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MYCOTOXINS IN FOODS AND FEEDS
5-Trichothecenes
A-T-2 Toxin

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REVIEW ARTICLE

ABSTRACT :

Trichothecenes (TCT) are secondary metabolites commonly found in cereals. They are produced in foods and feeds by various species of Fusarium: Myrothecium, Trichothecium, Trichoderma, Cephalosporium, Cylindrocarpon and Stachybotrys. More than 140 different TCT have now been isolated and described. T-2 toxin is the most cytotoxic mycotoxin of the group TCT. It is produced by Fusarium fungi (*F. acuminatum*, *F. poae* and *F. sporotrichioides*) in cereal crops and processed grains. The commonest clinical signs of alimentary toxic aleukia (ATA) caused by T-2 toxin in humans are weakness, vomiting, diarrhea, nausia and abdominal pain. The major toxic effects of T-2 toxin in ruminants include gastroenteritis, hemorrhages, bloody diarrhea and ruminal ulcers. Reduced feed intake and weight gain, diarrhea and impairment of the immune system are the effects caused by T-2 toxin in pigs. Signs of T-2 toxin in poultry comprised decreased feed intake, growth depression, oral lesions, abnormal feathering, decreased egg production, thinner egg shells and impaired hatchability.

INTRODUCTION:

Trichothecenes:

A total number of 148 TCT, (83 non-macrocyclic and 65 macrocyclic) have been isolated from fungal cultures and plants (Drove, 1988). The TCT are large family of metabolites produced by various species of Fusarium, Myrothecium, Trichothecium, Trichoderma, Cephalosporium, Cylindrocarpon and Stachybotrys (Ueno, 1989; Buck and Cote, 1991). These fungi affect grains in the field, but toxin production in accentuated by storage at cool temperatures; therefore, natural poisoning are most frequent in areas with cooler climates (Jones *et al.*, 1997). Fusarium and Stachybotrys grow at many temperatures but toxin production is highest in cold (< 20°C) and moist conditions. Trichothecenes are therefore associated with cool climates particularly when grain harvest have been delayed into the winter months, or infected grain has been stored in cold conditions (Jordan *et al.*, 2002).

Fusarium fungi are widespread natural producers of TCT and different species have

different toxin production profiles. The fungi are commonly occurring soil fungi where they grow and sporeulate both in soil and on plant material. Some of the fusarium species are also plant pathogens causing different plant diseases and the infection of plant by fusarium fungi may reduce the crop yield significantly (Snijders and Perkowski, 1990; Mesterhazy *et al.,* 1999; Eriksen, 2003). Not only are the separate toxins produced by several Fusarium species, but these Fusarium species may produce different mycotoxins depending on the substrate and growth conditions. Thus zearalenone, deoxynivalenol (DON), diacetoxyscirpenol (DAS), and T-2 toxin may be produced by *F. sporotrichioides*, *F. graminearum* and certain other species of fungi (Biberstein and Zee, 1990). There are other TCT toxins, namely T-2 toxin, DON, DAS, neosolaniol, HT-2 toxin, verrucarin, roridin, etc. (Garg, 2000).

TCT are potent cytotoxins possessing cytotoxic activity and exerting an inhibitory effect on protein synthesis. They damage the parenchymal organs (liver, kidney) as well as the immune, digestive and nervous systems (Glavits and Salyi, 1998). Compared to human beings, farm animals are at higher risk of intoxication because of their greater chances of consuming TCT in moldy feeds. All species of animals including human beings are affected (Garg, 2000).

Chemical structure:

Chemically, TCT are divided into two groups, namely macrocyclic and non-macrocyclic (Leeson *et al.,* 1995). They possess a tetracyclic 12, 13- epoxytrichothec- 9- ene skeleton (WHO, 1990). All naturally occurring TCT have at least one hydroxyl or ester group at C-3, C-4, C-7 and C-15, and can be conveniently divided into 4 major groups (Mirocha, 1979; Drove, 1988; WHO, 1990). The first group (A) is characterized by a functional group other than a ketone at C- 8 [T-2 toxin, HT-2 toxin, DAS and monoacetoxyscirpenol (MAS)]. The second group (B) has a ketone at C- 8 [scirpenol, T-2 tetroal., DON, nivalenol (NIV) and fusarenone]. The third group (C) is characterized by a second epoxide group at C-7, C- 8 or C- 9, C- 10 (crotocin), and the fourth group (D) contains a macrocyclic ring system between C- 4 and C- 15 with two linkages (diacetylverrucarol and verrucarol) (Mirocha, 1979; Ueno, 1987; Dove, 1988; WHO, 1990). The TCT mycotoxins are non- volatile, low molecular weight (MW 250- 550) compounds. They are relatively stable in water and highly stable in acetone, ethyl acetate, chloroform, dimethyl sulfoxide, ethanol, methanol and propylene glucol (Cole and Cox, 1981). They are stable compounds, both during storage milling and the processing or cooking food and do not degrade at high temperatures (Eriksen and Alexander, 1988). They are also stable at neutral and acidic pH and consequently not hydrolysed in the stomach after ingestion (Ueno, 1987).

