Ass. Univ. Bull. Environ. Res. Vol. 7 No. 1, March 2004

AUCES

MYCOTOXICOSIS
2-OCHRATOXIN A

B.I. Agag

Biochemistry Department, Animal Health Research Institute, Agriculture Research Center.

REVIEW ARTICLE

ABSTRACT :

Mycotoxins are toxic secondary metabolites synthesized by fungi when moisture and temperature are suitable. The mycotoxins of concern are aflatoxins, ochratoxins, fumonisins, zearalenone deoxynivalenol and T-2 toxin. Ochratoxins are a group of structurally related metabolites that are produced by several Aspergillus and Penicillium species. Ochratoxins A the most prevalent naturally occurring member of the group in a nephrotoxic, immunosuppressive, teratogenic and carcinogenic in many species.

Contamination of food and feed supplies with ochratoxins A could increase the health risks to humans and animals.

In human, OA is implicated in Balkan endemic nephropathy (BEN), a disease characterized by tubulonephritis. It induces in animals, a tubulointerstitial nephropathy similar to BEN in human. In this article, the toxicity of OA in human, animals and poultry was discussed.

INTRODUCTION:

The ochratoxins are a group of fungal metabolites composed of an isocoumarin moity (7- carboxyl-S-chloro-8- hydroxy-3, 4-dihydro-3-R- methylisocoumarin or ochratoxin α) linked to L-B-Phenylalanine (van der Nerwe *et al.*, 1965).

The ochratoxins are produced by several species of Aspergillus and Penicillium (most commonly *A. ochraceus* and *P. viridicatum*) on grains such corn (Ribelin, 1978).

The production of ochratoxin is influenced by strain of fungus, substrate, temperature and water activity (Shotwell *et al.*, 1969a). Ochratoxin production can occur at environmental temperatures as low as 4°C in grains with moisture content of 18.5- 40%. Water activity and temperature of the stored grains are the main factors controlling OA formation. Laboratory trials showed that the minimum water activity for OA product were 0.83-0.90 depending on the toxigenic strain, whereas optimum temperatures for OA production ranged from 4 to 37°C depending on the water activity value and toxigenic strain involved (Krogh, 1987). At optimum water activity, the temperature range for ochratoxin production by *A. ochraceus* was 12-37°C, whereas that of *P. cyclopium* and *P. viridicatum* was 4-31°C (WHO, 1990).

Although, seven metabolites are included in the ochratoxin group only ochratoxin A (OA) has been found widespread as a natural contaminant. Ochrotoxin B (OB) is rarely found as a natural contaminant and the remaining ochrotoxin metabolites have never been observed in naturally contaminated cereal grains (Krogh, 1987).

OA derives into name from *Aspergillus ochraceus*, the first mold from which it was isolated by van der Merw *et al,* in 1965. The natural occurrence of OA in plant products was first reported in 1969 in a sample of corn that contained 150 ppb OA (Shotwell *et al.,* 1969b). Contamination with OA is most common in cereal grains such as barley, wheat, rye and corn (Krogh, 1987).

OA occurs widely in plants and plant products but most frequently in cereal grains infected with *P. verrucosum*, particularly in north temperate growing areas. Compared to preharvest production, post-harvest OA formation is regarded as the predominant factor in the contamination of insufficiently dried starch-rich foodstuffs, cereals and derived products (Weidenborner, 2001).

OA is the major ochratoxin component and is the most toxic, followed by OB and OC (Thrasher, 2003). Ochratoxin C (OC) is almost equal in toxicity while ochratoxin B (OB) is about 1/10 as toxic and occurs extremely rarely (FDA, 1979). OA is carcinogenic, teratogenic mutagenic and immunosuppressive in several species of animals (Krogh, 1992; Kuiper-Goodman and Scott, 1989; SCF, 1998). Its target organs are the kidneys and the developing nervous system (Kuiper-Goodman and Scott, 1989; Krogh, 1992).

In 1993, the international agency for research on cancer (IARC) classified OA as a possible human carcinogen (group 2B) based on sufficient evidence for carcinogenicity in animal studies and in adequate evidence in humans (IARC, 1993). OA crosses the placenta and is also transferred to newborn rats and mice via lactation (Hallen *et al.,* 1998). In addition OA-DNA adduits are formed in liver, kidney and other tissues of the progeny (Pfohl- Leszkowicz *et al.,* 1993; Petkova- Bocharova *et al.,* 1998). Further it may be implicated as a factor in Balkan Endemic Nephropathy (BEN) and development of urinary tract tumours in humans and mycotoxin nephropathy in animals and poultry. Also, recent data from France and North Africa point towards a correlation between chronic interstitial nephritis in humans and higher exposure to OA (SCF, 1998).

Absorption, distribution and excretion:

In human, OA is rapidly absorbed throughout the entire gastrointestinal tract, binds to plasma albumin (like many acidic compounds) and transported into target organs especially the kidney. It is cleaved into phenylalanine and a less toxic iso-coumarin derivative (ochratoxin alpha) by microbial flora of the colon and by carboxypeptidase A and alpha-chymotrypsin (Bauer and Garies, 1987 and Hagelberg *et al.,* 1989).

In mammals, OA is absorbed primarily from the stomach and proximal jejunum, enters the circulation through the portal vein, although some of it can be absorbed by lymphatic vessels. Once absorbed, OA is transported and bound to plasma proteins, especially albumin. Binding of OA to the serum albumin and recycling in the bile and kidney contributes to its long half- life in animals (Krogh, 1991; Marquardt and Frolich, 1992).

Ruminants do not absorb much OA when the concentration in the feed is low because, it is hydrolyzed rapidly by their ruminal flora and intestinal microorganisms (IARC, 1993), to the isocoumarin moities ochratoxins alpha and beta.

These metabolites along with OA are found in the urine (FDA, 1979). With higher concentrations in the feed, considerable amounts of OA escape fermentation n the rumen and hindgut. It was estimated that the application of at least 1.66mg OA/ kg b.wt for 4 days is necessary to detect any residues of OA in the milk of ruminants. Therefore, OA levels commonly found in *P.verrucosum*-contaminated feeds do not represent a substantial health risk to these animals. However, significant contamination in a number of tissues of single stomach food animals (e.g. pigs and poultry), especially the kidneys, due to carry over from feed is possible. These animals belong to the group of susceptible monogastric livestock showing nephropathy (Weidenborner, 2001).

Absorbed OA is strongly bound to serum albumin (Galtier *et al.*, 1980) and other macromolecules (Hult and Fuchs, 1986), and maximum concentration is reached 4-8 hours after dosing. The overall percentage of OA absorbed is 66%, 56%, 56% and 40%, respectively, for the pig, rat, rabbit and chicken (Zuzuki *et al.*, 1977; Galtier *et al.*, 1981).

In the blood, OA is present bound to serum albumin and in its free form. Particularly in humans, cattle and pigs, OA is strongly bound to serum albumin (Weidenborner, 2001). Binding of OA to the serum albumin and recycling in the bile and kidney contributes to its long half- life in animals (Krogh, 1991; Marquardt and Frolich, 1992).

