TRICHOTHECENES: T-2 AND HT-2 TOXINS AND REPRODUCTIVE PHYSIOLOGY

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ABSTRACT

Mycotoxins are secondary metabolites produced by filamentous fungi. Mycotoxins are contaminats of animal feed, food and food products. T-2 toxin is one of the most toxic mycotoxin of type A trichothecenes, which is produced mainly by *Fusarium* species. T-2 toxin causes a different toxic effect in both animal and human. T-2 toxin is inhibitor of DNA and RNA synthesis and synthesis of proteins in several cellular systems, immunosuppressive agent, induce lesions in hematopoetic, lymphoid and digestive tract. T-2 toxin may reduce reproductive performance in animals furthermore many experiments indicate possible dose-dependent effect on endocrine regulation of reproduction. This review presents review about the role of T-2 and HT-2 toxins in animal reproduction.

Keywords: mycotoxins, T-2 toxin, HT-2 toxin, reproductive system

INTRODUCTION

All mycotoxins are low-molecular-weight natural products (i.e. small molecules) produced as secondary metabolites by filamentous fungi. These metabolites constitute a toxigenically and chemically heterogeneous assemblage that are grouped together only because the members can cause disease and death in human beings and other vertebrates **(Bennett, 1987)**. Mycotoxins may cause various toxic effects or mycotoxicosis **(Kanora and Maes, 2009)**. Mycotoxins cause a wide variety of adverse effect (decrease of immune response, clinical signs) depending on the nature and concentration of mycotoxins present, the duration of exposure, the animal species, its age, health and nutritional status during the exposure to mycotoxin contaminated feed **(Diaz, 2005)**. The main mycotoxins that occur frequently are aflatoxins, fumonisins, ochratoxin A, patulin, trichothecenes and zearalenone **(Josephs et al, 2004)**. The four main genera of mycotoxin-producing fungi are *Aspergillus spp., Fusarium spp., Penicillum spp. and Claviceps spp*. **(Kanora and Maes, 2009)**.

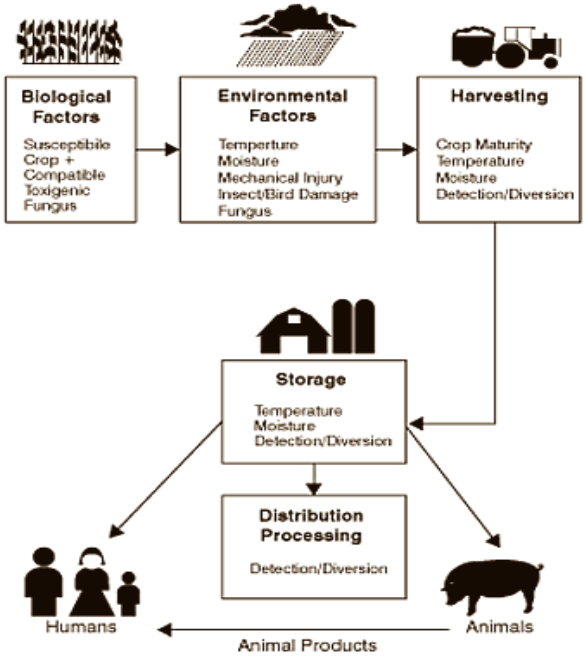

Figure 1. **Factors influencing mycotoxin occurrence in the food chain (Pestka and Casale, 1988)**.

TRICHOTHECENES

The trichothecenes are a very large family of chemically related toxins produced by various species of *Fusarium*, *Myrotecium*, *Trichoderma*, *Cephalosporium*, *Verticimonosporium* and *Stachybotrys* **(Ueno, 1989)**. Trichothecenes are classified into four groups (type A, B, C, D) based on their chemical structures as well as their producer fungi. Among these, diacetoxyscirpenol (DAS) and T-2 toxin in type A, and deoxynivalenol (DON) and nivalenol (NIV) in type B, are known to be the most naturally encountered and the most potent trichothecenes **(Ueno, 1985; Rocha et al., 2005)**.

