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REVIEW PAPER

Ochratoxin A in Food: An Overview

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Abstract

Ochratoxin A (L-phenylalanine-*N*-[(5-chloro-3, 4-dihydro-8-hydroxy-3-methyl-1-oxo-1*H*-2 benzopyrane-7-yl)carbonyl] -(*R*)-isocoumarin) (OTA) one of the most studied mycotoxins is produced by *Penicillium verrucosum* and by *Aspergillus ochraceus* but a few isolates of *Aspergillus niger.* It is one of the most important mycotoxin contaminants in agricultural products and continues to attract global attention concerning the hazard and impact on both human and animals due to its toxicity and occurrence. It has been detected in food commodities such as cereals, wine, coffee, figs, dried fruits and beer and in feeds for animals. The International Agency for Research on Cancer classifies it as a possible carcinogen to human (group 2B). Its symptom includes low appetite, weight loss, faintness, depression, high thirst and increased urination. OTA is one of the major causes of death in human beings and animals. These toxic fungi, contaminate food products in different phases of production and processing, especially in suitable environmental conditions viz., temperature and moisture conditions.

Keywords: Mycotoxins, Ochratoxin, toxic, food, carcinogenic, *Aspergillus*, environment

Food safety has been one of the important issues, since a number of toxicants are present in the environment. Mycotoxins are the natural contaminants in food stuffs that contaminate more than 25% of the world commodities (Reddy *et al.,* 2010). Mycotoxins are the secondary metabolites produced by different types of fungi mainly *Aspergillus, Penicilium, Fusarium, Claviceps* and *Alternaria,* capable of growing on a large variety of plants and foodstuffs, and are hazardous to human health and animals even at lower concentrations. The major mycotoxins contaminating food are aflatoxins, ochratoxins, citrinin, ergot alkaloids, fumonisins, patulin, trichothecenes, and zearalenone (Bennett and Klich, 2003; Joshi *et al.,* 2013; Vettorazzi *et al.,* 2013). Mycotoxins of major significance are shown in Table 1. Among these, aflatoxin B, fumonisins B and ochratoxin A are the most toxic compounds to humans (Donmez-Altuntas *et al.,* 2003). The main concern of these natural occurring toxins is their acute and/or chronic toxicity which can cause death and/or deleterious effects (nephrotoxic, hepatotoxic, carcinogenic, mutagenic, teratogenic and immunosuppressive) (Abnet, 2007; Bräse *et al.,* 2009; FAO, 2001).

The diseases they cause, are known as mycotoxicosis. Mycotoxins can also contaminate the food in the food chain because of fungal infection of crops. Besides, mycotoxin production in agricultural crops can occur at various points in the food chain: at pre-harvest, harvest, drying, and storage (Marin *et al.,* 2013).

Ochratoxins are a group of mycotoxins that were discovered in the 1960's by Van der Merve *et al.* (1965) who also established its structure (Fig. 1). The Ochratoxins, A, B and C occur are phenylalanine derivatives of an isocoumarin nucleus. They are

Table 1: Mycotoxins of major significance

Mould species	Mycotoxins	References
Aspergillus parasiticus	Aflatoxins B_1, B_2, G_1, G_2	Applebaum and Marth,1981; Pildain *et al.,* 2008
Aspergillus flavus	Aflatoxins B_1, B_2	Pildain *et al.,* 2008
Fusarium sporotrichiodes	T-2 toxin	WHO, 1990; Wang *et al.,* 1993
Fusarium graminearum	Deoxynivalenol, Zearalenone	Bhat *et al.,* 2010; Diekman and Green 1992
Fusarium moniliforme	Fumonisin B_1	Gelderblom *et al.,* 1988; Castelo *et al.,* 1998
Penicillium verrucosum	Ochratoxin A	Varga *et al.,* 1996; Heenan *et al.,* 1998
Aspergillus ochraceus	Ochratoxin A	Varga *et al.,* 1996; Heenan *et al.,* 1998
Penicillium expansum	Patulin	Dutton *et al.,* 1984; Fuchs et al 2008; Moss, 2008

