



MYCOTOXINS IN FOODS AND FEEDS

5-Trichothecenes

A-T-2 Toxin

B.I. Agag

Biochemistry Deficiency Diseases and Toxicology Department,
Animal Health Research Institute, Agricultural Research center

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, nausea 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-macrocytic and 65 macrocytic) 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 is 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, verrucarol, 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 tetraol., 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 glycol (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 35°C 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 Bamberg *et al.* (1968). They gave T-2 toxin its name from the *Fusarium tricinctum* 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 glucuronide 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-hydroxy T-2 triol, 4-deacetylneosolaniol which is converted to T-2 tetraol, 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 feces, 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 tetraol., 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 5th 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 tetraol) and 8 unknown derivatives (TB₁ to TB₈) 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 radiomimetic) (Jones *et al.*, 1997).

In vivo, inhibition of synthesis of proteins has been demonstrated in cells from bone 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 nausea, 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, petechial 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 LD₅₀s, 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 C₃) 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 B₂ 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 LD₅₀ 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 oesophageal 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 plaques 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 hemopoietic tissue within one hour and rapid cellular depletion after 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 fed 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 role 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 if 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 LD₅₀ 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 LD₅₀ 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).

REFERENCES:

- Bamburg, J.R.; Riggs, N.V. and Strong, F.M. (1968): "The structures of toxins from two strains of *Fusarium tricinctum*". *Tetrahedron*, 24 (8): 3329- 3336.
- Bata, A.; Vanyt, A. and Lasztity, R. (1983): "Simultaneous detection of some fusario toxins by gas liquid chromatography". *J. Assoc. Off. Anal. Chem.* 166: 577-581.
- Bauer, J., Gareis, M. and Gedek, B. (1989): Metabolism of the trichothecenes T-2 toxin, Diacetoxyscirpenol, and Deoxynivalenol by farm animals. pp. 167-177. J. Chelkowski (Ed.) *Fusarium mycotoxins. Taxonomy and Pathogenicity*, Vol. 2, Elsevier. Amsterdam, Oxford, New York, Tokyo.
- Beardall, J. M. and Miller, J.D. (1994): "Diseases in humans with mycotoxins as possible causes." In: Miller, J.D and Trenholm, H L. eds. *Mycotoxins in grain. Compounds other than aflatoxin*. Minnesota: Eagan Press, pp. 487-539.
- Bhat, R.V.; Ramakrishna, Y.; Rao, B.S. and Nahdi, S. (1987): "Trichothecene mycotoxicosis." Hyderabad: Food and Drug Toxicology Research Center, National Institute of Nutrition.
- Bhat, R.V.; Beedu, S.R.; Ramakrishna, Y. and Munshi, K.L. (1989): "Outbreak of trichothecene mycotoxicosis associated with consumption of mold damaged wheat products in kashmir valley, India." *Lancet*, 7: 35-37.
- Bhavanishankar, T.R. and Shantha, T. (1987): "Natural occurrence of *Fusarium* toxins in peanuts, sorghum and maize from mysore (India). " *J. Sci. food Agric.* 40: 327- 332.
- Biberstein, E. and Zee, Y.C. (1990): "Review of Veterinary Microbiology." pp. 352-353. Blackwell Scientific Publications, Inc. Boston, Oxford, London, Edinburgh, Melbourne.
- Bitay, Z.; Glavits, R.; Sandor, G. and Balazs, K. (1981): "A case of T-2 mycotoxicosis in broiler chicks." *Mag. Alla. Lapja*, 37: 491-495.
- Buck, W. B. and Cote, L.M. (1991): "Trichothecene mycotoxins." In R.F. Keeler and A.T. Tu (Eds.) *Handbook of*