The amount of unbound OA increases with higher doses of the mycotoxin. OA appears to deposit in all soft tissues. The highest concentrations occur in kidneys, liver and skeletal muscle with the kidney having the greatest unit concentration (FDA, 1979). Tissues distribution in pigs, rats, chickens and goats generally follows the order kidney > liver > muscle> fat (Harwing *et al.,* 1983) or in same recent studies kidney > muscle > liver > fat (Madsen *et al.,* 1982; Mortensen *et al.,* 1983).
Generally, ochratoxin metabolites in animals are primarily found in the urine and milk and a small fraction (<1%) of the ingested toxin is retained in the tissues. The half-life time of the toxin depends on both the dose and the animal species varying from 0.7 hours in fish to 120 hours in rats and 480 hours in monkey (Galtier, 1991). Wide species difference in the serum half-life of OA have been reported after oral administration, in the monkey (*Macaca mulata*) 510 hours (Hagelberg *et al.*, 1989), in the pig, 72-120 hours (Hagelbergc *et al.*, 1989) in permanent calf 77 hour (Sreemannarayana *et al.*, 1988) in rats 55-120 hours (Hagelberg *et al.*, 1989), in mice 24-39 hour (Fukui *et al.*, 1987), in quail 6.7 hours and in chickens 4.1 hours (Hagelberg *et al.*, 1989).

The fact that the half- life of OA in humans is 8- 12 times longer than in rats is important for risk assessment. Since this mycotoxin is fat soluble and not readily excreted, accumulation in fatty tissues occurs (Weiderborner, 2001)
The excretion of OA in milk was studied in rabbits intravenously injected with 1-4 mg/ kg b.wt., as single dose. At the highest dose injected, the milk contained 1 mg OA/liter. Ochratoxin alpha and 4-hydroxy-OA were not detected (Galtier *et al.*, 1977).

In a study on goats given a single dose of tritium-labled OA (0.5 mg/ kg b.wt., more than 90% of the ingested OA was excreted in 7 days. The comulative excretion amounted 53% in the feces, 38% in the urine, 6% in the milk and 2% in the serum (Nip and Chu, 1979). Detectable concentrations of OA disappear from the red and white muscles within 24 hours post-withdrawal, but persist in the liver and kidney for more than 48 hours (Prior and Sisodia, 1978).

In hens, residues of ochratoxin occur rapidly after the initiation of ochratoxin feeding, are diffuse throughout most tissues and are eliminated within 5 to 7 days after the removal of ochratoxin from the diet (Juszkiewicz *et al.,* 1982).

In the pigs OA at a level of 1 mg/ kg feed for one month and then kept on a toxin free diet for another month, the half residual life of the 4 tissues investigated (kidney, liver, muscle and adipose tissue ranged from 3.5 to 4.5 days. The toxin could still be detected in the kidneys one month after termination of exposure (Krogh *et al*., 1976 a).

Human ochratoxicosis:

Human exposure to ochratoxin A:

The main contributor to the OA intake in humans are cereals and cereal products, other possible contributors are coffee, bear, pork products containing pig blood, pulses and spices (Heohler, 1998) Ochratoxin A has been the mycotoxin most commonly found as a residue in pork and poultry meat (CAST, 1989). Although infection of meat and fish with *P. verrucosum* (and possible mycotoxin formation) has been reported, contamination of meat product is more usually due to carry over of OA from contaminated animal feed into blood, kidneys and muscles (Weidenborner, 2001). Human intake of hen's eggs may be one of the routes of exposure to the toxin because a permanent intake of OA by laying hens can lead to accumulation of the toxin in thee egg (Fuchs *et al.,* 1988). It is suggested that for humans the bioavailability for OA residues is higher in cereals than in meats, as in the latter OA is bound to proteins (Weidenborner, 2001).

Balkan endemic nephropathy (BEN):

The prevalence of human ochratoxicosis is being determined in several countries including Bulgaria, Yugoslavia, Germany, France, Italy, Canada, Japan and Northern Africa mainly Tunisia. In 1957 to 1958, an unusual chronic disease known as Balkan endemic nephropathy of the kidney occurred endemically in Bulgaria, Yugoslavia and Rumania (Hult *et al.,* 1982). Balkan endemic nephropathy is a chronic disease that predominately affects women and progress slowly up to death (WHO, 1990). Histopathologically, it is characterized by tubular degeneration, interstitial fibrosis and hayalization of glomeruli in the more superficial part of the cortex (Heptinsall, 1974).

The disease is of indefinite onset without acute manifestations. Among the earliest and most frequent complains are headache, lassitude, easy fatigue and anotoxia. The typical syndrome includes a shallow, copper colored skin, yellowing of the palms and soles, anemia in the preazatemic stage and perhaps occasional profuse intermittent hematuria, due to tumors of the urinary passages, there is no hypertension or edema (Angsubhakorn, 2000).

Age-specific incidence rates are highest above the age of 40.Younger cases occur in the 10-19 years-old age group (Stoyanov *et al*., 1978) In one of several endemic regions in Yugoslavia, the prevalence varied from 3% to 8% (Harbar *et al*., 1976), mainly in rural areas where food is home produced (cereal and bread).

A high incidence of tumors of the urinary system is strongly correlated with the prevalence of BEN (Ceovic *et al*., 1976; Chernozemsky *et al*., 1977; Nicolov *et al*., 1978). In one instance in Bulgaria, 14.6% of patients with tumors of the urinary system were also affected by EN. Among the tumors of the urinary system, cancers of the renal pelvis and ureters are more frequently associated with nephropathy than urinary bladder tumors. Recently, it has been suggested that OA can cause testicular cancer in humans. The incidence of rates of testicular cancer in 20

countries were significantly correlated with the percapita consumption of coffee and pig meat (Schwartz, 2002).

OA contents in foods:

Surveys an OA contents in foods from regions with high incidence rats of EN and urinary tract tumors were conducted.

In Yugoslavia, surveys indicated that the contamination of foodstuffs (grains, maize, pork meat) with OA occurred in 12.8% of samples in an area where the prevalence of BEN was 7.3%, compared with only 1.6% of contaminated samples in areas free of the disease (Krogh *et al.*, 1977).

The concentration of OA in maize was 5-90 µg/kg and that in pork meat, 5 µg/ kg (Krogh *et al.*, 1977), with levels of up to 27 µg/kg in pig kidneys (Pepeljnjak *et al.*, 1982). Similarly, studies in Bulgaria have revealed that 16.7% of beans and 27.3% of maize from an endemic area were contaminated with OA compared with 7.1% and 9%, respectively, from a non-endemic area (Petkova-Bocharova and Castegnaro, 1985a).

Blood and milk levels of OA:

Exposure rates of OA are measurable in blood of humans and are established in several countries including Scandinavia, Germany, France, Italy, Canada, Japan and Northern Africa mainly Tunisia and Egypt (Creppy *et al.,* 1998).

A survey on the presence of OA in blood samples in Yugoslavia reported a prevalence of 16.6% positive cases in an endemic village and 6% in non-affected one (Hult *et al.*, 1982). In Bulgaria reported rates were 17.7% in an endemic area and 7.7% in non-endemic one ((Petkova-Bocharova *et al.*, 1985b). In the Federal Republic of Germany, a study of human milk obtained from women in two hospitals (patient category not stated) revealed that 4 out of 36 samples (11.1%) contained OA, with a mean value of 0.024 ng/ml and a range of 0.017-0.030 ng/ml (Bauer and Gareis, 1987; Garies *et al.*, 1988).

In Hungary, 52 out of 100 human blood samples collected at random (52%) were found to contain OA (0.2- 12.9 ng/ ml), and 38 out of 92 colostrum samples (41.3%) collected from women in the first 24 hours post- partum, contained from 0.2 to 7.3 ng/ ml OA (Kovacs *et al.,* 1995).

The mean dietary intake for humans in the European Union was found to be in the range of 1 to 2 ng OA/Kg bw/day. Compared with the provisional tolerance daily intake proposed by WHO of 16 ng/Kg bw/day for humans. The average OA intake in Europe seems to be rather low (Heohlor, 1998). The Canadian Authorities have evaluated OA in 1998, 90, 91 and 96 and suggested a provisional tolerance daily intake of 1.2-5.7 ng OA/kg b.wt./day for a lifetime risk level of 10 (SCF, 1998).