Out of all TCT, T-2 toxin is the most cytotoxic (Garg, 2000). It was found to be easily produced and purified in quantities sufficient for animal feeding studies (Burmeister, 1971). Consequently much of the initial research on the TCT was done with T-2 toxin because of the relative ease of production and the assumption that it was a representative member of the TCT (Wyatt, 1991).

T-2 Toxin:

T-2 toxin and HT-2 toxin are mycotoxins of the group trichothecene produced by fungi of the fusarium genus (*F. acuminatum*, *F. poae* and *F. sporotrichioides*) which are mainly found in various cereal crops (wheat, maize, barley, oats and rye) and processed grains (malt, bear

and breed). T-2 and HT-2 toxins often occur together in infected cereals (SCF, 2001). The most important producer is *F. sporotrichioides*, a saprophyte which grows at -2 to 35ºC and only at high water activities above 0.88. The occurrence of *F. sporotrichioides* in cereals is mainly a result of water damage to grains occurring when the cereals remain for extended periods on the field at or after harvest or when the grain is wet during storage (JECFA, 2001).

Natural occurrence:

Because of its toxicity, analytical procedures for T-2 toxin were developed first and consequently early surveys for TCT tended to concentrate on T-2 toxin. However, it soon became apparent that other TCT, in particular, DON, NIV and DAS, were more frequent contaminants of food and animal feed than T-2 toxin (WHO, 1990). Surveys have revealed the presence of T-2 toxin and HT-2 toxin in grains such as wheat, maize, oats, barley, rye, beans and soyabeans as well as in some cereal- based products (SCF, 2001). Combinations of DON and T-2 toxin, T-2 toxin and HT-2 toxin and T-2 toxin and DAS, have been reported to occur in mixed feed and grains (Bata *et al.,* 1983).

It was reported that T-2 toxin at the level of 2 mg/ kg was present in moldy corn involved in lethal toxicosis in dairy cattle (Hsu *et al.,* 1972). Occasional samples were found to contain T-2 toxin (incidence was below 10% in most cases), most frequently at levels < 0.1 mg/ kg. Usually other TCT was also found (Vesonder, 1983). There are isolated reports of the finding of rather high levels of T-2 toxin as the finding of 25 mg T-2 toxin/ kg in barley (Puls and Greenway, 1976), and 38.9 mg T-2 toxin/ kg in peanuts (Bhavanishankar and Shantha, 1987; WHO, 1990). The chemical structure of T-2 toxin was revealed by Bamburg *et al.* (1968). They gave T-2 toxin its name from the *Fusarium tricinctium* T-2 strain. The structure of T-2 and HT-2 toxins differ only in the functional group at the C- 4 position. As T-2 toxin readily metabolized to HT-2 toxin (SCF, 2001).

Metabolism:

T-2 toxin is readily metabolized by mammalian gut microflora to several metabolites, HT-2 toxin is a primary metabolite in the gut and is absorbed into the blood after ingestion. Metabolism continues into the liver (with biliary excretion) resulting in a substantial, combined first-pass effect in the gut and liver (JECFA, 2001). T-2 toxin is rapidly absorbed after ingestion in most animal species and it is distributed in the organism with little or no accumulation in any specific organ or tissue (WHO, 1990; SCF, 2001). T-2 toxin is rapidly metabolized by deacetylation, hydroxylation glucoronide conjugation and de-epoxidation (Johnsen *et al.,* 1988).

The main biotransformation pathway is deacetylation of the C- 4 acetyl group of T-2 toxin with isolated microsomes from liver, kidney and spleen of various animals. This reaction is catalysed by a non- specific carboxyestrase in several tissues, mainly in the liver, but also blood plasma (Johnson *et al.,* 1988). HT-2 toxin may be further deacetylated, hydroxylated and conjugated by various metabolic pathways to 3–hydroxyl- HT-2 toxin, T-2 thiol, 3-hydrtoxy T-2 triol, 4-deacetylneosolaniol which is converted to T-2 tetroal., and glucuronide conjugates of these (WHO, 1990; IARC, 1993; SCF, 2001). The toxicity of these metabolites of T-2 toxin appears to be much less than that of the parent compound. Compared to several other species of animals, chickens, have very low hydrolysis and hydroxylation activities (Wyatt, 1991).

In ruminants, the rumen plays an important role in presystemic detoxification of T-2 toxin

(Bauer *et al.,* 1989). Kiessling *et al.* (1984) demonstrated that rumen fluid can convert T-2 toxin to HT-2 toxin. Munger *et al.* (1987) described the transformation of T-2 toxin in bovine rumen fluid to acetyl T-2 toxin, HT-2 toxin and 3- acetyl- HT2- toxin (iso- T-2 toxin), which may be the precursor of 3- hydroxy- iso- T-2 toxin. In lactating cows fed T-2 toxin at low doses, 30% of the dose is eliminated in the first 24 hours, mainly through the kidneys, after 24 hours the remaining toxin (70%) is eliminated in the feaces, presumably by bile (Yoshizawa *et al.,* 1981). Chatterjee *et al.* (1986) detected no T-2 toxin in the urine of Holstein cow after two oral doses of T-2 toxin (0.55 mg/ kg b.wt.) in a time interval of 48 hours, but they analysed HT-2 toxin, 3- hydroxyl- T-2 toxin, 3- hydroxyl- HT-2 toxin, T-2 tetraol, 3- hydroxy- 3 acetoxy- HT-2- toxin, de-epoxy- 3- hydroxyl- HT-2 toxin and de- epoxy- T-2 tetraol.

