AUCES

MYCOTOXINS IN FOODS AND FEEDS
3-ZEARALENONE

B.I. Agag

Biochemistry Department, Animal Health Research Institute, Agriculture Research Center

REVIEW ARTICLE

ABSTRACT :

Zearalenone (ZEN) is a nonsteroidal estrogenic mycotoxin occurring in corn, wheat, barley, sorghum and oats as well as other foods and feeds; when these substrates especially corn have contaminated by zearalenone producing fungi. It is produced by numerous species and subspecies of Fusarium in the presence of high humidity and low temperatures (10-15°C).

Zearalenone is suspected to cause human disease, including premature puberty syndrome, as well as hyperestrogenism in farm animals. Swine are the most sensitive of large domestic animals and most frequently affected on the farm. Cattle and sheep seem to be more resistant to ZEN toxicity.

High concentration of ZEN in feeds of cattle have been associated with infertility, enlargement of the mammary gland, reduced milk production, vaginitis and vaginal secretions especially in immature dairy heifers. In gilts, there are swelling of the vulva, vaginal prolapse, enlargement of the uterus, enlargement of the mammary gland, infertility, embryonic death and reduced litter size. While, in young boars the effects include testicular atrophy, swollen prepuce, mammary gland enlargement and decreased libido.

Poultry species are found to be less susceptible to the estrogenic effects of ZEN. A possible effect on the health of turkeys and young chicks may include vent enlargement and secondary sex characteristics, when very large concentrations are fed.

INTRODUCTION:

Natural occurrence: Zearalenone (ZEN) or F-2 toxin is a nonsteroidal estrogenic mycotoxin (Mitterbauer *et al.,* 2003). Under natural conditions ZEN and its derivatives are produced by numerous species and subspecies of Fusarium including: *F. roseum,* (*F. roseum* "graminearum", *F. roserm* "Gibbosum", *F. roseum* "Culmorum", *F. roseum* "Equiseti"), *F. tricinctum, F. sporotrichioides, F. oxysporum* and *F. moniliforme* (Mirocha *et al.,* 1977). These fungal species occurred naturally in corn, barley, commercial animal feeds, hay, oats, sesame and sorghum (Eugenio *et al.,* 1970; Shotwell *et al.,* 1971).

Studies indicate that greater portion of ZEN in nature is formed by *F. roseum* in high-moisture ear corn, either in plants left standing in the field, or in cribs or other places where ear corn is stored. Thus the presence of ZEN in pelleted or otherwise processed feed means that the feed was compounded in part of corn in

which the toxin was formed before the kernels were removed from the crob (FDA, 1979).

Fusarium graminearum is common on Kentucky farms where corn and or small grains are grown. The fungus best survives between crops of corn and small grains in residue on the soil surface (Vincelli and Parker, 1999). During warm, wet weather, spores of *F. graminearum* are produced on infested residue for 1- 3 years following harvest of the susceptible crop. These can be spread by rain splash or air movement to corn silks, where they germinate and colonize on the silks during wet weather. By growing down the silk channel, the fungus is able to attack the developing ear and cause an ear rot. A reddish- brown discoloration of kernels progresses from the tip downward in affected ears. A whitish- red mold growth may be present on highly affected ears (Vincelli and Parker, 1999).

The natural occurrence of ZEN is favoured by high humidity and low temperatures, 10 to 15°C (Caldwell *et al.,* 1970; CAST, 1989). Temperatures between 12 to 14°C are required for significant ZEN formation, but production also occurs at temperatures below 10°C and even below freezing (Weidenborner, 2001). *Fusarium graminearum* requires a minimum of 22 to 25 percent moisture to grow in cereal grains (Jacobsen *et al.,* 1993).

High levels of ZEN in cereals usually accumulate during storage of mature Fusarium infected grains that have not sufficiently dried because of wet weather at harvest or in grains that were stored wet (e.g. corn moisture content > 22%). Beside this, ZEN production has been reported on grains in the field, during harvest, commercial grain processing, and/or subsequently during storage of any food- or feedstuff containing the grain (Weidenborner, 2001).

Mycotoxins produced by Fusarium species are of two general types:

1- The non- estrogenic trichothecenes including deoxynivalenol (DON), nivalenol, monoacet-oxyscirpenol (MAS), diacetoxyscirpenol (DAS) and T- 2 toxin.