In Tunisia, OA has been detected in high amounts in human blood samples collected in nephrology departments from nephropathy patients under dialysis, especially those categorized as having a chronic interstitial nephropathy of unknown etiology.

The blood levels of OA were 0.1- 2.3 ng/ml and 0.7-1136 ng/ml, for healthy and nephropathy patients respectively. These results emphasize the likely endemic aspect of OArelated nephropathy in Tunisia (Maaroufi *et al.,* 1995).

Ochratoxicosis in animals:

OA has demonstrated to have a nephrotoxic effect in all monogastric mammalian species which have been tested (Kuiper-Goodman and Scott, 1989). Field cases of ochratoxicosis in farm animals (pigs, poultry) have been reported from several European countries, the primary

manifestation being chronic nephropathy. The lesions include tubular atrophy interstitial fibrosis and at later stages hyalinized glomeruli (WHO, 1990). The LD_{50} value for ochrotoxin is actually lower than that of aflatoxin, however aflatoxin is generally regarded as more toxic, based on exposure under field conditions and the diverse effects caused by aflatoxin in poultry (Huff *et al.,* 1975).

A comparison of LD_{50} values in different species (table, 1) indicates that in acute toxicity studies with OA, the dog and pig were the most sensitive species and rats and mice are the least sensitive. Moreover, younger birds appear to be more susceptible to OA than older ones.

Table (1): Median lethal single dose (LD_{50}) for OA given orally to different animals.

Animal species		LD_{50} (mg/kg b.wt.)	Reference
Broiler chicks	(1 day- old)	2.14	Huff *et al.,* 1974
	(21 days- old)	3.6	Huff *et al.,* 1974
Leghorn chicks	(1 day- old)	3.3	Peckham *et al.,* 1971
	(3 days- old)	3.4	Prior *et al.,* 1976
	(21 days- old)	3.6	Huff *et al.,* 1974
Ducklings	(3 days- old)	0.5	van der Merwe *et al.,* 1965
Japanses quail	(3 days- old)	16.5	Prior *et al.,* 1976
Turkey poults	(1 day- old)	4.63	Chang *et al.,* 1981
	(3 days- old)	5.9	Prior *et al.,* 1976
Dogs		0.20	Harwig *et al.,* 1983
Pigs		1.00	Harwig *et al.,* 1983
Rats	(males)	30.30	Galtier *et al.,* 1974
	(females)	21.40	Galtier *et al.,* 1974
Mouse		46- 58.30	Harwig *et al.,* 1983
Guinea pig	(males)	9.10	Thacker and Carlton, 1977
	(females)	8.10	Thacker and Carlton, 1977

Clinical features and pathological lesions:

Feeding of over 0.2 to 4 ppm in grain to livestock can cause nephropathy. Monogastric animals such as swine and horses are more sensitive to ochratoxin than ruminants (Smith, 2002).

1-Ruminants:

Ruminants are reported to be very resistant to the acutely toxic effects of OA (Ribelin, 1978). This resistance is commonly attributed to ruminal degradation of OA by rumen microflora primarily protozoa (Kiessling *et al.,* 1984).

Lioyd *et al.* (1985) reviewed three cases of suspected bovine ochratoxicosis in which the clinical signs included depression, hypothermia and dehydration. On postmortem examination, peri-renal edema and aseptic pneumonia were consistent findings, as were hyaline casts, dilated tubules and cortical fibrosis in the kidney. Fatty changes were frequently observed in the liver. Various feedstuffs from these cases contained from 1 to 6 ppm OA and variable trace amounts of citrinin.

Pier *et al.* (1976) administrated OA orally by gelatin capsules to one- month-old Jersey calves. Delectable abnormalities were limited to polyuria in calves gives oral doses of 0.1 and 0.5 mg OA/kg b.wt. for 30 days. Depression

Reduced weight gains, low urinary specific gravity and dehydration were observed in calves give 1 and 2 mg/kg b.wt. Necropsy findings were pale kidneys and mild enteritis. Histopathological alteration were mild tubular degeneration, protein material in tubular lumens and interstitial fibrosis in calves given 1 and 2 mg/ kg b.wt. (Pier *et al.,* 1976).

Ribelin *et al.* (1978) administered OA by stomach tube to 5- week- old Holstein calves and pregnant Holstein cows. Calves given single doses of 11 and 25 mg/ kg b.wt. were died within 24 hours of dosing and each had epicardial hemorrhages as the only gross or microscopic abnormality.

A cow given a single dose of 13.3 mg/ kg b.wt. had clinical signs of toxicity including difficulty in rising, diarrhoea, anorexia and cessation of milk production. Cows given OA for 4-5 days at doses of 0.2, 0.75 or 1.66 mg/kg b.wt. remained clinically normal and delivered normal calves.

Ribelin *et al.* (1978) administered OA to 3 female goats by stomach tube. Goats given 1 and 2 mg OA/kg b.wt. for 14 days remained clinically normal and had no gross lesions. The goat given 3 mg/kg b.wt. died on the 6^{th} day and developed a watery diarrhoea and dehydration before death.

2-Monogastric animals

Szczech *et al.* (1973) administered OA orally to male beagle dogs at graded doses from 0.1 up to 7.8 mg/kg b.wt. Clinical features of canine ochratoxicosis included anorexia, emesis, tenesmus, retching, elevated rectal temperature, passage of blood-stained mucus clots, polydipsia, polyuria, dehydration, prostration and death. Dogs given 0.1 mg/kg b.wt. for 21 days did not have detectable signs of tocicosis. For dogs given 0.2-0.4 mg/kg, the toxicosis developed gradually over 10-14 day period and characterized by progressive loss of body weight, fever, anorexia, tonsillitis and conjunctivitis with bilateral mucopuralent exudates. At doses 3.0 mg/ kg and higher the acute toxicosis was characterized by complete anoraxin after one dose. Emesis, diarrhea, tenesmus, fever and prostration was seen by day 2 and most dogs were dead by days 1.5-2.5.

Porcine nephropathy is a naturally occurring disease, so far recognized in Denmark and Sweden. The macroscopic renal characteristic of porcine nephropathy include colour change "pale kidneys", mottled surface and cortical fibrosis (FDA, 1979).

OA at low levels (0.2 ppm) for several weeks, can induce detectable renal; lesions. Additional clinical signs were diarrhoea, anorexia and dehydration. Sometimes clinical signs are not observed, the only gross evidence being the appearance of pale firm kidneys at slaughter (Osweiler, 1992). Oral doses of 1 or 2 mg/kg b.wt. are lethal in 5 to 6 days. The toxicosis was characterized by depression, reduction of feed intake and loss of body weight followed by diarrhea, polyuria, polydipsia and dehydration. Necropsy findings included dehydration, enteritis, pale- tan livers, edema and hyperemia of the mesenteric lymph nodes (Szczech *et al.,* 1973)

Based on the current literature, the mechanism involved in the toxicity of OA in animals indicate three major effects:

1-Inhibition of mitochondrial respiration correlated with a depletion of adenosin triphosphate (ATP) (Heohler, 1998).

2-Inhibition of protein synthesis by competition with phenylalanine in the phenylalanine–tRNA aminoacylation reaction (Roschenthaler *et al*., 1984; Kuiper-Goodman and Scott, 1989).

3-Enhanced lipid peroxidation and generation of free radicals. These in turn cause other

secondary effects associated with OA (Marquardt *et al.*, 1990).