In pigs, intravenously injected with T-2 toxin, the urine contained large quantities of HT-2 toxin, 3- hydroxy- T-2 toxin and 3- hydroxy- HT-2 toxin and small amounts of T-2 triol and T-2 tetroal., 72 hours after injection. The main metabolite detected in feces was HT-2 toxin in addition to T-2 triol, 3- hydroxy- HT-2 toxin and de- epoxy- T-2 tetraol were also found (Bauer *et al.,* 1989).

In birds dosed with 0.25 mg radiolabelled T-2 toxin/ kg b.wt., maximum residues in the eggs occurred 24 hours after dosing, the yolk contained 0.04% of the total dose and the white contained 0.13% (Chi *et al.,* 1978a; WHO, 1990). In those dosed with 0.1 mg T-2 toxin/ kg b.wt. per day for 8 consecutive days, the radioactivity in the egg accumulated until the 5^{th} day of dosing, remained unchanged until the last day of dosing, and rapidly decreased thereafter.

Trichothecenes such as T-2 toxin and DON are rapidly eliminated in the feces and urine. For example about 100% of an oral dose of T-2 toxin in cattle was eliminated within 48 hours after dosing (Feinbury and McLaughlin, 1989). In chickens, about 80% of T-2 toxin had been eliminated in the excreta, 48 hours after dosing as T-2 toxin or its metabolites (HT-2 toxin, neosolaniol, T-2 tetroal) and 8 unknown derivatives (TB_1 to TB_8) were detected (Yoshizawa *et al.,* 1980). The results of transmission of T-2 toxin in the laying hen and lactating cow showed that less than 1% of the administered dose of this toxin and its metabolites was present in eggs and milk. Tissue residues of oral T-2 toxin and its metabolites in chicken meat were below 2% of the dose, 24 hours after dosing (WHO, 1990).

Toxicity:

Trichothecenes are toxic to all tested animal species, but the sensitivity varies considerably between species and also between the different TCT. The toxic exposure also depends on which toxin the animal are exposed to, the duration of the exposure and the dose (Prelusky *et al.,* 1994). T-2 toxin is the most toxic trichothecene produced by fusarium fungi (Eriksen, 2003). The main toxic effect of T-2 toxin appears to be primary inhibition of protein synthesis followed by a secondary disruption of DNA and RNA synthesis. The mechanism of toxicity has been focused on protein and macromolecular synthesis, membrane function, enzyme activities and immune functions (Leeson *et al.,* 1995).

T-2 toxin is a potent inhibitor of protein synthesis in vivo and in vitro (JECFA, 2001). Protein synthesis can be inhibited at any of its steps of translation (inhibition, elongation or termination) (Feinburg and MaLaughlin, 1989). The inhibition of protein synthesis results from binding to peptidyl transferase and the DNA and RNA synthesis (Leeson *et al.,* 1995). This action of T-2 toxin could account at least in

part, for the numerous observations characterized by decrease in the proteineous fractions of blood and tissues (McLaughlin *et al.,* 1977). CAST (1989) described that the binding of T-2 toxin to cell membrane receptors may interfere with nucleic acid and protein synthesis.

Cells most susceptible to the action of TCT are actively dividing cells such as those lining the gastrointestinal tract, the skin and lymphoid and erythroid cells (Leeson *et al.,* 1995). T-2 toxin and DAS are highly toxic, causing necrosis of skin and mucous membranes (mouth, pharynx, esophagus, rumen, stomach) on contact, much like a caustic and also extensive necrosis of a variety of intestinal tissues (described as radiominetic) (Jones *et al.,* 1997).

In vivo, inhibition of synthesis of proteins has been demonstrated in cells from bane marrow, spleen and thymus (SCF, 2001). In vitro, T-2 toxin affect the permeability of cell membranes (Bunner and morris, 1988), and caused changes in the phospholipid turnover in bovine platelets (Grandoni *et al.,* 1992) and hemolysis of erythrocytes (Rizzo *et al.,* 1992). One of the significant effect of T-2 toxin is its immunosuppressive activity (Corrier and ziprin, 1986), probably linked to the inhibitory effect of this toxin on the biosynthesis of macromolecules (Bunner and Morris, 1988).

In humans:

Most information regarding the effects of T-2 mycotoxin on humans has been collected from many incidents of accidental ingestion of moldy wheat or corn (Locasto, 2001). In the period 1931-47, a human disease known alimentary toxic aleukia (ATA) occurred in the USSR that was suggested to be related to the presence of toxic Fusarium species in moldy over- wintered grain (WHO, 1990). Most men in the village were fighting in the war, leaving the wheat crop unharvested, which resulted in the crop remaining in the fields over the winter. It has harvested in the spring and consumed causing the clinical syndrome ATA, with varied reports of 10-60% mortality (Locasto, 2001).