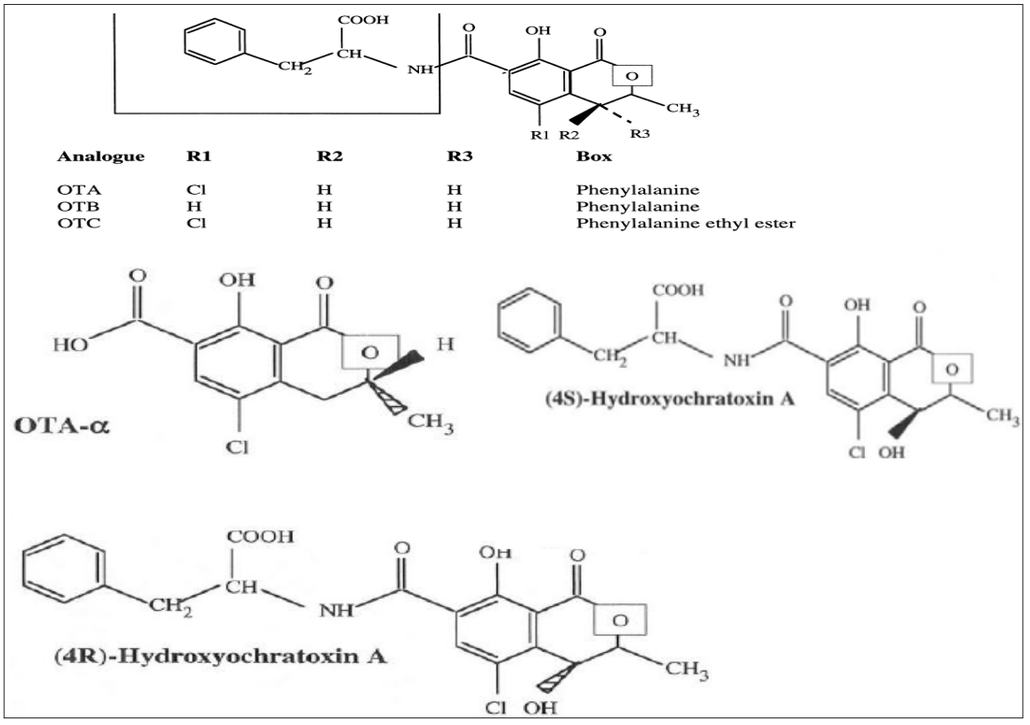

Fig. 1: Chemical structures of the Ochratoxins (***Source:*** O'Brien and Dietrich, 2005)

composed of a 3, 4 dihydro- 3 methylisocoumarin moiety linked via the 7-carboxy group to L-B-phenylalanine by an amide bond.

The chlorine containing metabolite, designated Ochratoxin A (OTA) is the major component of extracts from *Aspergillus ochraceus*. OTA is the most prevalent and toxic, and is classified as a carcinogenic (group 2b), because it has proven to be carcinogenic in kidney and liver (Pfohl-Leszkowicz *et al.,* 1998). Ochratoxin A is produced by several fungi, such as *Aspergillus carbonarius*, *Aspergillus niger*, *Aspergillus ochraceus* or *Penicillium verrucosum*, in food and feed products. It is a pentaketide derived from the dihydrocoumarins family coupled to β phenylalanine. Its chemical name is: L-phenylalanine-*N*-[(5-chloro-3, 4-dihydro-8-hydroxy-3-methyl-1-oxo-1*H*-2 benzopyrane-7-yl) carbonyl] -(*R*)-isocoumarin.

Ochratoxin A is commonly present in cereals, grapes, coffee, spices, nuts, cocoa, beer and wine. The critical factors that affect growth of OTA are producing

fungi temperature, moisture content and the time a product remains under adverse conditions. Other factors influencing the ochratoxin production are the presence of insect, mechanical injury, presence of spores, storm and rain damages, moisture stress, mineral nutrients availability, pH, oxygen and carbon dioxide levels, chemical and physical treatments, and, for some commodities, the product drying and re-wetting speed (Atalla *et al.,* 2003; Eskola, 2002; Magan *et al.,* 2003). Control of some of these factors could definitely lead to elimination or reduction of ochratoxin production in food commodities.