- natural toxins, Vol. 6: Toxicology of plant and fungal compounds, pp. 523-554. Marcel Dekker, New York.
- Bunner, D.L. and Morris, E.R. (1988): "Alteration of multiple cell membrane function in L-6 myoblasts by T-2 toxin: An important mechanism of action." *Toxicol. Appl. Pharmacol.*, 92: 113-121.
- Bunner, D.L.; Upshall, D.G. and Bhatti, A.R. (1985): "Toxicology data on T-2 toxin." In: Report of forces officers meeting on mycotoxin toxicology, September 23-24, 1985. Suffield, Alta, Canada: Defense Research Establishment at Suffield.
- Burdit, S.J.; Hagler, W. M., Hutchins, J.E. and Hamilton, P.B. (1983): "Models of feed refusal syndrome in poultry." *Poult. Sci.*, 65: 2158-2163.
- Burmeister, H.R. (1971): "T-2 toxin production by *Fusarium tricinctum* on solid substrate." *Appl. Microbiol.*, 1, 21 (4): 739-742.
- Calnek, B.W.; Barnes, H.J.; Beard, C.W.; McDoughald and Saif, Y.M. (1997): "Diseases of Poultry." 10th ed. pp. 952-956. Iowa State University Press, Iowa 50014.
- CAST, Council for Agricultural Science and Technology (1989): "Task Force." Report No. 116, November.
- Chatterjee, K.; Pawlosky, R.J.; Treeful, L. and Mirocha, C.J. (1986): "Kinetic study of T-2 toxin metabolites in a cow." *J. Fd Safety.*, 8: 25-34.
- Chi, M.S.; Mirocha, C.J.; Kurtz, H.J.; Weaver, G.; Bates, F. and Shimoda, W. (1977a): "Effects of T-2 toxin on reproductive performance and health of laying hens." *Poult. Sci.*, 56 (2): 628-637.
- Chi, M.S.; Mirocha, C.J.; Kurtz, H.J.; Weaver, G.; Bates, F. and Shimoda, W. (1977b): "Subacute toxicity of T-2 toxin in broiler chicks." *Poult. Sci.*, 56: 306.
- Chi, M.S., Mirocha, C.J., Kurtz, H.J.; Weaver, G.; Bates, F. and Shimoda, W. and Burmeister, H.R. (1977c): "Acute toxicity of T-2 toxin in broiler chickens and laying hens." *Poult. Sci.*, 56:103-116.
- Chi, M. S.; Robison, T.S.; Mirocha, C.J.; Behrens, J.C. and Shimoda, W. (1978a): "Transmission of radioactivity into eggs from laying hens administered tritium labeled T-2 toxin." *Poult. Sci.*, 57 (5): 1234- 1238.
- Chi, M.S.; Robison, T.S., Mirocha, C.T.; Swanson, S.P. and Shimoda, W. (1978 b): "Excretion and tissue distribution of radioactivity from tritium labeled T-2 toxin in chickens." *Tox. Appl. Pharm.*; 45: 391-402.
- Cole, R.J. and Cox, R.H. (1981): "The trichothecenes." In: R. J. Cole and R. H. Cox (eds) *Handbook of toxic fungal metabolites*. New York, NY: Academic Press. PP. 152-263.
- Corrier, D.E. and Ziprin, R.L. (1986): "Immunotoxic effects of T-2 toxin on cell mediated immunity to Listeriosis in mice: Comparison with cyclophosphamide." *Am. J. Vet. Res.*, 47: 1956- 1960.
- Drove, J.F. (1988): Non- macro cyclic trichothecenes. Natural products Reports: 181-209.
- Ember, L.R. (1984): "Yellow rain." *Chemical and Engineering News*, 62 (2):8-34.
- Eriksen, G. S. (2003): "Metabolism and toxicity of trichothecenes." Doctoral thesis, Swedish Univ. of Agric. Sci., Uppsala.
- Eriksen, G.S. and Alexander, J. (1998): "Fusarium toxins in cereals- a risk assessment." *Nordic Council of Ministers, Tema Nord*, 202: pp. 7-44, Copenhagen.
- Fairhurst, S.; Marrs, T.C.; Parker, H.C.; Scawin, J.W and Swanston, D.W. (1987): "Acute toxicity of T-2 toxin in rats, mice,