An association to *F. poae* and *F. sporotrichiodes*, which in later fungal cultures have been found to produce several TCT including T-2 and HT-2 toxin was established (SCF, 2001). The main pathological changes were pronounced leukopenia and necrotic lesions of the oral cavity, esophagus and stomach. The primary lesions were bone-marrow hyperplasia and aplasia. The disease was lethal in a high proportion of cases (Joff, 1986; Beardall and Miller, 1994; JECFA, 2001).

Scabby grain toxicosis is a disease of both humans and animals, that reported from Japan and Korea during 1946- 63. The commonest clinical symptoms were nausea, vomiting, diarrhea and abdominal pain. All the cases were acute with recovery within few days without deaths. Fusarium fungi, *F. graminearum* in particular, were isolated from suspected cereals (JECFA, 2001).

In an outbreak of toxicosis in a Chinese country 165 subjects consumed rice infected with *F. heterosporum* and *F. Graminearum*. About 50% of the persons consuming the rice fell ill with symptoms consisting of nausia, dizziness, vomiting, abdominal distension and pain, chills and diarrhea. Samples of the suspected rice were analyzed for T-2 toxin and a level of 180-420 μg/ kg was found. Analysis of the other toxins was not reported (Wang *et al.,* 1993; SCF, 2001).

A similar outbreak was reported in Kashmir, India, in 1987 (Bhat *et al.,* 1987, 1989). It was ascribed to the consumption of bread made from flour that had become moldy

in storage following unseasoned rains in the wheat. Harvesting season, from which Fusarium species was grown and which were found to contain mycotoxins. Of the 224 persons investigated on a random sample basis, 97 were affected with symptoms including abdominal pain (100%), throat irritation (63%) diarrhea (39%), blood in stools (5%) and vomiting (7%). In 12 out of 24 samples of refined wheat flour used in the preparation of bread, the following mycotoxins were found: T-2 toxin (0.55–0.8 mg/kg), DON (0.35- 8.38 mg / kg), acetyl – DON (0.64- 2.49 mg/ kg) and NIV (0.03- 01 mg/kg).

The clinical course of ATA is divided into four stages (Joffe, 1971; Wannemacher and Wiener, 1997). The first stage develops immediately or several days after consumption of grain products that are contaminated with TCT mycotoxins. Inflammation of the gastric and intestinal mucosa causing vomiting, diarrhea and abdominal pain. In most cases, excessive salivation, headache, dizziness, weakness, fatigue and tachycardia accompanied this stage, and fever and sweating may also be present.

The disease progress to the second stage, the leukopenic or latent stage, which is characterized by leukopenia, granulopenia and progressive lymphocytosis. When the ingestion of the toxin- contaminated food is not interrupted or if large doses in consumed, the next stage develops. The third stage is characterized by the appearance of brightened, or dark sherry- red, petecheal rash on the skin of the chest and other areas, but they then spread and become more numerous.

In the most severe cases, intensive ulceration and gangrenous processes develop in the larynx, leading to aphonia and death by strangulation. At the same time, the affected individuals have severe hemorrhagic diathesis of the nasal, oral, gastric and intestinal mucosa. As the necrotic lesions heal and the body temperature falls, the fourth stage begins. During this period, exposed patients susceptible to various secondary infections, inducing pneumonia. Convalescence is prolonged and last for several weeks. Usually, 2 months or more are require for the blood forming capacity of the bone marrow to return to normal.

The T-2 mycotoxin which is classified as a TCT mycotoxin, is elaborated from fusarial species of fungus. According to the current declassified literature, the T-2 toxin is the only mycotoxin known to have been used as a biological weapon. The TCT mycotoxins are low molecular weight compounds (250 – 500 d) that are nonvolatile relatively insoluble in water and highly soluble in ethanol, methanol and propylene glycol (Locasto, 2001).

Trichothecene mycotoxins cause skin, eye and gastrointestinal problems when delivered at low doses, in macrogram amounts, they (T-2 toxin, in particular) cause severe skin irritation (erythema, edema and necrosis) (Ueno, 1989; Wannemacher and Wiener, 1997). Skin visication has been observed in a number of humans exposed to yellow rain attacks (Seagrave, 1981; Ember, 1984; Ueno, 1989). T-2 toxin is about 400 fold more potent (50 ng Vs 20 µg) than mustard in producing skin injury (Bunner *et al.,* 1985). Lower- microgram quantities of TCT mycotoxins cause severe eye irritation, corneal damage and impaired vision (Watson *et al.,* 1984; Bunner *et al.,* 1985; Stahl *et al.,* 1985; Ueno, 1989). Emesis and diarrhea have been observed at amounts that are one fifth to one tenth the lethal doses of TCT mycotoxins (Bunner *et al.,* 1985; Wannemacher and Wiener, 1997).

Reports exist of T-2 mycotoxin used as a biological warfare agent. The first suggested use was in the country of Laos during the Vietnam war. The report of "yellow rain" in

remote sections of Jungle in Laos (1975-81) has been viewed as used of T-2 toxin as a biological weapon. Other reports uses of T-2 toxin as a biological weapon by Soviet forces against Kampuchea (1979-81) and Afghanistan (1979-81). The air attacks in Laos have been described as "yellow rain" and consisted of a shower of sticky, yellow liquid that sounded like rain as it fell from the sky. Other accounts described a yellow cloud of dust or powder a mist- like smoke or insert spray- like martial (Haig, 1982). Lethality of the attacks is documented by a minimum of 6310 deaths in Laos (from 226 attacks), 981 deaths in Kampuchea (from 124 attacks), and 3042 deaths in Afghanistan (from 47 attacks) (Haig, 1982; Wannemacher and Wiener, 1997).