CHEMICAL AND PHYSICAL PROPERTIES OF OCHRATOXIN (OTA)

OTA is a crystalline and colourless compound. It is soluble in polar organic solvents and aqueous sodium hydrogen carbonate but only slightly soluble in water. OTA is structurally similar to the amino acid phenylalanine and has a melting point of about 90°C when crystallized from benzene as a solvate and 169°C when crystallised in pure form of xylene. It is optically active and exhibits blue fluorescence under UV light, but the ultraviolet spectrum varies with pH and with the solvent polarity (IARC, 1976). OTA has weak acidic properties and its pKa values are in the ranges 4.2−4.4 and 7.0−.7.3 for the carboxylic group of phenylalanine moiety and the phenolic group of isocoumarin part (Ringot *et al.,* 2006). OTA is a stable compound which is not destroyed by common food preparation and is also fairly stable to heat; in cereal products, up to 35% of the toxin withstands autoclaving (up to 3 hours).Thus in raw and processed food products OTA residues can be detected (IARC, 1976; EFSA, 2006) and is thus, a serious situation.

OCHRATOXIN A PRODUCERS

OTA is produced in foodstuffs by microfungi of the genera, *Aspergillus*, mainly in subtropical and tropical areas, and *Penicillium*, especially in temperate and colder zones (Van der Merwe *et al.,* 1965; Battilani, 2007). These toxigenic microfungi almost always produce several toxins at the same time, for example ochratoxin A, ochratoxin B or ochratoxin C (Stark, 2005). The simultaneous occurrence of these toxins can result in synergetic toxic effects. Table 2 gives an overview of the *Aspergillus* and *Penicillium* species that are apparently able to produce OTA in foodstuffs (Samson and Pitt, 2000; Samson and Frisvad, 2004).

Table 2: OTA producers in foodstuffs

Genera	Species	Foodstuffs (e.g.)	References
Penicillium	*P. Verrucosum* Dierckx	Cereals	Zinedine *et al.,* 2007; FAO, 2004
	P. nordicum Dragoni and Cantoni	Dry ham, salami, sausages	Leistner, 1984; Gareis and Scheuer, 2000
Aspergillus	*A. ochraceus*	Soya bean, nuts, red pepper, cereals, green coffee beans	Majerus *et al.,* 1993; Pitt and Hocking, 1997
	A. steynii	Coffee beans	Leong *et al.,* 2007; Noonim *et al.,* 2008
	A. carbonarius	Grapes, grape products, including grape juice, wines and dried vine fruits	IARC, 1993; Leong *et al.,* 2004
	A. westerdijkiae	Grapes, red pepper, Coffee beans	Frisvad *et al.,* 2004
	A. foetidus	Grapes	Ponsone *et al.,* 2007
	A. lacticoffeatus	Coffee beans	Samson *et al.,* 2004; Bokhari, 2007
	A. niger	Grapes, peanuts	Burdaspal and Legarda, 2007
	A. sclerotioniger	Coffee beans	Frisvad *et al.,* 2004
	A. tubingensis	Grapes	Samson *et al.,* 2004

Source: Samson and Frisvad, 2004; Ostry *et al.* 2013.

Table 3: Maximum Levels of Ochratoxin-A of Some Food Stuffs According To EU-Regulation and Point 2.2.11 is replaced by the 2.2.11.1, 2.2.12, 2.2.12.1 and 2.2.12.2 (Commission Regulation (EC) No 1881/2006)