The pathophysiological studies on different animal species revealed that OA acts on different sites along the nephron depending on the dose and time of exposure. Acute ochratoxicosis leads to decreased renal blood flow and impairment of proximal nephron function, predominantly of the collecting duct resulting in altered electrolyte and titratable acid excretion. The resorptive capacity for small molecules like amino acids is affected only to a minor content, whereas uptake of albumin is clearly reduced. Chronic ochratoxicosis leads to an additional reduction in the urine concentration ability (Gekle and Silbernagi, 1996).

3-Poultry:

Ochratoxins A and B are extremely toxic at levels exceeding 0.3 ppm in chickens and turkeys (Kubena *et al.,* 1983). Turkeys are less sensitive and Japanese quail much less so to OA toxicosis than chickens (Prior *et al.,* 1976). Consequently, the no effect concentration for these species would be higher than one that could be proposed for the chicken. Chickens fed 0.3 ppm OA from 1 day to 341 days had detectable alterations of renal function and structure (Krogh *et al.*, 1976a) and white Leghorn hens fed 0.5 ppm OA for 6 weeks had reduced egg production and feed consumption (Prior and Sisodia, 1978).

Thus for continuous chronic exposure to OA a no effect level based on renal function tests of exposed birds would be less than 0.3 ppm, and a no effect concentration in which egg production was evaluated during dietary exposure of hens to OA would be of less than 0.5 ppm (FDA, 1979).

In broilers acute intoxication causes clinical signs of reduced spontaneous activity, huddling, diarrhea, rapid reduction in body weight tremors and other neural abnormalities and prostration leading to death (Huff *et al.,* 1974; Galtier *et al.,* 1976; Prior *et al.,* 1976). Sublethal intoxication can seriously impair performance parameters including weight gain, feed conversion, pigmentation and carcass yield (Huff *et al.,* 1984). However, under filed conditions with relatively low deity levels and chronic or subchronic exposure to the toxin, the major clinical signs are poor growth, increased water consumption and increased manure moisture (Huff *et al.,* 1974 & 1975).

In addition to the adverse effects of OA on the performance parameters, broiler chickens receiving dietary OA are less well pigmented, which is an undesirable feature in many marketing areas. OA induces a hypocarotenoidemia more severe than that caused by aflatoxin and impairs the ability of chickens to utilize dietary carotenoids for carcass pigmentation (Osborne *et al.,* 1982; Schaeffer *et al.,* 1987).

In laying hens, ochratoxin A in the feed of hens influenced embryo mortality and embryonic anomalies with most changes reflected in liver and kidney disorders (Niemiec *et al.,* 1990).

Ochratoxicosis in laying hens was characterized by severe nephropathy, body weight loss, increased feed intake with impaired feed efficiency, a delay in sexual maturity, decreased egg production, depressed hatchability of fertile eggs, and poor progeny performance in chicks from eggs laid by hens with ochratoxicosis (Choudhury *et al.,* 1971; Juszkiewicz *et al.,* 1982).

Leghorn hens developed chronic renal disease and diarrhea that caused yellow stains on egg shells resulting in deceased market value (Page *et al.,* 1980). A high incidence of stains

attributable to a substance on the egg shells that tended to encourage adhesion of dust, fecal material and other debris commonly found in a poultry house. It is concluded that the renal pathology associated with ochratoxicosis in laying hens, caused the production of urine with an altered (sticky) consistency. An excessive amount of urine appeared to be retained in the coloaca, such that eggs passing through this area during ovoposition became coated with the unused sticky substance. Consequently during transportation of eggs from cage to processing facilities, debris would adhere to the egg and could not be removed during, normal washing (Smith and Henderson, 1991).

In duckling and turkeys, ochratoxin has been demonstrated to cause retarded growth, enlargement of the kidneys and liver and regression of the thymus in ducklings fed 2 ppm OA in diet for 18 days (Burns and Maxwell, 1987). Ochratoxicosis in turkey poults causes decreased growth rate, enlarged proventriculus and gizzard and a regressed thymus and bursa of fabricius (Chang *et al.,* 1981; Dwivedi and Burns, 1985). Feed refusal and mortality due to nephrotoxicity and airsaculitis were also observed by Hamilton *et al.* (1982).

In rabbits, the toxicity of OA was studied by Mir *et al.* (1999). Acute oral LD_{50} for OA (administered in 1 ml ethanol) was evaluated in 8 week- old New Zealand white rabbits to be 10 mg/ kg. In another trial OA was administered at 5, 10 and 15 mg/ kg b.wt. in methanol, as single oral dose. The higher dose levels 10 and 15 mg/ kg, caused 100% mortality in 5 days and 24 hours, respectively. While, at lower dose level 5 mg/ kg, 50% of the animals died within 26 days. Degenerative changes and hemorrhages in various organs especially kidneys, brain, lungs were present in different groups. Dwivedi (2000) fed OA to rabbits at doses of 1 and 2 ppm and found that diarrhoea was the first sign noticed. Other clinical signs include hypothermia, dullness, anorexia, progressive anemia, swollen hyperaemic rectum and death.

Pathology of ochratoxicosis in poultry:

Postmortem lesions: In growing chicks, postmortem lesions observed after OA administration include emaciation, dehydration, a dry and firm gizzard sometimes with erosions on the koilin layer, proventricular mucosal hemorrhages and catarrhal enteritis. The kidneys are pale, swollen and enlarged. The liver can be enlarged, pale and friable or hemorrhagic, while the gall bladder may be distended with bile (Burns and Dwivedi, 1986).

Acute ochratoxicosis typically result in dramatic losses of poultry characterized primarily by nephrotoxicity (Huff *et al.,* 1975). The nephrotoxicity of ochrotaxin is readily obvious upon necropsy of affected birds. The kidneys appear extremely swollen and pale in color. The ureters will often be distinct due to the accumulation of urates (Peckham *et al.,* 1971; Prior *et al.,* 1976). Ureate deposits on the kidney, heart, pericardium, liver and spleen (visceral gout) are characteristic (Huff *et al.,* 1975; Galtier *et al.,* 1976).

Subacute ochratoxicosis in ducklings, turkeys and chickens is characterized by increased weight of liver and kidneys and decreased weight of lymphoid organs. The kidneys is pale (Dwivedi and Burns, 1984b). Bile may be pale and less viscous and the intestine has catarrhal content (Calnek *et al.,* 1991). The fragile large intestine was characterized as enlarged with increased fat content, decreased collagen content and enlarged radial length of the collagenous longitudinal folds. Increased intestinal fragility can cause increased carcass condemnation due to intestinal rupture on the processing line (Warner and Hamilton, 1980).

Microscopic lesion: In acute ochrotoxicosis, histologic alterations are most prominent in

kidneys and liver. Acute tubular necrosis is characterized by proteinaceous and urate casts and fecal necrosis of tubular epithelium. The liver showed cytoplasmic vacuolation and focal necrosis of hepatocytes, followed by foci of fibrosis (Peckham *et al.,* 1971).

The histopathological alterations in subacute toxicity include; tubular casts, tubular dilation and hyperplasia of tubular epithelium (Huff *et al.,* 1975; Manning *et al.,* 1985) in kidneys. The toxin principally affect convoluted tubules causing severe distension, enlargement, hypertrophy as well as thickening of the glomerular basement membrane (Dwivedi and Burns, 1984b). The liver revealed vacuolar change in hepatocytes associated with reversible increases in glycogen content (Huff *et al.,* 1979; Warner and Hamilton, 1981; Dwivedi *et al.,* 1984) an chickens. In ducks, hepatocyte vacuolation is due to lipid accumulation (Burus and Maxwell, 1987).

