter, crown rump length, and somite

number count; it can also increase the frequency of defective embryos. Anomalies can include growth retardation, hypoplasia of the mesencephalon and telencephalon, and hyperplasia and/or blisters of the mandibular process (Smith et al., 1993).

At a cellular level, PAT is believed to cause cell damage by forming adducts with thiol-containing cellular components (Barhoumi & Burghardt, 1996); in fact, many enzymes with a sulfhydryl group in their active site are sensitive to PAT. PAT has also been shown to induce intra- and intermolecular protein cross-links (Fliege & Metzler, 1999). Finally, PAT can interact directly with DNA and RNA inhibiting transcription and translation (Lee & Roschenthaler, 1987).

7. References

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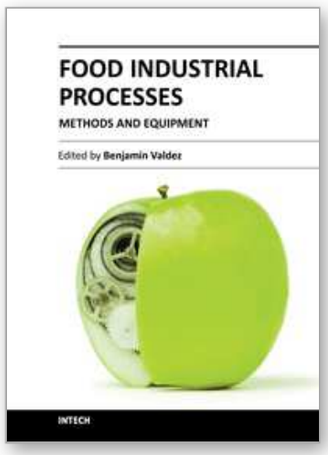

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The global food industry has the largest number of demanding and knowledgeable consumers: the world population of seven billion inhabitants, since every person eats! This population requires food products that fulfill the high quality standards established by the food industry organizations. Food shortages threaten human health and are aggravated by the disastrous, extreme climatic events such as floods, droughts, fires, storms connected to climate change, global warming and greenhouse gas emissions that modify the environment and, consequently, the production of foods in the agriculture and husbandry sectors. This collection of articles is a timely contribution to issues relating to the food industry. They were selected for use as a primer, an investigation guide and documentation based on modern, scientific and technical references. This volume is therefore appropriate for use by university researchers and practicing food developers and producers. The control of food processing and production is not only discussed in scientific terms; engineering, economic and financial aspects are also considered for the advantage of food industry managers.

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