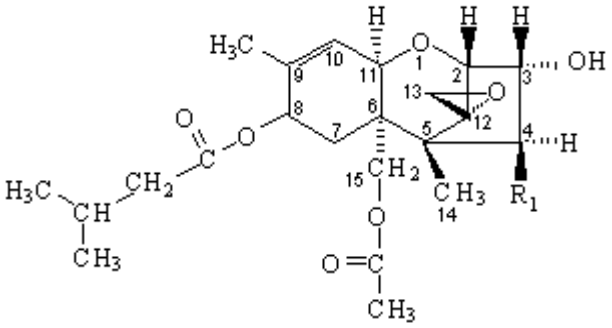

Figure 2. **Structure of type A trichothecenes: T-2 (R_1=OAc) and HT-2 (R_2=OH) toxins (Canady et al., 2010)**.

Pottentially hazardous concentrations of the trichothecene mycotoxins can occur naturally in moldy grains, cereals and agricultural products **(Ueno, 1989; CPAM, 1983)**. In acute tests with trichothecenes, type A members such as DAS and T-2 toxin have been found to be more toxic than type B components such as DON and NIV **(Leeson et al., 1995)**.This family of mycotoxins causes multiorgans effects including emesis and diarrhea, weight loss, nervous disorders, cardiovascular alterations, immunodepression, hemostatic derangements, skin toxicity, decreased reproductive capacity, and bone marrow damage **(Ueno, 1989; Wannemacher et al., 1991)**. Reproductive failure and

drop in reproductive performances brought on by mycotoxins can be defined as reproductive mycotoxicoses **(Desjardins, 2006)**.

T-2 AND HT-2 TOXINS

T-2 toxin is one of the mycotoxins, of type A trichothecenes produced by several fungal genera including *Fusarium species* **(Chen et al., 2005)**. The structures of T-2 and HT-2 toxins differ only in the functional group at the C-4 position. As T-2 toxin is readily metabolized to HT-2 toxin, these two mycotoxins were evaluated together **(Canady et al., 2010)**. The toxic effects of T-2 toxin and its metabolite HT-2 toxin could not be differentiated, and the toxicity of T-2 toxin in vivo might be due at least partly to HT-2 toxin **(Creppy, 2002)**. T-2 toxin was first isolated from the mould *F. tricinctum* (*F. sporotrichioides*) **(Ueno, 1977; Burmeister et al., 1971)**. T-2 and HT-2 toxins have been reported to be produced by *Fusarium sporotrichioides*, *F. poae*, *F. equiseti*, and *F. acuminatum* **(Canady et al., 2010)**. Species spectrum of the genus *Fusarium* isolated from Slovak wheat in season 2008 was found by **Maškova et al. (2010)**.

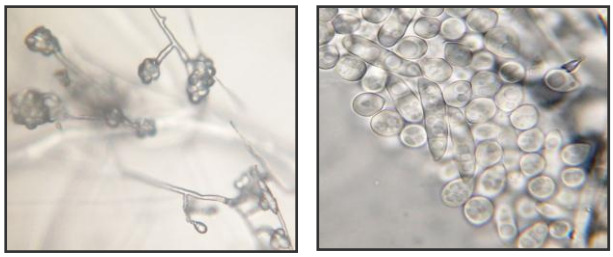

***Figure 3. Fusarium poae*;** micropicture of macro- and microconidia **(Labuda, 2008)**

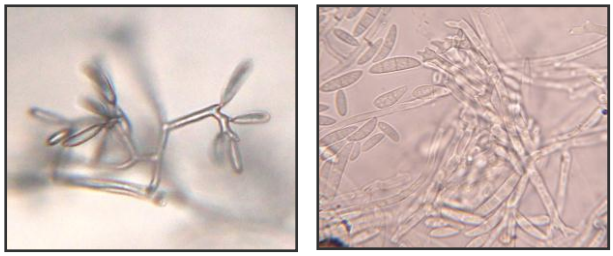

Figure 4. Fusarium sporotrichioides; micropicture of macro- and microconidia **(Labuda, 2008)**