- guinea pigs and pigeons." *Toxicol.* 43: 31-49.
- FAO, Food and Agricultural Organization (1997): FAO, Food and Nutrition, paper No. 64, pp: 143, Rome.
- Fazekas, B.; Tanyi, J.; Salyi, G.; Bistyok, A. and Kerekes, L. (1993): "Effect of T-2 toxin on the hatchability of turkey eggs and viability of day-old turkey poults." *Mag. Alla. Lapja*, 84- 221-225.
- Feinberg, B. and McLaughlin. C.S. (1989): "Biochemical mechanism of action of trichothecene mycotoxins." In: V. R. Beasley (Ed.) *Trichothecene mycotoxins. Pathophysiologic effects. Vol. I.* pp. 27-35 CRC, Boca Raton.
- Friend, S.C.E.; Hancock, D.S. and Schiefer, H.B. (1983): "Experimental T-2 toxicosis in sheep." *Can. J. Comp. Med.*, 47:291-297.
- Garg, S.K. (2000): "Veterinary Toxicology." pp. 224-228. CBS Publishers & Distributors, New Delhi.
- Gentry, P.A.; Ross, M.L. and Chan, P.K. (1984): Effect of T-2 toxin on bovine hematological and serum enzyme parameters. *Vet. Hum. Toxicol.*, 26: 24.
- Glavits, R. and Salyi, G. (1998): "The most important mycotoxicosis of poultry." Central Veterinary Institute, H-1581 Budapest, P.O. Box, Hungary, Kutatási Levegősega OAI.
- Grandoni, K.M.; Gentry, P.A.; Holub, B.J. and Yagen, B. (1992): "Trichothecene mycotoxins inhibit phosphoinositide hydrolysis in bovine platelets stimulated with platelet activating factor." *Toxicol.*, 72: 60.
- Haig, A.M. Jr. (1982): "Chemical warfare on southeast Asia and Afghanistan." Washington. DC: US Government printing office; March 22. Report to the Congress.
- Harris, J.R. (1984): "Case report on T-2 mycotoxicosis in chickens." Keeping current (CEVA laboratories, Inc.) Jan-Feb: 2-3.
- Hayes, M. A. and wobeser, G. A. (1983): "Subacute toxic effects of dietary T-2 Toxin in young Mallard ducks." *Can. J. comp. Med.*, 47: 180-187.
- Hibbs, C.M.; Osweiler, G.D.; Buck, W.B. and Macfee, G.P. (1975): "Bovine hemorrhagic syndrome related to T-2 mycotoxin." *Proc. Ann. Meet. Am. Assoc. Vet. Lab. Diagn.*, 17: 305-310.
- Hoerr. F.J.; Carlton, W.W. and Yagen, B. (1981): "Mycotoxicosis caused by a single dose of T-2 toxin or diacetoxyscirpenol in broiler chickens." *Vet. Pathol.*, 18: 652-664.
- Hook, B.S. (1987): "Effects of T-2 toxin in cattle." Ph. D. thesis, University of Missouri, Columbia.
- Howard, J.L. and Smith, R.A. (1999): "Current Veterinary Therapy, Food Animal Practice." pp. 256-257. W.B. Saunders Co., Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.
- Hsu, I.H. Chang, Smalley, E.B.; Strong, F.M. and Ribelin, W.E (1972): "Identification of T-2 toxin in moldy corn associated with a lethal toxicosis in dairy cattle." *Microbiol.* 24: 684-690.
- IARC, International Agency for Research on Cancer (1993): "Monographs on the evaluation of carcinogenic risks to humans." Vol. 56: Some naturally occurring substances, Food items and constituents, heterocyclic aromatic amines and mycotoxins, Health organization. pp. 297-333, Lyon.