2- The mycoestrogens including zearalenone and zearolenol (Diekman and Green, 1992; Vincelli and Parker, 1999).

Concurrent occurrence with other mycotoxins:

Fusarium species may produce some ZEN and other toxins (Chistensen *et al.,* 1988) simultaneously including deoxynivalenol and T-2 toxin (Mirocha *et al.,* 1971). ZEN (25 to 135 ppm) was detected along with zearalenol (1.5 to 4 ppm) in finish oats samples of animal feeds (Mirocha *et al.,* 1979). ZEN was found together with aflatoxin in samples of preharvest grain from 64 sorghum fields in Georgia (McMillian *et al.,* 1983). ZEN was identified together with deoxynivalenol and/or aflatoxin in scabby wheat samples from Midwestern United States (Hagler *et al.,* 1984). Abnormally high concentration of both nivalenol and ZEN have been observed in some Japanese barley samples (up to 26 and 15 ppm, respectively), and in maize production in New Zealand (up to 7 and 10.5 ppm, respectively) (Placinta *et al.,* 1999).

Concentrations associated with animal health problems:

The estrogenic metabolite ZEN was first characterized from *F.graminearum* NRRL 2830, which was isolated from corn associated with field outbreaks of porcine hyperestrogenism in the United States (Stob *et al.,* 1962). Barley grains associated with stillbirth, neonatal mortality and small litter in swine contained 0.5 to 0.75 ppm of ZEN (Miller *et al.,* 1973). Grain

sorghum contained 12 ppm ZEN were involved in bovine abortion (Mirocha *et al.*, 1976).

ZEN at concentrations of 2 to 5.6 and 1.5 ppm, respectively, was deteted in Milo and sesame meal associated with swine hyperestrogenism, and concentrains of 0.02 to 8.1 ppm were found in sorghum implicated in abnormal estrus in swine (Mirocha *et al.*, 1974, 1976). Maize containing up to 8 ppm of ZEN resulted in clinical signs of hyperestrogenism in pigs on two farms in Northern Queensland (Blancy *et al.*, 1984).

Chemical structure:

The structure of ZEN was first determined by Urry *et al.* (1966). Zearalenone is the generic name for [6- (10- hydroxyl-6-oxo-trans-1-undecenyl)-B-resorcylic acid lactone]. It has the empirical formula of $C_{18}H_{22}O_5$, with a molecular weight of 318 (FDA, 1979). The name is derived partly from the generic name of the host plant infected by Fusarium (Zea) and partly from its chemistry (ral from resorcylic acid lactone, en= double bond at C-1-2, and one= ketone) (Urry *et al.*, 1966). Zearalenone and zearalenol are both estrogenic resorcylic acid lactone compounds produced by the fungi Fusarium spp.(Diekman and Green, 1992). Zearalenol (α- zearalenol) is a hydroxylated derivative of ZEN due to ZEN reductases present in animal tissues. Formation of zearalenone by *F. semitectum* has been reported (Weidenborner, 2001).

Zearalenone and some of its derivatives fluoresce blue- green when exhibited by ultraviolet radiation (360 nm) and fluoresce even more intensely when irradiated at 260 nm. This property can be used as a convenient and simple confirmatory test for ZEN resolved on thin- layer chromatography plates (Gillepsie and Schenk, 1977).

Mode of action:

As described by Hayes (1994); Gentry (1986) summarized the mode of action of ZEN as involving interaction with estrogen receptors, translocation of receptor-ZEN complex to the nucleus, combination with chromatin receptors, selective RNA transcription leading to biochemical effects including increased water and lowered lipid content in muscle, and increased permeability of the uterus to glucose, RNA and protein precursors. Zearalenone also induces biophasic changes in the luteinzing hormone but not the follicle stimulating hormone in serum (Bongiovanni, 1983).

Several trials with ZEN have revealed that ZEN competes with estradiol 17B (E_2) in the binding to cytosolic estrogen receptors, activates the expression of initial protein, and increases RNA polymerase I and II activities in nuclei (Boyd and Wittliff, 1978; Kawabata *et al.*, 1982).