T-2 toxin has been found to contaminate human foods, animal foods and agricultural products, which has been reported in many parts of the world **(WHO, 1990)**. Surveys for T-2 toxin and HT-2 toxin revealed their presence in grains such as wheat, maize, oats, barley, rice, beans, and soya beans as well as in some cereal-based products. There have been occasional reports of the presence of T-2 and HT-2 toxins in human foods. Bread, breakfast cereals, and other cereal foods were found to be contaminated with T-2 toxin, and infant foods, bread, noodles, and cereal foods were found to contain HT-2 toxin **(Patel et al., 1996; Schollenberger et al., 1999, 2000a,b)**. The toxic effects of T-2 toxin have been studied in experimental animals – poultry, cattle, sheep and pigs – all of which appear to be sensitive to this mycotoxin. Among farm animals, pigs are the most sensitive species **(Eriksen and Petterson, 2004)** and ruminants are more resistant to the adverse effects of T-2 toxin due to microbial degradation within rumen microorganisms **(Donal et al., 2008)**. Exposure to the toxin results in skin pain, pruritis, redness, vesicles, necrosis, epidermal sloughing, nausea, weight loss, vomiting and diarrhea. Severe poisoning results in prostration, weakness, ataxia, collapse, reduced cardiac output, shock and death **(WHO, 2001)**. Oral, parenteral and cutaneous exposures to T-2 toxin induce lesions in hematopoietic, lymphoid and gastrointestinal tissues and suppress reproductive organ functions **(Stanford et al., 1975; Williams, 1989; IARC, 1993; Sharma, 1993)**. T-2 toxin is a well-known inhibitor of protein synthesis through its high binding afinity to peptidyltransferase which is an integral part of the 60s ribosomal subunit **(Shifrin and Anderson, 1999; Bennet and Klich, 2003; Eriksen and Petterson, 2004)**. T-2 toxin also inhibits the synthesis of DNA and RNA, probably secondary to inhibition of protein synthesis **(Eriksen and Petterson, 2004; Thompson and Wannenmacher, 1990)**. The immune system is a primary target of T-2 toxin **(Creppy, 2002)**. T-2 toxin has also been found to produce significant immunosuppression and suggested that effect of T-2 toxin might be related to apoptosis of immune cells **(Islam et al., 1998)**. Leukopenia, granulopenia, exhaustion of bone marrow, progressive lymphocytosis and thymic apoptosis are the most important pathological symptoms **(Islam et al., 1998)**. T-2 toxin interferes with the metabolism of membrane phospholipids and increase liver lipid peroxides **(Chang and Mar, 1988; Eriksen et al., 2004)**.

EFFECT OF T-2 AND HT-2 TOXINS ON REPRODUCTIVE SYSTEM

Developmental toxicity

Mycotoxins as contaminants of animal feed can impair growth and/or reproductive effeciency. This is especially prominent in prepubertal gilts **(Dänicke, 2002)**. T-2 toxin also has an important impact on reproductive performance in pigs **(Kanora and Maes, 2009)**. Furthermore, in sows, T-2 toxin may cause infertility, and after parenteral administration during the last trimester of gestation, is able to precipitate abortion within 48 h **(Weaver et al., 1986)**. One study, feeding contaminated feed of 1-2 ppm to sows during the last third of gestation, found an inhibitory effect on the ovaries, with histological degeneration and accompanying atrophy **(Glavits et al., 1983)**. **Ishigami et al. (1999)** first reported that T-2 toxin (3 $mg.kg^{-1}$) can induce apoptosis, especially in the central nervous and skeletal systems after oral administration to pregnant mice, indicating the direct cytotoxic effect of T-2 toxin on fetal tissues. Another study looked at the impact of T-2 toxin on piglets following an experimental intoxication of pregnant sows with a daily dose of 24 mg of T-2 toxin during the final third of gestation. The piglets from these sows showed diarrhea, wasting and coma, and died soon after birth. T-2

metabolities were found in the sow´s milk and in the piglets´stomach content **(Vanyi et al., 1991)**. Single oral dose of T-2 toxin in propylene glycol to CD-1 mice was primarily maternally toxic and embryolethal; the defective development was possibly secondary to the maternal toxicity **(Rousseaux and Schiefer, 1987)**. Pregnant CD-1 mice were given T-2 toxin dissolved in propylene glycol intraperitoneally at a dose of 0.5 $mg.kg^{1}$ bw on day 8 or 10 of gestation. Treatment induced grossly malformed fetuses, principally with tail and limb anomalies. A higher incidence of malformations was observed when T-2 toxin was combined with ochratoxin A at 4 $mg.kg^{-1}$ bw **(Hood et al., 1978)**. **Huszenicza et al. (2000)** have studied T-2 toxin effects on heifers fertility. After T-2 toxin administration at the dose of 0,3-0,9 $mg.d^{-1}$ no abnormality in follicles number and size was observed, while an increase in the duration of the interval between parental PGF2α admimnistration and ovulation (about two days) was found. According to **Huszenicza et al. (2000)** this toxic effects are probably related to direct toxic activity of T-2-toxin on granulosa cells and luteal cells.