- Jacopsen, B.J.; Bowen, K.L.; Shelby, R.A.; Diener, U.L.; Kempainen, B.W. and Floyd, J. (1993): "Mycotoxins and mycotoxicosis." Circular ANR- 767, Alabama and Auburn Universities.
- JECFA, Joint FAO/ WHO Expert Committee on Food Additives (2001): 56th report on T-2 and HT-2 toxins. Safety evaluation of certain mycotoxins in food. WHO food additive series 47. WHO, Geneva, 419-556.
- Joffe, A.Z. (1971): "Alimentary toxic aleukia." In: Kadis, S., Ciegler, A. and Ajl, S.J (eds). Microbial toxins. Vol. 7, pp. 139-189. New York, Academic press.
- Joffe, A.Z. (1986): "Fusarium species. Their Biology and Toxicology.", New York: J. Wiley and Sons.
- Johnsen, H.; odden, E.; Jhonsen, B.A. and Fonnum, F. (1988): "Metabolism of T-2 toxin by blood cell carboxyestrases." Biochem Pharmacol., 37: 3193- 3197.
- Jones, T.C.; Hunt, R.D. and King, N.W. (1997): "Veterinary Pathology." 6th Ed. pp. 545-547 Williams and Wilkins Co.
- Jordan, F.; Pattison, M.; Alexander, D. and Farogher, T. (2002): "Poultry Diseases." 5th Ed. pp. 397-401. W.B. Saunders Comp., London.
- Kegl, T. and Vanyi, A. (1991): "T-2 fusariotoxicosis in a cattle stock." Magyar Allatorvosok Lapja, 64: 467- 471.
- Kiessling, K.; Petterson, K.; Sandholm and Olsen, M. (1984): "Metabolism of aflatoxion, ochratoxin, zearalenone and three trichothecenes by intact rumen fluid, rumen protozoa and rumen bacteria." Appl. Environ. Microbiol., 47: 1070-1073.
- King, R.; McQueen, R.E.; Levesque, D. and Greenhalgh, R. (1984): "Transformation of deoxynivalenol by rumen microorganisms." J. Agric. Food. Chem., 32:1118.
- Kosuri, N.R.;Grove, M.D.; Yates, S.G.; Tallent, W.H.; Ellis, J.J.; wolf, I.A. and Nichols, R.E. (1970): Response of cattle to mycotexins of *Fusarium tricinctum* isolated from corn and fescue." J. Am. Vet. Med. Assoc., 157: 938.
- Leeson, S.; Diaz, G.J. and Summers. J.D. (1995): "Poultry metabolic disorders and mycotoxins." pp. 190-226. University Books, Guelph, Ontario, Canada.
- Locasto, D.A. (2001): "T-2 toxin." eMedicine J., December 11, Vol. 2, No 12, Medicine. Com, Inc.
- Lorenzana, R.M.; Beasley, V.R.; Buck, M.B.; Ghent, A.W.; Lundren, G.R. and Poppenga, R.H. (1985): "Experimental toxicosis in swine. I. Changes in cardiac output, aortic pressure, catecholemines, 6-keto PGF_á and thromboxane B2 and acid base parameters." Fundem. Appl. Toxicol., 5: 879- 892.
- Mann, D.D., Buening, G.M., Hook, B.S. and Osweiler, G.D, (1982): "The effect of T-2 toxin on the bovine immune system: humoral factors." Infect. Immune, 36: 1249.
- Mann, D.D.; Buening. G.M.; Hook, B. and Osweiler, G.D. (1983): "Effect of T-2 toxin on bovine serum proteins." Am. J. Vet. Res., 44: 1757.
- Marquardt, H.; Schafer, S.G.; McClellan, R. and Welsch, F. (1999): "Toxicology." pp. 980-981. Academic Press, San Diego, London, Boston, New York, Sydney, Tokyo, Toronto.
- Mclaughin, C.S.; Vaughon, M.H.; Campbell, I.M.; Wei, C.M.; Stafford, M.E. and Hansen, B.S. (1977): "Inhibition of protein synthesis by trichothecenes." In: Rodericks, J. V.; Hesselstine, C. W.,