Code	Ochratoxin A	Maximum limit (µg/kg)
2.2.1	Unprocessed cereals	5.0
2.2.2	All products derived from unprocessed cereals, including processed cereal products and cereals intended for direct human consumption with the exception of foodstuffs listed in 9 and 10	3.0
2.2.3	Dried vine fruit (currants, raisins and sultanas)	10.0
2.2.4	Roasted coffee beans and ground roasted coffee, excluding soluble coffee	5.0
2.2.5	Soluble coffee (instant coffee)	10.0
2.2.6	Wine (including sparkling wine, excluding liqueur wine and wine with an alcoholic strength of not less than 15 % vol) and fruit wine (11)	2.0 (12)
2.2.7	Aromatised wine, aromatised wine-based drinks and aromatized wine-product cocktails (13)	2.0 (12)
2.2.8	Grape juice, concentrated grape juice as reconstituted, grape nectar, grape must and concentrated grape must as reconstituted, intended for direct human consumption (14)	2.0 (12)
2.2.9	Processed cereal-based foods and baby foods for infants and young children (3) (7)	0.50
2.2.10	Dietary foods for special medical purposes (9) (10) intended specifically for infants	0.50
2.2.11	Green coffee, dried fruit other than dried vine fruit, beer, cocoa and cocoa products, liqueur wines, meat products, spices and liquorice	—
2.2.11.1	Spices *Capsicum* spp. (dried fruits thereof, whole or ground, including chillies, chilli powder, cayenne and paprika) *Piper* spp. (fruits thereof, including white and black pepper)	30 µg/kg as from 1.7.2010 until 30.6.2012
	Myristica fragrans (nutmeg) *Zingiber officinale* (ginger) *Curcuma longa* (turmeric) Mixtures of spices containing one or more of the above mentioned spices	15 µg/kg as from 1.7.2012
2.2.12	Liquorice (*Glycyrrhizaglabra, Glycyrrhiza inflate* and other species	
2.2.12.1	Liquorice root, ingredient for herbal infusion	20 µg/kg
2.2.12.2	Liquorice extract (42), for use in food, in particular beverages and confectionary	80 µg/kg

(3) Foodstuffs listed in this category as defined in Commission Directive 96/5/EC of 16 February 1996 on processed cereal-based foods and baby foods for infants and young children (OJ L 49, 28.2.1996, p. 17) as last amended by Directive 2003/13/EC (OJ L 41, 14.2.2003, p. 33).

(7) The maximum level refers to the dry matter which is determined in accordance with Regulation (EC) No 401/2006.

(9) Foodstuffs listed in this category as defined in Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes (OJ L 91, 7.4.1999, p. 29

(10) The maximum level refers to the milk and milk products, to the products ready-for-use (marketed as such or reconstituted as instructed by the manufacturer) and in the case of products other than milk and milk products, to the dry matter. The dry matter is determined in accordance with Regulation (EC) No 401/2006.

(11) Foodstuffs listed in this category as defined in Council Regulation (EC) No 1493/1999 of 17 May 1999 on the common organisation of the market in wine (OJ L 179, 14.7.1999, p. 1) as last amended by the Protocol concerning the conditions and arrangements for admission of the Republic of Bulgaria and Romania to the European Union (OJ L 157, 21.6.2005, p. 29).

(12) The maximum level applies to the products produced from the 2005 harvest onwards.

(13) Foodstuffs listed in this category as defined in Council Regulation (EEC) No 1601/91 of 10 June 1991 laying down general rules on the definition, description and presentation of aromatised wines, aromatised wine-based drinks and aromatised wine-product cocktails.

(OJ L 149, 14.6.1991, p. 1) as last amended by the Protocol concerning the conditions and arrangements for admission of the Republic of Bulgaria and Romania to the European Union. The maximum level for OTA applicable to these beverages is function of the proportion of wine and/or grape must present in the finished product.

(14) Foodstuffs listed in this category as defined in Council Directive 2001/112/EC of 20 December 2001 relating to fruit juices and certain similar products intended for human consumption (OJ L 10, 12.1.2002, p. 58).

(42) The maximum level applies to the pure and undiluted extract, obtained whereby 1 kg of extract is obtained from 3 to 4 kg liquorice root).

Source: Ramesh and Jayagoudar, 2017.

Three major OTA producing species, *Aspergillus ochraceus*, *Aspergillus carbonarius* and *Penicillium verrucosum*, have quite different ecologies as well as physiologies. OTA production is higher at 0.98 a_w, regardless of temperature level and its production is higher at temperatures between 25 to 30°C (Futagami *et al.*, 2011; Wang *et al.*, 2016). *Aspergillus ochraceus* and closely related species grow at low water activities and at moderate temperatures and are mostly associated with dried and stored foods, especially cereals. The second producing *Aspergillus* species, *Aspergillus carbonarius* and closely related *Aspergillus niger* grows well at high temperatures, on the other hand *Aspergillus carbonarius* is commonly found in grapes and similar fruit that mature in sunlight and at high temperatures. *Aspergilli (*Black spores) are considered as the primary source of OTA on grapes (Ostry *et al.*, 2013).