Since glycogen can be synthesized at a relatively normal rate, but can not be mobilized, the net result is increased glycogen content in the liver and increased glycogen granules can be observed during a microscopic evaluation (Smith and Henderson, 1991). Chronic ochratoxicosis revealed mild histologic lesions in proximal and distal tubules as ballooning of epithelial cells, karyomegalic cells, reduction of the brush border and necrosis. Mitotic figures are increased in number and appear abnormal (Krogh *et al.,* 1976b).

Clinical pathology and biochemistry in poultry:

Dietary OA to chickens causes a significant decrease in PCV and Hb concentrations, RBCs, WBCs, lymphocyte and heterophil counts (Chang *et al.,* 1979; Ayed *et al.,* 1991; El- Karim *et al.,* 1991; Mohiuddin *et al.,* 1992). OA induces iron-deficiency anemia in broiler chickens (Huff *et al.,* 1979). Reductions in PCV occur without reduction in circulating RBCs, but the mean corpuscular volume and corpuscular hemoglobin concentration are reduced. This is accompanied by reduction in serum iron concentration and transferring saturation, total iron binding capacity is unaffected (Huff *et al.,* 1979). Broiler chickens and turkeys develop a reduction in total circulating leukocytes, due to decreases in lymphocytes and monocytes (Chang *et al.,* 1979; 1981).

Doer *et al.,* (1981) reported a severe coagulopathy associated with ochrotoxicosis in broilers. The impairment in coagulation associated with ochrotoxicosis was found to result primarily from lypofibrinogenemia, whereas the coagulopathy during aflatoxicosis resulted primarily from a hypoprothrom-binemia (Smith and Henderson, 1991).

Administration of OA to day-old chicks raised the blood glucose levels (Subramanian and Govindasamy, 1985). Increased serum uric acid is a consistent indicator of toxin- induced renal disease in poultry (Chang *et al.,* 1981 and Kubena *et al.,* 1983). Reductions occur in concentrations of serum total protein, albumin, immunoglobulins (Dwivedi and Burns, 1984), cholesterol, triglycerides, blood urea nitrogen and carotenoids (Schaeffer *et al.,* 1987), calcium, phosphorous, potassium and glucose (Kubena *et al.,* 1985; Huff *et al.,* 1988), serum protein, albumin, phosphorus, potassium and cholesterol (Sreemannarayana *et al.,* 1989).

Serum alkaline phosphatase, gamma glutamyltransferase, uric acid, and creatinine (Sreemannarayana *et al.,* 1989), alkaline phosphatase, cholinesterase, gamma glutamyl-transferase and creatine (Kubena *et al.,* 1986; Huff *et al.,* 1988), sorbitol dehydrogenase, glutamic dehydrogenase and uric acid (Ayed *et al.,* 1991), aspartate aminotrandferase, alanine aminotransferase, lactate dehydrogenase and

acid phosphatase (Raina *et al.,* 1991) are increased in chickens fed OA.

Cell mediated and humoral immunity are influenced by OA. Phagocytic activity of chicken heterophils is impaired by OA (Chang and Hamilton, 1980). Serum immunoglobulin concentrations are reduced in toxicated hens lymphoid organ atrophy is attributable, in part, to fewer immunoglobulin-containing cells (Dwivedi and Buras, 1984a).

Cell mediated response as measured by dehayed hypersensitivity reactions to avian tuberculin and to bovine serum albumin in presensitized birds were significantly depressed in growing turkeys fed OA (Dwivedi and Burns, 1985). Phagocytic activity of chicken heretrophils is impaired by OA (Chang and Hamilton, 1980).

Regulations for ochratoxin A:

Only very few countries have regulations for OA in food and feed products. At least 11 countries have proposed an official limits for OA (Tables, 2& 3). The acceptable levels ranged from 1 to 50 ppb for human and from 100 to 1000 ppb for animal feed (van Egmond, 1991). The mean dietary intake for humans in the European Union was found to be in the range of 1 to 2 ng/kg b.wt./day. Compared with the provisional tolerable daily intake proposed by WHO of 16 ng OA/kg for humans, the average OA intake in Europe seems to be rather low (Hoehler, 1998).

Table (2): Maximum tolerated level of OA in foodstuffs (FAO, 1997).

Commodity (product)	Recommended maximum level (ppb)	Country
All foods	20 5	Czech Republic Rumania
Cereals	5	France
Corn, barley, beans, rice	50	Brazil, Uruguay
Cereal products	5 50 2	Denmark Israel Switzerland
Children foods	5	Czech Republic
Pig kidneys	25	Denmark

Table (3): Maximum tolerated levels of OA in animal feedstuffs (FAO, 1997).

Commodity (product)	Animal	Recommended maximum level (ppb)	Country
Complete feedstuffs	Poultry Swine	200 100	Sweden Sweden
Feedstuffs	All animals	5	Rumania
Grain for feed	All animals	300	Israel

REFERENCE

Angsubhakorn, S. (2000): "Mycotoxins and human health risks an overview." In: mycotoxin prevention and control in food grains. A collaborative publication of the UNDP/FAO Regional Network Intercountry cooperation on pre-harvest technology and quality control of food grains and ASEAN grain post-harvest programe, Bangkok, Thailand.

Ayed, I.A.; Defalla, R.; Yagi, A.I. and Adams, S.E. (1991): "Effect of OA on chicks" Toxicol., 33: 557- 560.

Bauer, J. and Gareis, M. (1987): "OA in the food chain" J. Vet. Med., B34: 613- 627 (in german).

Burns, R.B. and Dwivedi, P. (1986): "The natural occurrence of OA and its effects in poultry" A review. Part II. Pathology and Immunology. World's Poult. Sci. J., 42: 28- 55.

Burns, R.B. and Maxwell, M.H. (1987): "OA in young Khaki Campbell ducklings." Res. Vet. Sci., 42: 395-403.

Calnek, B.W.; John Barnes, H.; Beard, C.W.; Reid, W.M. and Yoder, H.W. (1991): "Diseases of poultry." 9th ed. Pp. 897-900, Wolfe publishing Ltd.

CAST, Council for Agric, Sci. and Technol. (1989): "Mycotoxins: Economic and health risks." Task free report No. 116, Nov. 1989.

Ceovic, S.; Grims, P. and Mitar, J. (1976): "The incidence of tumours of the urinary organs in region of EN and in a control region." Lijec. Vjesn., 98: 301- 304.

Chang, C.F. and Hamilton, P.B. (1980): "Impairment of phagocytosis by heterophils from chickens during ochratoxicosis." Appl. Environ. Microbiol., 39: 572- 575.

Chang, C.F.; Huff, W.E. and Hamilton, P.B. (1979): "A leucocytopenia induced in chickens by dietary OA." Poult. Sci., 58: 555- 558.

Chang, C.F.; Doerr, J.A. and Hamitton, P.B. (1981): "Experimental ochratoxicosis in turkey poults." Poult. Sci., 60(1):114-119.

Chernozemsky, I.N.; Stoyanov, I.S.; Petkova-Bocharova, P.; Nocolov, I.G.; Draganov, I.V.; Stoichev, I.; Tanchev, Y.; Naidenov, D. and Kalcheva, N.D.(1977): "Geographic correlation between the occurrence of EN and urinary tract tumors in vratza district Bulgaria." J. Cancer, 19: 1- 11.

Choudhury, H.; Carlson, C.W. and Semeniuk, G. (1971): "A study of ochratoxin toxicity in hens." Poult. Sci., 52: 1202- 1203.

Creppy, E.E.; Baudrimont, I. and Marie, A. (1998):"How aspartame prevents the toxicity of OA." J. Toxicol. Sci., Suppl. 2: 165- 172.