- Mehlman, M.A., eds. *Mycotoxins in human and animal health*. pp. 263-275. Park Forest South. III. Pathotox-pubishers.
- Mesterhazy, A.; Bartok, T.; Mirocha, C.G. and komoroczy, R. (1999): "Nature of wheat resistance to *Fusarium* head blight and the role of deoxynivalenol for breeding." *Plant breeding*, 118: 97- 110.
- Mirocha, C.J. (1976): "Metabolism and residue of trichothecene toxins in animal and plant systems." In: Steyn, P.S. and Vleggier, R., eds; *Mycotoxins and phytotoxins*, Elsevier, Amsterdam, 409.
- Mirocha, C.J. (1979): "Trichothecene toxins produced by *fusarium*." In: W. Shimoda (ed.). *Conference on mycotoxins in animal feeds and grains related to animal health*. FDA Report No. 79/139, pp. 289-373.
- Mirocha, C.J.; Pathre, S.V.; schauerhamer, B. and Christensen, C.M. (1976): "Natural occurrence of *fusarium* toxins in feedstuffs." *Appl. Environ. Microbiol.*, 32: 553-556.
- Munger, C.E.; Ivie, G.W.; Christopher, R.J.; Hammock, B.D. and Phillips, T.D. (1987): "Acetylating, deacetylation fraction of T-2, acetyl T-2, H T-2 and acetyt H T-2 toxin in bovine rumen fluid in vitro." *J. Agr. Food Chem.*, 35: 354- 358.
- Osweiler, G.D.; Hook, B.S.; Mann, D.D.; Buening, G.M. and Rottinghans, G.E. (1981): "Effects of T-2 toxin in cattle." *Proc. U.S. Anim. Health Assoc.*, 85: 214.
- Petrie, L.; Robb, J. and Stewart, A.F. (1977): "The identification of T-2 toxin and its association with a hemorrhagic syndrome in cattle." *Vet. Rec.*, 101: 326-336.
- Pier, A.C. (1981): "Mycotoxins and animal health." *Adv. Vet. Sci. Comp. Med*, 25: 185.
- Pier, A. C.; Cysewski, S.J.; Richard, J.L.; Baetz, A.L. and Mitchell, L. (1976): "Experimental mycototoxicosis in calves with aflatoxin, ochratoxin, rubratoxin, and T-2 toxin." In: *Proceedings of the 80th Annual Meeting of the US Animal Health Association*, Miam, Beach, Florida 7-12 Nov., pp. 130-148.
- Pier, A.C.; Richard, J.L. and Cysewski, S.J. (1980): "The implication of mycotoxins in animal disease." *J. Am. Vet. Med. Assoc.*, 176: 719- 722.
- Prelusky, D.B.; Rotter, B.A. and Rotter, R.G. (1994): "Toxicology of mycotoxins." *Mycotcoxis in grains: Compounds other than aflatoxin*. Eds. Miller, J.D. and Trenholm, H. L., Eagan press. St. Paul, MN, 359-403.
- Puls. R. and Greenway, J.A. (1976): "Fusariotoxicosis from barley in British Columbia. II. Analysis of suspected barley." *Can. J. Comp. Med.*, 40 (1): 16-19.
- Rafai, P.; Bata, A.; Vanyi, A.; Papp, Z.; Brydl, E.; Jakab, L.; Tuboly, S. and Tury, E. (1995): "Effects of various levels of T-2 toxin on the clinical status, performance and metabolism of growing pigs." *Vet. Rec.*, 136: 485- 489.
- Raisbek, M.F.; Rottinghaus, G.E. and Kendall, J.D. (1991): "Effects of naturally occurring mycotoxins on ruminants." pp. 647-677. in: Smith, J.E. and Henderson, R.S.
- Richard, J.L.; Cysewski, S.J.; Pier, A.C. and Booth, G.D. (1978): "Comparison of effects of dietary T-2 toxin on growth, immunogeic organs, antibody formation, and pathologic changes in turkeys and chickens." *Am.J.Vet. Ras.*, 39:1674-1679.
- Rizzo, A.; Atroshi, R.; Hirvi, T. and Saloniemi, H. (1992): "The hemolytic activity of