The main food habitat for *Penicillium verrucosum* is cereals grown in the cool temperate Zones. Higher amounts of OTA could be produced on wheat than on other crops, including peanuts, maize and soybeans (Pitt *et al.*, 2002).

OTA can also be produced by toxigenic microfungi that grow on products made of pork meat during their ripening. *Penicillium nordicum*, a potent OTA producer, has been proven to grow on meat and meat products (Dall'Asta, 2010; Rodriguez *et al.*, 2012). OTA is also found in meat products originating from animals that are fed with feedstuffs made from contaminated cereals as a major dietary component (Pitt *et al.*, 2002).

BIOSYNTHESIS OF OCHRATOXIN A

It is widely believed that the isocoumarin group is a pentaketide formed from acetate and malonate *via* a polyketide synthesis pathway. Thus, a polyketide synthase, which is considered as a key enzyme, is involved in the OTA biosynthesis in a similar way of other polyketide mycotoxins such as fumonisins (Proctor *et al.*, 1999) and aflatoxins. Huff and Hamilton (Huff and Hamilton, 1979) proposed a biosynthetic pathway of OTA. According to Huff and Hamilton, three distinct steps occur in OTA biosynthesis (Fig. 2):

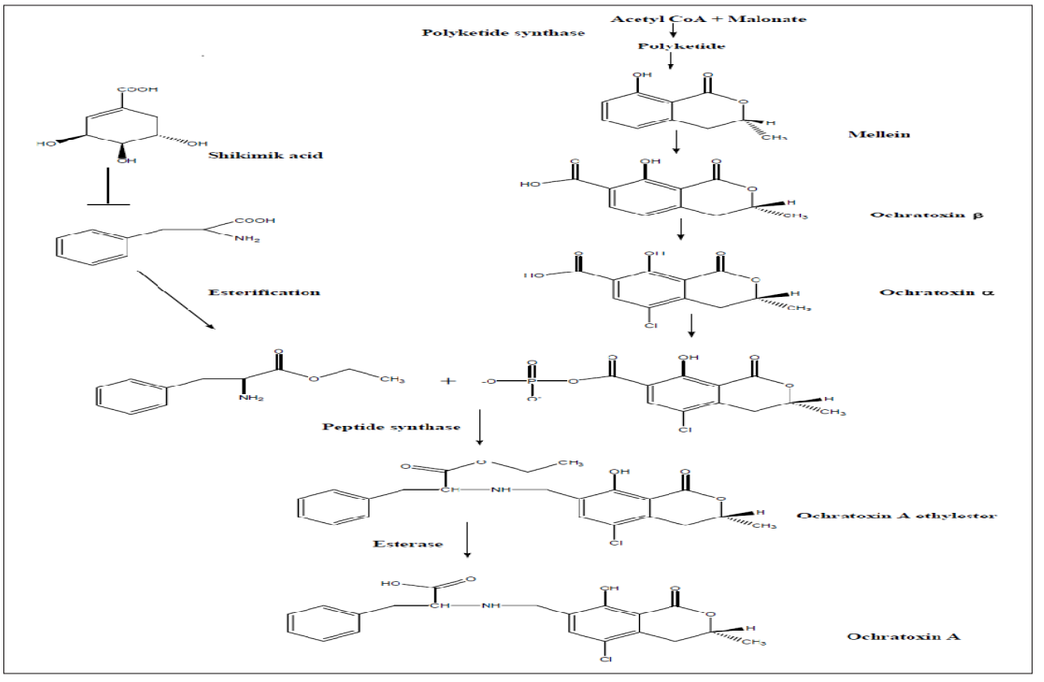

Fig. 2: Schematic representation of the hypothetical OTA biosynthetic pathway as proposed by Huff and Hamilton

- The first part is polyketide synthesis of ochratoxin α *via* mellein involving a polyketide synthase.
- The second step includes acyl activation: mellein is methylated and oxidized to 7-Carboxy-Mellein (=OTβ). Chlorination by a chloroperoxidase leads to OTα.
- In the third step, linkage of those activated precursors *via* a synthetase takes place, generating OTC.
- In the last step an ethyl ester of OTA: de-esterification by an esterase or transesterification takes place in this biosynthetic pathway.