Doerr, J.A.; Huff, W.E.; Hamilton, P.B. and Lillehoj, E.B. (1981): "Severe coagulopathy in young chickens produced by OA." Toxicol. Appl. Pharmacol., 59: 157- 163.

Dwivedi, P. (2000): "Clinical studies on experimental subacute ochratoxicosis in rabbits." Ind. J. Vet. Pathol., 24 (2): 99-101.

Dwivedi, P. and Burns, R.B. (1984a): "Effect of OA on immunoglobulins in broiler chicks." Res. Vet. Sci., 36: 117.

Dwivedi, P. and Burns, R.B. (1984b): "Pathology of ochratoxicosis A in young broiler chicks." Res. Vet. Sci., 36 (1): 92-103.

Dwivedi, P. and Burns, R.B. (1985):"Immuno suppressive effects of OA in young turkeys." Avian Pathol., 14: 213- 225.

Dwivedi, P.; Burns, R.B. and Maxwell, M.H. (1984): "Ultrastructural study of the liver and kidney in ochratoxicosis A in young broiler chicks." Res. Vet. Sci., 36: 104-116.

El- Karim, S.A.; Arbid, M.S.; Soufy, A.H.; Bastamy, M. and Effat, M.M. (1991): "Influence of metabolite OA on chicken immune response." Egypt. J. Comp. Pathol. Clin. Pathol., 159- 172.

FAO, Food and Agricultural Organization (1997):"FAO, food and nutrition." Paper, No. 64, Pp., 1- 43, Rome.

FDA, Food and Drug Administration (1979): "Conference on mycotoxins in animal feeds and grains related to animal

health." June, 1979, P.173, FDA, Rockville, Maryland.

Fuchs, R.; Applegren, L.E.; Hagelberg, S. and Hult, K. (1988): "Carbon- 14- OA distribution in the Japanese quail monitored by whole body radiography." Poult. Sci. 67: 707- 714.

Fukui, Y.; Hoshino, K.; Kameyana, Y.; Yasui, T.; Toda, C. and Nagano, H. (1987): "Placental transfer of ochratoxin A and its cytotoxic effect on the mouse embryonic brain" Food Chem. Toxicol., 25: 17- 24.

Galtier, P. (1991): "International Agency for Research in cancer." Sci. Pub., 115: 187- 200.

Galtier, P.; More, J. and Bodin, G. (1974): "Toxines d' Aspergillua ochraceous Wihelm III. Toxicite aigue de I' ochratoxins A chez le rat et la souris adultes." Ann. Rech. Vel., 5: 233- 247.

Galtier, P.; More, J. and Alvineric, M. (1976): "Acute and short- term toxicity of ochratoxin A in 10- day- old chicks." Food Cosmetol. Toxicol., 14: 129- 131.

Galtier, P.; Boradat, C. and Alvinerie, M. (1977): "Del'elimination d'ochratoxine A per le lait chez la lapine." Ann. Nutr. Aliment., 31: 911- 918.

Galtier, P.; Camguilhem, R. and Bodin, G. (1980): "Evidence for in vitro and in vivo interaction between ochratoxin A and three acidic drugs." Food Cosmet. Toxicol., 18: 493- 496.

Galtier, P.; Alvineric, M. and Charpenteau, J.L. (1981): "The pharmacokinetic profiles of OA in pigs, rabbits and chickens." Food Cosmet. Toxicol., 19: 735- 738.

Gareis, M.; Martlbauer, E.; Bauer, J. and Gedek, B. (1988): "Determination of OA in breast milk. Z. lebensm." Unters. Forsch., 186: 114- 117 (In German).

Gekle, M. and Silbernagi, S. (1996): "Renal toxicodynamics of OA: A pathophysiological approach." Kidney Blood Press. Res., 19 (5): 225- 235.

Hagelberg, S.; Hult, K.; and Fuchs, R. (1989): "Toxicokinetics of OA in several species and its plasma- binding, properties." J. Appl. Toxicol., 9: 91- 96.

Hallen, I.P. *et al.* (1998): "Placental and lactational transfer of OA in rats." Nat. Toxins, 6: 43. In: Thrasher, J.D. (2003).

Hamilton, P.B.; Huff, W.E.; Harris, J.R. and Wyatt, R.D. (1982): "Natural occurrence of ochratoxicosis in poultry" Poult. Sci., 61: 1832- 1841.

Harbar, A.; Suljaga, K.; Borcic, B.; Aleraj, B.; Ceovic, S. and Cvoriscec, D. (1976): "Endemic nephropathy morbidity and mortality in the village of Kaniza." Arch. Ind. Hyg. Toxicol., 27: 137- 145.

Harwing, J.; Kuiper- Goodman, T. and Scott, P.M. (1983): "Microbiol food toxicants: Ochratoxins." In: Handbook of foodborne diseases of biological origin (M. Recheigl, Ed.), Pp. 193- 238. CRC press, Boca Raton, Fl.

Heohlor, D. (1998): "OA in food and feed: Occurrence, Legislation and Mode of action." Z. Ernahrungswiss, 37 (ISS 1): 2- 12.

Heptinstall, R.H. (1974): "Pathology of the kidney." Boston, little Brown and Co., Vol. 11, Pp. 828- 836.

Huff, W.E.; Doerr, J.A. and Hamilton, P.B. (1979): "Decreased glycogen mobilization during ochratoxicosis in broiler chickens." Appl. Environ. Microbiol., 37: 122- 126.

Huff, W.E.; Doerr, J.A.; Wabeck, C.J.; Chaloupka, C.W.; May, J.D. and Merkley, J.W. (1984): "The individual and combined effects of Aflatoxin and

OA on various processing parameters of broiler chickens." Poult. Sci., 63: 2153- 2161.

Huff, W.E.; Kubena, L.F. and Harvey, R.B. (1988): "Progression of ochratoxicosis in broiler chickens." Poult. Sci., 67: 1139- 1146.

Huff, W.E.; Wyatt, R.D. and Hamilton, P.B. (1975): "Nephrotoxicity of dietary OA in broiler chickens." Appl. Microbial., 30: 48.

Huff, W.E.; Wyatt, R.D.; Tucker, T.L. and Hamilton, P.B. (1974): "Ochratoxicosis in the broiler chicken." Poult. Sci, 53: 1585- 1591.

Hult, K. and Fuchs, R. (1986): "Analysis and dynamics of OA in biological systems." In: mycotoxins and phytotoxins. Sixth International IUPAC Symposium on Mycotoxins and Phytotoxins. Pretoria, Rep. of south Africa, July 22- 25, 1995, Pp. 365- 376.

Hult, K.; Plestina, R.; Habazin- Novac, V.; Radia, B. and Ceovia, S. (1982): "OA human blood and BEN" Arch. Toxicol., 51: 313- 321.

IARC, International Agency for Research on Cancer (1993): "Some raturally occurring substances: some food items and constituents, heterocyclic aromatic amines and mycotoxins." Vol. 56, Pp. 489- 521.

Juszkiewicz, T.; Piskorska- Pliszczynska, J. and Wisniewska, H. (1982): "OA in laying hens, tissue deposition and passage into eggs." Proc. 5th Int. IUPAC Symp. on Mycotoxins and Phytotoxins, Vienna, 1982: 122.

Juszkiewicz, T.; Piskorska- Ploszczynska, J. and Wisniewska, H. (1982): " Ochratoxin A in laying hens, tissue deposition and passage into eggs." Proc. 5th Int. IUPAC Symp. Mycotoxins and Phytotoxins. Vienna, 122.