- deoxynivalenol and T-2 toxin." *Nat. Toxins*, 1: 106-110.
- SCF, Scientific Committee on Food (2001): "Opinion on the Fusarium toxins.", Part 5: T-2 toxin and HT-2 toxin. European Commission, Health and consumer protection Directorate- General., SCF/CS/ CNTMMYC/ 25 Eev 6 Final.
- Seagrave, S. (1981): "Yellow rain: A Journey through the terror of chemical warfare." New York: M Evans.
- Shlosberg, A.S.; Klinger, Y. and Malkinson, M.H. (1986): "Muscovy ducklings; a particularly sensitive avian bioassay for T-2 toxin and diacetoxyscirpenol." *Avian Dis.*, 30: 820-824.
- Shlosberg, A.S.; Weisman Y.; Handji, V.; Yagen, B. and Shore, L. (1984): A severe reduction in egg laying in a flock of hens associated with trichothecene mycotoxicosis in the feed." *Vet. Human Toxicol.*, 26: 384-386.
- Smith, T.K and Seddon, I.R. (1998): "Synergism demonstrated between Fusarium mycotoxins." *Feedstuffs*, June 22nd: 12-17.
- Snijders, C.H. and Perkowski, J. (1990): "Effects of head blight caused by *Fusarium culmorum* on toxin content and weight of wheat kernels." *Pharmacology*, 80: 566- 570.
- Stahl, C.J.; Green, C.C. and Farnum, J.B. (1985): "Pathological and toxicological examination of a casualty after chemical attack." *J. Forensic Sci.*, 30 (2): 317-337.
- Swanson, S.P.; Nicoletti, J.; Rood, H. D.; Buck, W.B. and Cote, L.M. (1987): "Metabolism of three trichothecene mycotoxins, T-2 toxin, diacetoxyscirpenol and deoxynivalenol by bovine rumen microorganisms." *J.Agric. Food Chem.*, 32: 1118.
- Tobias, S.; Rajic, I. and Vanyi A. (1992): "Effect of T-2 toxin on egg production and hatchability in laying hens." *Acta Vet. Hung.*, 40: 47-54.
- Ueno, Y. (1987): "Trichothecenes in food." *Mycotoxins in food. Food Science and Technology.* Ed Krogh, P., Academic Press. London. pp. 123-147.
- Ueno Y. (1989): "Trichothecene Mycotoxins. Mycology, Chemistry and Toxicology." *Adv. Nutr. Res.*, 3: 301-353.
- Ueno, Y. and Ishi, K. (1985): "Chemical and biological properties of trichothecene and *Fusarium sportorichoides*. Trichothecenes and other mycotoxins.", Lacey, J. (ed.) John Wiley and Sons, New York, 307.
- Vesonder, R.F. (1983): "Natural occurrence of trichothecenes in North America." *Dev. Food Sci.*, 4: 210-217.
- Wang, Z.G.; Feng, J. and Tong, Z. (1993): "Human toxicosis caused by moldy rice contaminated with *Fusarium* and T-2 toxin." *Biomed. Environ. Sci.*, 6: 65-70.
- Wannemacher, R.W. and Wiener, S.L. (1997): "Trichothecene mycotoxins." *Textbook of Military Medicine: Medical aspects of chemical and biological warfare*, Chapter 34, The University of Iowa, Iowa State, USA.
- Watson, S.A.; Mirocha, C.J. and Hayes, A.W. (1984): "Analysis for trichothecenes in samples from Southeast Asia associated with "Yellow rain"". *Fundam. Appl. Toxicol.*, 5: 700-717.
- Weaver, G. A.; Kurtz, H.J.; Bates, F.Y.; Chi, M.S.; Mirocha, C.J.; Behrens, J.C and Robison, T.S. (1978): "Acute and chronic toxicity of T-2 mycotoxin in swine." *Vet. Rec.*, 103: 531-535.
- Weaver, G.A.; Kurtz, H.J.; Mirocha, C.J.; Bates, F.Y, Behrens, J.C.; Robison, T. and Swanson, S.P. (1980): "The failure of