While Harris and Mantle (2001) postulated different pathway, in which mullein and ochratoxin C plays no role in ochratoxin A biosynthesis and they proposed a pathway leading from ochratoxin B (de-chlorinated form of OTA), in which the isocoumarin moiety was formed from acetate units *via* the pentaketide pathway and then, carboxylated and chlorinated to form ochratoxin A. The final step is the linkage of isocoumarin moiety to phenylalanine through a carboxyl group, which is catalyzed by the ochratoxin A synthetase (Harris and Mantle, 2001).

OCCURRENCE OF OCHRATOXIN AND COMMON FOOD PRODUCTS INVOLVED

OTA has been detected in foodstuffs of both plant and animal origin and found mostly in cereal and cereal products all over the world. It has been also found in other commodities particular, in flour, bread, pasta (Majerus *et al.,* 1993), beer, coffee, cacao, chocolate, spices, vegetables, green tea, pistachios, figs, raisins, grape juice, wine (Skarkova *et al.,* 2013) liquorice and chestnuts. Animal origin food, such as raw pork meat, pork blood products, kidney or poultry liver, are indirectly contaminated by OTA when animals are fed with contaminated feedstuffs (EFSA 2006; Duart *et al*., 2012; Skarkova *et al.,* 2013; Bertuzzi *et al*., 2013). However, meat products, such as raw ham muscle, cured meats, salami or ham and cheese are also directly contaminated by OTA (Dall'Asta *et al*., 2008).

OTA in Cereal

It was reported that approximately 25% of cereals produced in the world are contaminated by mycotoxins (Devegowda *et al.,* 1998). *Penicillium verrucosum* has been found to survive between crops on grain and dust remaining on machinery and in stores. Efficient cleaning of machinery and stores will reduce the "carry over" of this fungus between the seasons. The contents of Ochratoxin A in cereals of different types reported have been shown in Table 4.

Table 4: Contents of ochratoxin A in cereal grains reported in the SCOOP-2 report (European Commission 2002)

Cereal grains	Mean (mg/kg)	Maximum (mg/kg)	>EU limit of 5 mg/kg (%)	Number of samples
Wheat	0.27	32	0.8	979
Rye	0.60	33	2.0	444
Barley	0.30	6.4	0.7	142
Maize	0.17	4.9	0	267
Oat	0.19	5.9	0.6	164

EU maximum limit for raw cereal grains

Source: Jorgensen, 2005.

OTA in wine

OTA is a frequent contaminant of wine (Ottender and Majerus, 2000). The presence of OTA in wine was reported for the first time in 1995 (Zimmerli and Dick, 1995; Murillo-Arbizu *et al*., 2010) and accordingly maximum permitted level of 2 µg/L for wine was enforced in the EU (Chiodini *et al.,* 2006). Further, the OTA levels in wine depend on different factors such as the climate, the date of harvesting and different wine-making procedures (Burdaspal and Legarda, 2007; Lopez *et al.,* 2002). The reported Ochratoxin A levels in different wine are reportrd in Table 5.

Ochratoxin A in Coffee

OTA can be introduced to coffee in growing, processing, and storage (Sibanda, 2006). Drying of the coffee is another source of mold which can lead to OTA contamination. Finally, if beans are stored

Table 5: Reported Ochratoxin A concentrations in wines from different regions

Average OTA concentration μg/l	N	Origin (observations)	Reference
White table wines - <3 to 0,178 μg/l	118		Zimmerli and Dick, 1996
Red table wines - <3 to 0,338 μg/l	15	Switzerland	
Dessert - 0,003 – 0,017 μg/l	114 vinhos	Europe (one from	Majerus *et al.*, 1996
White table wines - 0,007 μg/l		Algeria-1,85 μg/l)	
Red wine - <10 to 7,63 μg/l	56	Italy	Visconti *et al.*, 1999
White wines – 0,02 μg/l av.	69	Portugal and Hungary	Otteneder *et al.*, 2000
Red and white wines<1	96 red	Italy (Northern – 100 % < 0,2 μg/l	Pietri *et al.*, 2001
a 3,856 μg/l	15 white		
Rosé - 0,031 μg/l av.	32	Wines from Spain, France, Italy,	Burdarspal *et al.*, 1999
White wines – 0,02 μg/l av.	69	Portugal and Hungary	Otteneder *et al.*, 2000

N = Number of samples.