Kiessling, K.H.; Pettersson, H.; Sandholm, K. and Olsen, M. (1984): "Metabolism of aflatoxin, ochratoxin, zearalenone and three trichothecenes by intact rumen fluid, rumen protozoa, and rumen bacteria." Appl. Environ. Microbiol., 47: 170.

Kovacs, F.; Sandor, G.; Vanyi, A.; Domany, S.; Kovacs, Z.M. (1995): "Detection of OA in human blood and colostrum"Acta Vet. Hung., 43 (4): 393- 400.

Krogh, P. (1987): "Ochratoxins in food." In: Krogh, P. (Ed) mycotoxins in food. pp. 97- 121, Academic press, London.

Krogh, P. (1991): "Porcine nephropathy associated with Ochratoxin A." In: Smith, J.E. and Henderson, R.S. (Eds) Mycotoxins and Animal foods. Boca Raton, CRC press, pp. 627- 645.

Krogh, P. (1992): "Role of ochratoxin in disease causation." Food Chem. Toxicol., 30: 213.

Krogh, P.; Elling, B.; Hold, B.; Syllin, V.E.; Skadhange, E. and Svensen, C.K. (1976a): "Experimental avian nephropathy- changes of renal function and structure induced by OA-contaminated feed." Acta Pathol. Microbiol. Scand., 84: 215- 221.

Krogh, P.; Elling, F.; Hold, B.; Larsen, A.F.; Lillehoj, E.R.; Madsen, A. and Mortensen, H.P. (1976b): "Time-dependent disappearance of OA residues of bacon pigs." Toxical., 6: 335- 342.

Krogh, P.; Hold, B.; Plestina, R. and Ceovic, S. (1977): "Balkan endemic nephropathy and food- born OA: preliminary results of a survey of foodstuff." Acta. Path. Microbiol. Scand, A84: 429- 434.

Kubena, L.F.; Harvey, R.B. and Fletcher, O.J. (1986): "Influence of OA and vanadium

on various parameters in growing chicks." Poult. Sci., 65: 1671- 1678.

Kubena, L.F.; Harvey, R.B.; Fletcher, O.J.; Phillips, T.D.; Mollenhauer, H.H.; Witzel, D.A. and Heidelbaugh, N.D. (1985): "Toxicity of OA and vanadium to growing chicks." Poult. Sci. 64: 620- 628.

Kubena, L.F.; Phillips, T.D.; Creger, C.R.; Witzel, D.A. and Heidelbaugh, N. (1983): "Toxicity resulting from feeding experimentally molded corn to broiler chicks" Poult. Sci., 62: 1786- 1792.

Kuiper- Goodman, T. and Scott, P.M. (1989): "Risk assessment of the mycotoxin OA" Biomed. Environ. Sci., 2: 179-248.

Lioyd, W.E.; Daniels, G.N. and Stahr, H.M. (1985): "Cases of nephrotoxic mycotoxicosis in cattle and swine in the United states." In: Trichothecenes and other mycotoxins. Lacey, J., Ed., John Wiley and Sons New York: 545.

Maaroufi, K.; Achour, A.; Betbeder, A.M.; Hammami, M.; Ellouz, F.; Creppy, E.E. and Bacha, H. (1995): "Foodstuffs and human blood contamination by OA: correlation with chronic interstitial nephropathy in Tunisia." Arch. Toxicol., 69 (8): 552- 558.

Madsen, A.; Mortensen, H.P. and Hald, B. (1982): "Feeding experiments with OA-contaminated barley for bacon pigs." I- Influence on pig performance and residues. Acta Agric. Scand., 32: 225- 239.

Manning, R.O.; Brown, T.P.; Wyatt, R.D. and Fletcher, O.J. (1985): "The individual and combined effects of citrinin and OA in broiler chicks." Avian Dis., 29: 986.

Marquardt, R.R.; Frohlich, A. and Abramson, D. (1990): "Ochratoxin A- An important Western Canadian storage mycotoxin." Can. J. Physiol. Pharmacol., 68 (7): 991- 999.

Marquardt, R.R. and Frolich, A.A. (1992): "A review of recent advances in understanding ochratoxicosis." J. Anim. Sci., 70: 3968- 3988.

Mir, M.S.; Dwivedi, P. and Charan, K. (1999): "OA induced acute toxicity in rabbits." Ind. J. Vet. Pathol., 23 (1- 2): 8- 13.

Mohiuddin, S.M.; Reddy, M.V. and Ahmed, S.R. (1992): "Studies on ochratoxicosis in broiler chicks" Ind. Vet. J., 69: 1011- 1014.

Mohler, D. (1998): "OA in food and feed occurrence, legislation and mode of action." Z. Ernahrungswiss, 37 (1): 2- 12.

Mortensen, H.P.; Hald, B.; Larsen, A.E. and Madsen, A. (1983): "OA contaminated barley for sows and piglets. Pig performance and residues milk and pigs." Acta Agric. Scand., 23: 349- 352.

Niclov, I.G.; Chernozemsmsky, I.N.; Petkova-Bocharova, T.; Stoyanov, I.S. and Stoichev, I.I. (1978): "Epidemiologic characteristics of urinary system tumors and BN in an endemic region of Bulgaria." Eur. J. Cancer, 14:1237- 1242.

Niemiec, J.; Borzemska, W.; Roszkowski, J. and Karpinska, E. (1990): "Influence of OA-contaminated feed on chick embryogenesis." Archiv. Fur. Geflugelkunde, 54 (2): 70- 73.

Nip, W.K. and Chu, F.S. (1979): "Fate of OA in goat." J. Environ. Sci. Health, B14: 319- 333.

Osborne, D.J.; Huff, W.E.; Hamilton, P.B. and Burmeister, H.R. (1982): "Comparison of Ochratoxin, Aflatoxin and T- 2 toxin for their effects on selected parameters related to digestion and evidence for specific metabolism of carotenoids in chickens." Poult. Sci., 61: 1646- 1652.

Osweller, C.D. (1992): "Mycotoxin." In: Diseases of swine., 7th ed. Pp. 735- 743. Edited by Leman, A.D.; Straw B.E.; Mengeling, W.L.; Allaire, S.D. and Taylor, D.J. (1992) London, Wolfe Publishing.

Page, R.K.; Stewart, G.; Wyatt, R.; Bush, P.; Fletcher, O.J. and Brown, J. (1980): "Influence of low levels of OA on egg production, egg- shell stains and serum uric acid levels in leghorn- type hens." Avian Dis., 24: 777- 780.

Peckham, J.C.; Douonik, B. and Jones, O.H. (1971): "Acute toxicity of OA and B in chicks." Appl. Microbiol., 21: 492- 494.

Pepeljnjak, S.; Blazevic, N. and Culjak, N. (1982): "Histopathological changes and finding of OA in organs of pig in the area of EN in Yugoslavia." In: Mycotoxins and Phytotoxins, Proceedings of the 5th international IUPAC symposium, Vienna, Technical Univ. Vienna publ., pp. 346- 348.

Petkova- Bocharova, T. *et al.* (1998): "Formation of DNA adducts in tissues of mouse progeny through transplacental and/ or lactation after administration of a single dose of OA to the pregnant mother." Environ. Mol. Mutagen, 32: 155. In: In: Thrasher, J.D. (2003).

Petkova- Bocharova, T. and Castegnaro, M. (1985a): "OA contamination of cereals in an area of high incidence of BEN in Bulgaria." Food Addit. Contam., 2: 267- 270.

Petkova- Bocharova, T.; Chernozemsky, I.N. and Castegnaro, M. (1985b): "OA in human blood in relation to BEN and urinary system tumors in Bulgaria." Food Addit. Contam., 5: 299- 301.