In ruminants: Ruminants are rather resistant towards TCT compared to monogastric animals. It is generally considered that the de- epoxidation activity in the rumen plays a significant role in the protection of cows to TCT (Prelusky *et al* 1994, Eriksen, 2003). Ruminal metabolism seems to offer some protection against TCT (Raisbeck *et al.,* 1991). T –2 toxin, DAS and DON were metabolized to variety of de- epoxy and de- acetylated products by bovine rumen microorganisms in vitro (King *et al.,* 1984, Swanson *et al.,* 1987), and no parent compound (i.e. T-2 toxin) was found in the excreta and tissues of cattle given two oral doses of 200 mg T-2 toxin (Mirocha, 1986). These findings may help to explain the relative resistance of ruminants to these compounds (king *et al.,* 1984, Swanson *et al.,* 1987). Although the exposure of ruminant species research does not lend itself to experimental determination of LD_{50}s, the median lethal single oral dose of T-2 toxin in calves seems to be of the order 2 to 5 mg / Kg b.wt. (Hook, 1987).

Newborn animals are more sensitive to the toxic effects of TCT than adults (WHO, 1990). The major toxic effects of TCT in mammals included reduced production and reproduction, dermatonecrosis, gastroenteritis, feed refusal, coagulopathy, immunosuppression and bone marrow depression (Raisbeck *et al.,* 1991; Howard and smith, 1999). The high cytotoxic potential is responsible for the irritation of mucous membranes in the gastrointestinal tract, causing nausea, vomiting and severe diarrhea. After absorption, the toxic symptoms are dominated by the cytotoxic action on the bone marrow (Marquardt *et al.,* 1999).

Typical exposure of skin or mucous membranes result in severe inflammation at low concentrations and necrosis at higher concentrations (Ueno and Ishi, 1985). The oral and intestinal lesions are a frequent finding in animals forced to consume high contaminated rations or dosed with acutely toxic dosages (Weaver *et al.,* 1980, Osweiler *et al.,* 1981, Pier, 1981).

T-2 toxin is a very potent mycotoxin and in cattle has been associated with gastroenteritis, intestinal hemorrhages (Mirocha *et al.,* 1976, Petrie *et al.,* 1977), and at a level of 0.64 ppm for 20 days, resulted in death and bloody feces, enteritis, and abdominal and ruminal ulcers (Pier *et al.*, 1980). Kegl and Vanyi (1991) observed bloody diarrhea, low feed consumption, decreased milk production and absence of estrus cycles in cows exposed to T-2 toxin. Anorexia and gastroenteritis were noted in a cow intubated with 0.44 mg/kg pure T-2 toxin for 15 days (Weaver *et al.,* 1980).

Intramuscular administration of crude T-2 toxin to cows reportedly produced epistaxis, bloody diarrhea and petechial hemorrhage (Kosuri *et al.,* 1970). Dairy cows refused a grain ration containing 50 ppm T-2 toxin (weaver *et al.,* 1980). Calves given T-2 toxin 0.6 mg/ Kg b.

wt via gelatin capsule consistently refused their grain ration, those given 0.3 mg/ kg refused intermittently (Osweiler *et al.,* 1981). Feed refusal associated with TCT could be attributed to the irritant properties of the toxins and decreased feed intake may result from possibly centrally mediated mechanism in addition to their irritant properties (Raisbeck *et al.,* 1991).

A field outbreak involving the death of 20% of a dairy herd was associated with prolonged ingestion of a diet containing 60% moldy corn infected with *F. tricinctam*. The concentration of T-2 toxin in the feed was approximately 2 mg/kg dry weight (Hsu *et al.,* 1972). The lesions in the cattle included extensive hemorrhages on the serosal surface of the intestinal viscera. An outbreak of hemorrhagic syndrome in cows was associated with commercial feed containing T-2 toxin or T-2 like toxin. The affected animals showed an extremely prolonged prothrombin time. Necropsy findings in 2 adult cows were marked serosal, mucosal and subcutaneous hemorrhages (Hibbs *et al.,* 1975, WHO, 1990).

In calves, clinical effects include necrosis of the lips, beak and oral mucosa and enteritis, which are caused by levels of T-2 toxin approximating 4 to 10 ppm (Biberstein and Zee, 1990). Some evidence of mild enteritis with loose feces was observed in calves received 0.08-0.6 mg T-2 toxin/ kg b.wt. orally in capsules for 30 days (Pier *et al.,* 1976). The high dose calf developed a hunch stance and died on day 20. Clinically apparent signs were confirmed at doses 0.16 mg/kg or more, and bloody feces at doses of 0.32 mg/ kg or more. At necropsy abomasal ulcers were present in the calves given the 2 higher doses.