Source: Alves, A. and Herbet, P. 2011.

in high humidity environments, it is possible to introduce OTA during storage. The detection of Ochratoxin levels in coffee are shown in Table 6.

Table 6: Positivity of OTA in 81 instant coffee samples

Concentration range of OTA (ng/g)	of OTA (ng/g) (number of positive samples)	Relative frequency (%)
< LOD*	1	1.2
0.16 – 0.50	13	16.0
0.51 – 1.00	22	24.7
1.01 – 1.50	20	27.2
1.51 – 2.00	18	22.2
2.01 – 2.50	3	3.7
2.51 – 5.00	3	3.7
5.01 – 10.00	1	1.2

*LOD = Limit of detection (0.16 ng/g)

Source: Almeida *et al.* 2007.

OTA in Meat, Eggs and Milk

Transfer of OTA along the food chain of animal products depends essentially on several factors. Some of these factors include; the extent of exposure of animals to an OTA-contaminated diet; the level of transfer of intact OTA into the bloodstream of animals; the degree of OTA persistency in the blood and its accumulation in different tissues; and the magnitude of the transfer of OTA from blood to milk, meat or eggs (Battacone *et al.*, 2010).

TOXICITY AND HEALTH IMPLICATIONS

OTA is the most toxic member of the ochratoxin group. Several studies have shown the toxic effect of OTA such as nephrotoxic, hepatotoxic, teratogenic and immunotoxic properties. OTA has also been associated with the development of kidney and liver tumors in mice and rats. For these reasons, the International Agency for Research on Cancer (IARC) of the WHO classified OTA in 1993 as possible carcinogenic to humans (group 2B) based on sufficient evidence in humans (Balconi *et al.*, 2005). OTA is relatively stable in human blood and its half–life may reach about 35 days in serum **(**Studer-Rohr *et al.*, 2000**;** Fapohunda *et al.*, 2014). It binds almost completely to plasma proteins and accumulates in kidney and liver tissue. In all species examined, OTA is hydrolyzed (detoxified) to ochratoxin α, mainly by the bacterial microflora in the intestine (Saez *et al.*, 1987). Human exposure to OTA is worldwide and occurs mainly through consumption of contaminated crops or food. Animal derived food products, however, contribute

to a lesser extent to human OTA exposure, with the exception of babies and infants, due to their high consumption of milk and milk products, and their specific metabolism (Kuiper-Goodman, 1998). OTA in human can be detected in human blood and breast milk (Biasucci *et al.,* 2011). The major targets for OTA toxicity in all mammalian species are the kidney, and endemic nephropathies. OTA is also teratogenic, and in the foetus the major target is the developing central nervous system (Kuiper-Goodman, 1989).

The mechanism of OTA toxicity involved the inhibition of protein synthesis, impairment of calcium homeostasis, induction of lipid peroxidation, oxidative stress and DNA damage with tissue–specific differences (EFSA, 2006).

Acute toxicity

The acute toxicity of OTA is relatively low, although large species differences and sensitivity are seen with oral LD_{50} values ranging widely in different species. Oral LD_{50} values have ranged from 0.2 mg/kg bw in dogs, 1 mg/kg bw in pigs, and 46-58 mg/kg bw in mouse. Dogs and pigs have been reported to be the most sensitive species (Harwig *et al.,* 1983). Acute poisoning effects include multifocal haemorrhages in various organs and fibrin thrombin in the spleen, brain, liver, kidney and heart. Nephrosis, hepatic and lymphoid necrosis, and enteritis with villous atrophy have also been observed in the test species **(**JECFA, 2001).