Reproductive endocrine effects

The reproductive health of animals could be affected by a number of endogenous as well as exogenous factors, such as exposure to heavy metal **(Massanyi et al., 2010; Kňažická et al., 2010; Schneidgenová et al., 2007)** and mycotoxins **(Maruniaková et al., 2010; Medveďová et al., 2011)**. Actively dividing cells in ovaries and testes are very susceptible to damage induce by T-2 toxin **(Chang and Mar, 1988)**. In a 1988 report, T-2 toxin-treated rats exhibited significantly lower granulosa cell protein levels than controls **(Miller-Patrick et al., 1988)**. **Caloni et al. (2009)** present that T-2 toxin may be able to alter in growth of the granulosa layer within ovarian follicles in addition to their effect on steroidogenesis. They results revealed that T-2 toxin had potent inhibitory effects on insulin-like growth factor-I (IGF-I) and follicle stimulating hormone (FSH)-induced estradiol and progesterone production, T-2 toxin inhibited cell numbers at $\geq$ $3ng.ml^{-1}$. The results of their study indicate that T-2 toxin has direct and potent dose-dependent effect on granulosa cell steroidogenesis and proliferation. Study with New Zealand white rabbits were fed a diet consisting of 'naturally infected' wheat containing T-2 toxin at for 32 days. The treated animals were then given gonadotropin-releasing hormone to induce false gestation plus T-2 toxin for a total duration of T-2 toxin treatment of 50 days. Three of the five animals given T-2 toxin and gonadotropin-releasing hormone showed abnormal progression of progesterone concentrations, and one of these animals died about 1 week after initiation of hormone treatment **(Fekete and Huszenicza, 1993)**. **Maruniaková et al. (2010)** have found a dose-dependent effect of T-2 and HT-2 toxins on secretory activity of porcine ovarian granulosa cells. In these experiments progesterone release was stimulated by T-2 toxin at 1000 $ng.ml^{-1}$. After addition of HT-2 toxin the release of progesterone was significantly stimulated at the dose of 1000 and 100 $ng.ml^{-1}$. **Yang et al. (2010)** indicated that T-2 toxin had toxic effects on reproductive system of adult male mice. Their results showed a significant increase of abnormal spermatozoa and a significant decrease in spermatozoa with integrated acrosome, the amount of live spermatozoa decreased significantly in mice treated with T-2 toxin. Testicular and cauda epididymal sperm counts, efficiency of sperm production were significantly reduced in mice treated with T-2 toxin at all doses in a dose-dependent manner. In another study T-2 toxin inhibited testosterone secretion in gerbil testicular interstitial cells *in vitro.* The median inhibitory dose was 0.042 $nmol.l^{-1}$, equivalent to 0.02 $ng.ml^{-1}$ **(Fenske and Fink-Gremmels, 1990)**. Another authors indicate significantly reduced serum testosterone concentration in mice treated with T-2 toxin at all doses in a dose-dependent manner **(Yang et al. 2010).**

CONCLUSION

Synthesis of mycotoxins by molds in livestock feedstuffs decrease animal performance via impaired growth and reproductive effeciency **(Diekman and Green, 1992)**. Mycotoxins produced by *Fusarium* fungi include trichothecenes, such as DON and T-2 toxin, as well as zearalenon and fumonisin **(D´Mello et al., 1999; Larsen et al., 2004)**, and may reduce reproductive performance in pigs **(Glávits et al., 1983; Glávits and Vanyi, 1995; Alm et al., 2002; Drochner et al., 2006)**. Furthermore other authors have found that porcine ovarian granulosa cells are sensitive to the effects of DON. Exposure of this mycotoxin has affected the release of progesterone and IGF-I by porcine ovarian granulosa cells **(Medveďová et al., 2011)**. Trichothecenes: T-2 and HT-2 toxins can cause infertility, histological degeneration, malformations in fetuses, have a direct toxic effect on ovaries and testes, as well as on their secretion activity. These findings indicate that trichothecenes have a great impact on the reproductive system.

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