A calf intubated with T-2 toxin developed severe depression, hindquarter ataxia, knuckling of the rear feet, listlessness and anorexia (Weaver *et al.,* 1980). Neutropenia was described in calves given single intravenous dose of 0.25 mg T-2 toxin /kg b.wt. (Gentry *et al.,* 1984). Depressed humoral immunity indicators (IgG, IgM, serum globulins and C_3) was recorded in calves given T-2 toxin (0.2 mg/ kg b.wt./day) via gelatin capsule for 28 days (Mann *et al.,* 1982; 1983). The no effect- level of T-2 toxin in calves is less than 0.08 mg/kg b.wt./day, which is equivalent to a 50 kg animal ingesting 2 kg of corn contaminated with 2 ppm of toxin per day (Mirocha, 1979).

Experimental lambs fed T-2 toxin at 0.3 or 0.6 mg/ kg ration for 21 days, developed focal hyperemia and dermatitis at the mucocutaneous junction of the commissure of the lips, diarrhea, leukopenia, lymphopenia and lymphoid depletion of the mesenteric lymph nodes and spleen (Friend *et al.,* 1983).

In pigs: The pig is the farm animal most sensitive to TCT (Ereksen, 2003). In pigs fed graded levels of T-2 toxin in standard pig ration for 8 weeks, no significant differences in body weight gain and feed consumption were observed between the test and control pigs. Young pigs refused a ration containing 16 ppm T-2 toxin, but not a diet containing 10-12 ppm. The no observed effect level in ration was estimated to be less than 1 ppm based on differences in body weight gain (Weaver *et al.,* 1978).

Dietary levels of T-2 toxin as low as 0.5 ppm were found to cause a reduction in feed intake in pigs (Rafai *et al*., 1995). T-2 toxicosis is due to elevation of tryptophan in the brain. Tryptophan is a precursor of serotonin, a mediator of appetite (Smith and seddon, 1998). Infertility with some lesions in the uteri and ovaries result from consumption of feed contaminated with 1 to 2 ppm of T-2 toxin (Jacobsen *et al.,* 1993).

The intravenous administration of T-2 toxin to pigs at doses of 4 or 8 mg/ kg b.wt, resulted in

increased plasma concentrations of epinephrine, norepinephrine, thromboxane B_2 and 6- keto- prostaglandin F (Lorenzana *et al.,* 1985, WHO, 1990). The pigs in the high- dose group produced such sign as persistent vomiting, watery diarrhea, abdominal straining, cold extremities, coma and death.

It is found that T-2 toxin when administered by intravenous injection (0.21- 0.41 mg/ kg b.wt) in to sows, will act as abortifacient but not when administered per os in the diet at 12 ppm. Moreover, when dietary T-2 toxin is administered in the third trimester of gestation, there is no effect on gestation, however, when administered prior to mating, no conception occurs, sows which do conceive produce small litters and weak piglets (WHO, 1979).

In poultry: Chickens are more sensitive to TCT than ruminants. Turkey may be more sensitive towards TCT than chickens (Richard *et al.,* 1978, Eriksen, 2003). The single LD_{50} dose of T-2 toxin for one- day- old broiler chicks was 5 mg/ kg b.wt. It was 5 and 6.3 mg/ kg for 8- week- old broiler chicks and laying hens, respectively (Chi *et al.,* 1978 b, WHO, 1990). Death of the birds occurred within 48 hour of T-2 toxin administration. Within 4 hours of receiving the toxin, birds developed asthenia, inappetence, diarrhea and panting. The abdominal cavities of birds given lethal doses contained a white chalk- like material that covered much of the viscera.

Broilers: Signs and lesions of T-2 toxicosis in broilers comprised growth depression accompanied by decreased feed intake, decreased spleen and bursa size, and increased pancreas size (Wyatt *et al.,* 1972a, 1973b, 1975, Chi *et al.,* 1977b). An increase in the incidence of liver hematomas, formation and development of an inflammation in oral cavity with white to cream- coloured raised necrotic lesions were also noted (Wyatt, 1991).

Batches of 40 broiler chickens fed graded concentrations of 1-16 ppm of T-2 toxin for 3 weeks developed an abnormal positioning of the wings, hysteroid seizures and impaired righting reflex (Wyatt *et al.,* 1973a, chi *et al.,* 1977a). The incidence of neural signs was dependent on the length of exposure to T-2 toxin and its dietary concentration. Neural signs were observed at dietary concentration above 4 ppm, which are the same levels causing growth retardation (Leeson *et al.,* 1995). Neural toxicity might have been related to alterations in brain amines.

T-2 toxin contaminated feed and litter caused reduced growth, vesicular lesions on the feet and legs and ulcerated and crusted oral mucosa (Wyatt *et al.,* 1972 b; Calnek *et al.*, 1997). An outbreak of T-2 toxin mycotoxicosis in a commercial flock of broiler chickens was reported by Bitay *et al* (1981). Altered feathering, depression, necrosis of the oral and oesophegeal mucosa and visible atrophy of lymphoid organs were observed. Feed analysis revealed 2.5 ppm T-2 toxin.