- purified T-2 mycotoxin to produce hemorrhaging in dairy cattle." *Can. Vet. J.*, 21: 210.
- WHO, World Health Organization (1979): "Environmental Health Criteria, Safety evaluation of certain food additives." pp. 288-373. Y.R., IP : VI: 11.
- WHO, World Health Organization (1990): "Selected mycotoxins: Ochrotoxins, Trichothecenes, Ergot." *Environmental Health Criteria 105*, Geneva.
- Wyatt, R.D. (1991): "Poultry." pp. 573- 604. In: Smith, J. and Hamilton, R.S.
- Wyatt, R.D., Harris, J.R. Hamilton, P.B. and Burmeister H.R. (1972a): "Possible outbreaks of fusariotoxicosis in avians." *Avian Dis.*, 16: 1123- 1130.
- Wyatt, R. D., Weeks, B.A.; Hamilton, P.B and Burmeister, P.B. (1972b): "Severe oral lesions in chickens caused by ingestion of dietary fusariotoxin T-2." *Appl. Microbiol.*, 24: 251.
- Wyatt, R.D.; Colwell, W. M.; Hamilton, P.B.; Burmeister, H. R. (1973a): "Neural disturbances in chickens caused by dietary T-2 toxin." *Appl. Microbiol.*, 26 (5): 757-761.
- Wyatt, R. D.; Hamilton, P.B. and Burmeister, H.R. (1973b): "The effects of T-2 toxin in broiler chickens." *Poult. Sci.*, 52: 1853.
- Wyatt, R.D.; Hamilton, P.B. and Burmeister, H.R. (1975): "Altered feathering of chickens caused by T-2 toxin." *Poult. Sci.*, 54: 1042.
- Yoshizawa, T., Swanson, S. P. and Mirocha (1980): "T-2 metabolism in the excreta of broiler chickens administered 3 H-labeled T-2 toxin." *Appl. Environ. Microbiol.*, 39: 1172-1177.
- Yoshizawa, T.; Mirocha, C.J.; Behrins, J.C and swanson S.P. (1981): "Metabolic fate of T-2 toxin in a lactating cow." *Food Cosmet. Toxicol.*, 19 (1): 31-39.

السموم الفطرية فى الأغذية والأعلاف

٥- الترايكوثيسينات

أ- ت-٢ توكسين

بدير إبراهيم عجاج

قسم بحوث الكيمياء الحيوية والسموم - معهد بحوث صحة الحيوان بالدقى - مركز البحوث الزراعية
السموم الفطرية هي مركبات كيميائية تنتجها أنواع مختلفة من الفطريات التي تنمو على المواد الغذائية والأعلاف وتسبب
أضراراً صحية لكل من الإنسان والحيوان. ومن أهم السموم الفطرية التي استخدمت في بعض أماكن من العالم كسلاح
بيولوجي نظراً لسهولة امتصاصها عن طريق الجلد والجهاز التنفسي والجهاز الهضمي سموم الترايكوثيسينات ومنها ت-٢
توكسين الذى تفرزه فطريات الفيوزاريوم، حيث تتميز بشدة تأثيرها السمي على الخلايا الطلائية للجهاز الهضمي والخلايا
الليمفاوية وخلايا الدم الحمراء وخلايا الجلد. وقد تسبب تغذية الإنسان والحيوان على أغذية وأعلاف ملوثة بهذا المركب إلى
حدوث تهيج بالغشاء المخاطي للقناة الهضمية يؤدي إلى الغثيان والقئ والإسهال بالإضافة إلى حدوث التهابات وتتركز
وتقرح بالقناة الهضمية خاصة الفم، وتختلف التغيرات الباثولوجية والأعراض التي يحدثها ت-٢ توكسين باختلاف تركيزها
بالأغذية والأعلاف وكذلك مدة التعرض له.