Nephrotoxicity

Nephropathy is the major toxic effect of OTA. Ochratoxin A has been found to be nephrotoxic in all mammalian species, although differences in toxicity have been found among species and sex (Hope and Hope, 2012). OTA has been associated with human nephropathy (Lopez de Cerain *et al.,* 2002; Pfohl-Leszkowicz, 2009) and cause the human fatal diseases known as Balkan Endemic Nephropathy, a severe and fatal renal disease affecting populations in the Balkan Peninsula. It is also considered to be the major cause of the Tunisian Nephropathy (Hassen *et al.,* 2004). The main nephrotoxic effect is in the postproximal nephron and proximal tubules (Gekle *et al.,* 1993). Maaroufi *et al.* (1995) reported OTA in human blood samples comparing persons with various types of chronic kidney disease with controls showed elevations in serum ochratoxin which were highest in those diagnosed with chronic interstitial nephropathy.

Genotoxicity

Ochratoxin A has been shown to induce DNA damage and chromosomal aberrations in mammalian cells *in vitro* as well as DNA damage and chromosomal aberrations in mice treated *in vivo*. However, the mechanism for genotoxicity is unclear and there is no evidence that it is mediated by direct interaction with DNA (Dommez-Altunatas *et al.,* 2012).

Neurotoxicity

OTA was shown to be neurotoxic in rats at oral doses of 0.12-0.29 mg/kg body weight per day given for 1 to 6 weeks (EFSA, 2006) while Soleas *et al*. (2001) reported that OTA can be regarded as a possible cause of certain lesions as well as damage at the cerebral level. Thus, this substance seems to be highly toxic for the nervous cells and able to reach at any time the neural tissue (brain, retina).

Teratogenicity

OTA also acts as potent teratogen to various laboratory animals. It can cross the placenta and accumulate in faetal tissue causing various morphological anomalies. Mayura *et al.* (1984) have reported elicitisation of prenatal dysmorphogenesis in rats and mice. The mechanism of OTA induced teratogenesis has not however been clearly defined and may involve an indirect effect through maternal action and/or a direct effect on the developing conceptus (Petzinger and Weidenbach, 2002) and osteoblasts, and osteoclasts and interference in the calcium homeostasis (Khan *et al.,* 1989). Thus, the intensity of malformations depends on the route of administration and the gestative period.

Immunotoxicity

OTA in certain conditions act as a powerful immunosuppressor which is observed at low or high doses. Necroses of lymphoid tissues were reported indicating their earlier high sensitivity to the OTA (Creppy *et al*., 1991), humoral and cellular immunity affections were also described. OTA seems to play a role in the inhibition of the peripherals T and B lymphocytes proliferation and stops the production of interleukin 2 (IL2) and its receptors. Moreover, it blocks the activity of killer cells as well as the production of interferon (Pfohl-Leszkowicz *et al*., 1999).

Carcinogenesis

OTA is proved to be a carcinogen and in 1993, the International Agency for Research on Cancer (IARC) classified ochratoxin A as a possible human carcinogen (Group 2B) and concluded that there was sufficient evidence in experimental animals for the carcinogenicity of OTA and inadequate evidence in humans for the carcinogenicity of ochratoxin A (IARC, 1993).

CONCLUSION

Ochratoxin A (OTA) is the single most potent member of this group of mycotoxins, known to occur in commodities like cereals, coffee, dried fruit and red wine. It is considered a human carcinogen and is of special interest as it can be accumulated even in the meat of animals. Ochratoxins are a group of mycotoxins produced as secondary metabolites by several fungi of the *Aspergillus* or *Penicillium* families and are weak organic acids consisting of a derivative of an isocoumarin. Although the fungi capable of producing ochratoxins are frequently encountered on foods and feeds, surveys have shown that contamination of raw agricultural products is region-dependent. As might be expected, occurrence rates and levels of ochratoxin A have been far lower in human foods than in raw agricultural products.

Various strategies have been developed to prevent OTA contamination of foods. Some microorganisms have been proven to prevent the growth of ochratoxigenic fungi and OTA production. They could be used as natural control material. The impact of the treatment on food quality should also be investigated. Thermal treatment does not completely eliminate OTA, therefore the contaminated food contains, after thermal treatment, OTA rennant. Some microorganisms have been detected to reduce the amount of OTA in cultivating media.

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