Oral lesions were caused by T-2 toxin at a concentration as low as 0.4 ppm. These lesions were circumscribed proliferative yellow caseous plagues that occurred at the margin of beak, mucosa of the hard palate and angle of the mouth and the tongue. The severity increased with a longer feeding period and with higher dietary levels (Chi *et al.,* 1977 b, Leeson, *et al.,* 1995). The no observed effect doses of T-2 toxin in broilers were 0.2 ppm for weight gain for oral lesions (Chi *et al.,* 1977 b).

A detailed investigation of the oral lesions associated with T-2 toxicosis revealed the rapid development of an intense inflammation with localized necrosis following initial exposure to

the toxin (Wyatt *et al.,* 1972a). The lesions were also colonized by the normal bacterial microflora of the mouth parts which appeared to intensify the inflammation and necrosis (Wyatt, 1991). The healing process in the oral cavity will usually be complete with only a slight degree of scar tissue remaining in the previously affected area. During recovery from the toxicosis previously affected chickens will show compensatory growth and feed consumption will usually return to normal (Wyatt, 1991).

Refusal of feed, the clinical sign of TCT mycotoxicosis in swine, has been reported to occur in chickens. T-2 toxin added to feed and water, produced a dose- related refusal in broiler chickens (Burditt *et al.,* 1983). Presentation in water caused more sensitive refusal since the minimum effective dose was 0.31 ppm in water compared with 5 ppm in feed. Abnormal feathering was observed in chickens receiving dietary T-2 toxin levels of 4 ppm or higher (Wyatt *et al.,* 1975). Feather lesions appeared as necrosis of the layer of regenerative cells in the feather base and of the basilar layer of the ramus and of the barb ridges (Hoerr *et al.,* 1981, Leeson *et al.,* 1995).

Histopathological findings: Oral histopathology confirms mucosal necrosis and ulceration, submucosal granulation tissue and inflammatory cells and crusts of exudates, bacterial colonies and feed components (Calnek *et al.,* 1997). Acute lethal oral intoxication with T-2 toxin causes necrosis of lymphoid and hemopoeitic tissue within one hour and rapid cellular depletion alter 72 hours (Hoerr *et al.,* 1981; Calnek *et al.,* 1997).

Discrete foci of hepatocyte necrosis and hemorrhage and necrosis and inflammation of the gallbladder mucosa are followed by mild proliferation of bile ductules. Necrosis of intestinal epithelium proceeds transient shortening of villi and fewer mitotic figures in crypt epithelium. Necrosis also occurs in the mucosa of the proventriculus and gizzard and in feather epithelium (Hoerr *et al.,* 1981; Calnek *et al.,* 1997).

Laying hens: Feed consumption, egg production and shell thickness were significantly decreased in hens ford 8 ppm T-2 toxin. Fertility was not affected by feeding T-2 toxin, but hatchability of fertile eggs of hens fed 2 and 8 ppm was significantly lower than that of hens fed the control diet. Oral lesions were observed from the second week in hens fed 4 and 8 ppm T-2 toxin and after 3 weeks in hens fed as little as 0.5 ppm (Chi *et al.,* 1977c; Leeson *et al.,* 1995).

Feed contamination with 3 ppm T-2 toxin caused decreases in feed consumption and egg production, and a thin- shelled eggs (Harris, 1984; Calnek *et al.,* 1997). Yellow crusts and ulcers on the oral mucosa made closing the mouth difficult and feathers were uneven and poorly formed. Birds with oral lesion also had yellow-tan, friable livers, swollen kidneys, urate deposits in ureters focal ulceration and inflammation of the crop mucosa and thickened rough lining in the gizzard. Depression, recumbency, feed refusal and cyanosis of the comb and wattles also occurred. The ovary and oviduct became atrophied (Shlosberg *et al.,* 1984; Calnek *et al.,* 1997).

T-2 toxin depresses egg production and causes a decrease in layer body weight and egg weight as well as the vitamin content of eggs and the calcium, copper, iron, manganese and lysozyme content of the egg white. The degree of production drop depending on the amount of ingested toxin and the duration of the toxin exposure (Glavits and Salyi, 1998). Tobias *et al.* (1992) reported a dose related reduction in egg

production and impaired hatchability in laying hens fed diets containing up to 10 ppm purified T-2 toxin for 28 days. Levels of 1.5 and 10 ppm dietary T-2 toxin reduced egg production by 12.5, 68.0 and 78.9%, respectively. Eggs with pigmented shell exhibit pigmentation disturbances. Initially some of the eggs assume "freckled" appearance resembling that of turkey's eggs, while later on entirely pigmented- free eggs are also encountered (Glavits and Salyi, 1998).

The drop of production is due to the inhibition of ovarian function. According to certain observations and research results, certain hormonal changes (reduction in hypophyseal LH secretion) may also play a rule in its development (Glavits and Salyi, 1998). Decreases in hatchability can be caused by decreases in feed intake of laying hens. However, based upon the observation of Chi (1978a), Wyatt, (1991) described that transfer of T-2 toxin or its metabolites to the egg may account for decreased hatchability associated with T-2 toxicosis.