Pfohl- Leszkowicz, A. *et al.* (1993): "Differential DNA adduct formation and disappearance in three mice tissues after treatment by the mycotoxin OA." Mutat. Res., 289: 265. In: Thrasher, J.D. (2003).

Pier, A.C.; Cysewski, S.J.; Richard, J.L.; Baetz, A.L. and Mitchell, L. (1976): "Experimental mycotoxicosis in calves with aflatoxin, ochratoxin, rubrotoxin and t- 2 toxin." Ann. Metting. U.S. Anim. Hlth. Assoc., Pp. 130- 148.

Prior, M.G. and Sisodia, C.S. (1978): "Ochratoxicosis in white Leghorn hens." Poult. Sci., 57: 619- 623.

Prior, M.G.; Sisodia, C.S. and O'Neil, J.B. (1976): "Acute oral ochratoxicosis in day-old white Leghorns turkeys and Japanese quail." Poult. Sci., 55: 786- 790.

Raina, J.S.; Roy, K.S. and Singh, B. (1991): "Biochemical and histochemical studies in experimental mycotoxicosis in chicks." Indian J. Anim. Sci., 61: 1276- 1281.

Rebelin, W.E.; Fukushima and Still, P.E. (1978): "The toxicity of ochratoxin to ruminants" Can. J. Comp. Med., 42: 172- 176.

Ribelin, W.E. (1978): "Ochratoxicosis in cattle." In: Mycotoxic fungi, mycotoxins, mycotoxicosis, Vol. 2, Wyllie, T.D. and Morehouse, L.G.; Eds., Marcel Dekker, New York, 1978.

Roschenthetaler, R.; Creppy, E.E. and Dinheimer, G. (1984):"OA on the mode of action of a ubiquitous mycotoxin" J. Toxicol. Toxin. Rev. I, 53- 86.

SCF, Scientific Committee on Food (1998): "Health scientific committees, Opinion on OA (expresses on 17 September, 1998)"

Schaeffer, J.L.; Jyczkowski, L. and Hamilton, P.B. (1987): "Alterations in carotenoid metabolism during ochratoxicosis in young broiler chickens" Poult. Sci., 66: 318- 324.

Schwartz, G.G. (2002): "Hypothesis: Does OA cause Testicular cancer" Cancer Causes and Control, 13: 91.

Shotwell, O.L.; Hesseltin, C.W. and Goulden, M.L. (1969a): "Note on the natural occurrence of OA." J. Assoc. Off. Chem.., 52: 81- 83.

Shotwell, O.L.; Hesseltine, C.W. and Goulden, M.L. (1969b): "OA: occurrence as a natural contaminant of a corn sample." Appl. Microbiol., 17: 765.

Smith, B.P. (2002): "Large animal internal medicine." 3rd ed. P. 1630, Mosby, L., Inc. USA.

Smith, J.E. and Henderson, R.S. (1991): "Mycotoxins and animal foods." Pp. 549 CRC press, Inc., London.

Sreemannarayana, O.; Frohlich, A.A.; Vitti, T.G.; Marquardty, R.R. and Abramson, D. (1988): "Studies of the tolerance and disposition of OA in young calves." Anim. Sci., 66: 1703- 1711.

Sreemannarayana, O.; Marquardt, R.R.; Frohlich, A.A.; Abramson, D. and Phillips, G.D. (1989): "Organ weight, liver constituents and serum components in growing chicks fed OA." Arch. Environ. Contam. Toxical., 18: 404- 410.

Stoyanov, I.S.; Chernozemsky, I.N.; Nicolov, I.G.; Stoicheie, I.I. and Betkova-Bocharova, T.K. (1978): "Epidemiologic association between endemic nephropathy and urinary system tumors in an endemic region." J. Chron. Dis., 31: 721- 724.

Subramanian, S. and Govindasamy, S. (1985): "*Aspergillus ochraceus* toxicity on carbohydrate metabolism in chicks" "Cur. Sc., 17:860-872.

Szczech, G.M.; Carlton, W.W. and Tuite, J. (1973): "Ochratoxicosis in beagle dogs 1- clinical and clinicopathological features." Vet. Path., 10: 135- 154.

Szczech, G.M.; Carlton, W.W.; Tuite, J. and Caldwell, R. (1973): "OA toxicosis in swine." Vet. Pathol., 10: 347- 364.

Thacker, H.L. and Carlton, W.W. (1977): "OA mycotoxicosis in the guinea pig." Food Cosmat Toxical., 15: 563- 574.

Thrasher, J.D. (2003): "Ochratoxins and ochratoxicosis." Alto, New Mixico 88312. toxicology @ drthrasher. Org.

van Der Merwe, K.J.; Steyn, P.S.; Fourie, L.; Scott, D.B. and Theron, J.J. (1965): "OA, a toxic metabolite produced by *A. ochraceus*" Wilh. Nature, 205:1112- 1113.

Van Egmod, H.P. (1991): "World wide regulations for OA." IARC Sci. Publ. ISS (115): 331- 336.

Warner, M.F. and Hamilton, P.B. (1980): "Intestinal fragility during ochratoxicosis and aflatoxicosis in broiler chickens." Appl. Environ. Microbiol., 40: 641- 645.

Weidenborner, M. (2001): "Encyclopedia of food mycotoxins." Springer publisher, Berlin, New York and London.

Warner, M.F. and Hamilton, P.B. (1981): "Glycogen storage disease type X caused by OA in broiler chicks" Poult. Sci., 60: 120- 123.

WHO, World Health Organization (1990): "Selected mycotoxins: ochratoxins, trichothecenes, Ergot." Environmental Health Criteria 105, Geneva.

Zuzuki, S.; Satoh, T. and Yamazaki, M. (1977): "The pharmacokinetics of ochratoxin A in rats" Jpn. J. pharmacol., 27: 735-744.

Ass. Univ. Bull. Environ. Res. Vol. 7 No. 1, March 2004

التسمم الفطري
٢- الأوكراتوكسين

بدير إبراهيم عجاج

قسم بحوث الكيمياء والنقص الغذائى والسموم – معهد بحوث صحة الحيوان بالدقى – مركز البحوث الزراعية

السموم الفطرية هي مركبات كيميائية سامة تفرزها بعض أنواع الفطريات التي تنمو علي الأغذية والأعلاف وتختلف هذه السموم باختلاف تركيبها الكيميائي وتأثيرها السمي ودرجة ضراوته. ومن أهم السموم الفطرية الأفلاتوكسن والأوكراتوكسين والفيومونيزين والزيرالينون والدي اوكس نيفالينول والتى-٢ توكسين.

وتعتبر سموم الأوكراتوكسين من أهم السموم الفطرية التي تسبب أضرار صحية بالغة للإنسان والحيوان والطيور ، حيث يؤدي التعرض لسموم الأوكراتوكسين خاصة الأوكراتوكسين أ إلى تغيرات باثولوجية متعددة بالكلى قد تصل إلى الفشل الكلوي وتسرطن الكلي بالإضافة إلى بعض أعضاء الجسم خاصة الكبد.

وقد استهدفت هذه الورقة إلقاء الضوء علي كيفيه التعرض لسموم الأوكراتوكسين والأعراض الأكلينيكيه والتغيرات الباثولوجية المصاحبة لذلك في كل من الإنسان والحيوانات والطيور وكذلك الحدود المسموح بها بالنسبة لتركيزات الأوكراتوكسين في الأغذية والأعلاف محليا وعالميا حتى يمكن اتباع الإجراءات الوقائية ضد الفطريات المفرزة للاوكراتوكسين أو التخلص من سمومها في الأغذية والأعلاف بالطرق الخاصة بذلك.