Depending on the amount of toxin passing into the egg, the disturbance of embryonic development will assume different forms. If large toxin doses get into the egg, oocyte segmentation will not even begin, in such cases, eggs appear as it they were infertile. At lower toxin contamination embryonic development will commence but subsequently, the embryo will die at a later stage of development, mostly before the first candling (blood- spotted egg). Alternatively, the fully developed embryo may fail to hatch due to its reduced vitality, or may die after hatching (Glavits and Salyi, 1998).

Since T-2 toxin does not affect testicular function, semen production will not be impaired even later the ingestion of large toxin doses. However, the mating disposition of birds may decrease already after the ingestion of relatively moderate toxin concentrations (Glavits and Salyi, 1998).

Turkey poults: Oral lesions occurred at numerous foci through the mouth in poultry fed 10 ppm T-2 toxin after 2 weeks (Richard *et al.,* 1978). The thymus of the poults given 10 ppm T-2 toxin was markedly decreased in size compared to controls, but no effect was seen on the size of spleen or bursa.

A field outbreak of T-2 toxicosis was reported in laying turkey hens receiving feed contaminated with 0.75- 0.83 ppm T-2 toxin (Fazekas *et al.,* 1993; Leeson *et al.,* 1995), main effects include 20% decrease in hatchability, doubling of embryo mortality and 16% mortality in turkey poults within 8 days after hatching. Egg production was not reduced but the quality of the egg shell was impaired. Fazekas *et al* (1993) fed laying turkey hens a diet containing 1.5 ppm T-2, in an attempt to reproduce the outbreak. No clinical signs, mortality or effect on egg production were observed but a decrease in hatchability comparable to the field case was noticed.

Ducks: Duckling have been shown to be particularly sensitive to TCT mycotoxins (Leeson *et al.,* 1995). Young Mallard ducks fed diets containing 20-30 ppm pure T-2 toxin for 2-3 weeks, developed necrotizing upper alimentary tract lesions, oral and esophageal lesions, ulcerative proventriculitis, and severe depletion of the lymphoid tissues, characterized by thymic, bursal and splenic atrophy (Hayes and Wobeser, 1983).

Day-old Muscovy ducklings receiving dietary T-2 toxin or DAS at 0.25- 1.0 ppm for 7 days, developed dose- related lesions in the roof of the oral cavity (Shlosberg *et al.,* 1986; Leeson *et al.,* 1995). Muscovy ducklings showed these signs in a shorter period of time (Less than 16

hours in some cases) and at a lower concentration of these mycotoxins than did other avian species in similar studies. The author proposed to use this species as a bioassay to detect mycotoxins in contaminated grain.

Pigeons: The LD_{50} value of T-2 toxin for pigeons was determined to be 1.7 mg/ kg b.wt. (Fairhurst, *et al.,* 1987), which is about one third of the reported LD_{50} value for broiler chickens (Chi *et al.,* 1977 c). Acute toxicity was manifested by vomiting, ataxia and abnormal wing positioning (Fairhurst *et al.,* 1987; Leeson *et al.,* 1995).

Guidelines:

Despite the toxic effects of T-2 toxin, only few countries (Russia, Israel) have set limits for T-2 toxin in food or feed. The maximum tolerated level is 0.1 mg/ kg for cereals, flour and wheat bran in Russia and for grain used for feed in Israel (FAO, 1997). A guideline value of 0.2 mg T-2 toxin/kg feed is proved in pig feed. The guideline should apply to the sum of T-2 toxin and H T-2 toxin. The concentration of T-2 toxin in poultry feed should not exceed 0.5 mg/kg feed, this guideline should apply to the sum of T-2 toxin and H T- toxin, since T-2 toxin is rapidly metabolized to H T-2 in vivo, and toxic effect of the two toxins can not easily be separated in animal experiments (Eriksen, 2003).

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السموم الفطرية فى الأغذية والأعلاف

5- الترايكوثيسينات

أ- ت-2 توكسين

بدير إبراهيم عجاج

قسم بحوث الكيمياء الحيوية والسموم- معهد بحوث صحة الحيوان بالدقى- مركز البحوث الزراعية

السموم الفطرية هى مركبات كيمائية تنتجها أنواع مختلفة من الفطريات التى تنمو على المواد الغذائية والأعلاف وتسبب أضراراً صحية لكل من الإنسان والحيوان. ومن أهم السموم الفطرية التى استخدمت فى بعض أماكن من العالم كسلاح بيولوجى نظرا لسهولة امتصاصها عن طريق الجلد والجهاز التنفسى والجهاز الهضمى سموم الترايكوثيسينات ومنها ت-2 توكسين الذى تفرزه فطريات الفيوزاريوم، حيث تتميز بشدة تأثيرها السمى على الخلايا الطلائية للجهاز الهضمى والخلايا الليمفاوية وخلايا الدم الحمراء وخلايا الجلد. وقد تسبب تغذية الإنسان والحيوان على أغذية وأعلاف ملوثة بهذا المركب إلى حدوث تهيج بالغشاء المخاطى للقناه الهضمية يؤدى إلى الغثيان والقئ والإسهال بالإضافة إلى حدوث التهابات وتنكرز وتقرح بالقناة الهضمية خاصة الفم، وتختلف التغيرات الباثولوجية والأعراض التى يحدثها ت-2 توكسين باختلاف تركيزها بالأغذية والأعلاف وكذلك مدة التعرض له.