The effects of zearalenol are similar to ZEN, but zearalenol is generally considered to produce estrogenic effects five- to ten- times greater than those of ZEN (Jacobson *et al.*, 1993). Alpha zearalenol possess a ten- times higher estrogenic activity than ZEN, whereas the B- isomer is considerably, less than that of ZEN (Weidenborner, 2001).

Despite their structural dissimilarity to the steroidal estrogens, ZEN and several of its derivatives possess estrogenic activity (Weidenborner, 2001) by depressing gonadotrophin levels (Radostits *et al.*, 1994). Zearalenone undergoes a folding such that hydroxyl or potential hydroxyl groups become appropriately orientated to facilitate binding to tissues receptors that normally bind estrogens. Similar binding affinities for ZEN have been determined for estrogen receptors in sheep and calf uterus (Diekman and Green, 1992).

Zearalenol derivative of zearalenone, has been found in oats and maize. Synthetic zearalenol is available for use as an agent for accelerating growth and fattening in animals (Humphreys, 1998). Parenteral zearalenol altered normal patterns of pituitary secretion of luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin by mechanisms analogous to estradiol in overectomized ewes and wethers (Elsasser et al., 1983).

Absorption, metabolism and excretion:

Zearalenone is rapidly absorbed after oral administration. Although the degree of absorption is difficult to measure owing to extensive biliary excretion, it appears to be extensively absorbed in rats, rabbits and humans (Kuiper-Goodman et al., 1987; WHO, 2000). The uptake in pigs after a single oral dose of 10 mg/ kg b.wt. was estimated to be 80- 85% (Biehl et al., 1993). In mice, studies with radiolabelled ZEN showed that it is distributed to estrogen target tissues such as the uterus, interstitial cells of the testes and ovarian follicles. Some radiolabel was also found in adipose tissues indicating that storage in fat may take place (Kuiper-Goodman et al., 1987).

The mean metabolites of ZEN are α- and β- zearalenol and glucuronide conjugates of both the parent compound and its metabolites (WHO, 2000). In comparative on the metabolism of ZEN, significant differences between species were found in the metabolic profile in urine and feces. A higher proportion of the administered ZEN was metabolized to α- zearalenol in pigs than in rats or cows (WHO, 2000). Consequently, the reduction of ZEN to α- zearalenol involves an activation of the toxin, while the reduction to β- zearalenol possible means the contrary (Olsen, 1986). While, the more resistant broiler, cows and sheep form 9

substantial share of the less active metabolite β- zearalenol (Mirocha et al., 1981; Mirocha et al., 1982; Hagler et al., 1980). In contrast to these findings is that ZEN caused androgenic response in male turkey poults (Allen et al., 1981a; Olsen et al., 1986), which transforms ZEN principally into α- zearalenol (Olsen et al., 1986).

In both humans and pigs, ZEA was found mainly as glucuronide conjugates of ZEN and α- zearalenol in urine. All of the metabolites found in humans during the 24 hours of sampling were glucuronides (Mirocha et al., 1981). In turkeys ZEN is metabolized primarily to α- zearalenol, while chickens tend to produce essentially equal amounts of α and β- zearalenol. Turkeys also convert a very high percentage of ZEN to the highly active α- zearalenol (Wyatt, 1991).

Hagler et al., (1979) determined α- zearalenol to be approximately three times more estrogenic than β-zearalenol, based upon a rat uterotrpic assay. This may be a partial explanatation for the apparent increased sensitivity of turkey poults to dietary ZEN (Wyatt, 1991). Olesn et al., (1986) also found a significant increase in the percentage of α- zearalenol (of total α- zearalenol plus ZEN) in both plasma and excreta. They postulated that since reduction of ZEN to the active metabolites probably occurs in the liver by 3-α- hydroxysteroid dehydrogenase, the increase in metabolite formation indicates an increased capacity for reduction of ZEN with increasing age of the poults.

Zearalenone and its metabolites are excreted mainly in the bile in most animal species except rabbits, in which urine is the main route. Most of an administered dose is excreted within 72 hours (Kuiper-Goodman et al., 1987). In the pigs dosed orally with ZEN,

45% of the administered dose was recovered in the urine during the first 48 hours, 22% was recovered in the feces, and the total accumulated recovery in urine and feces after 48 hours was 67% (Biehl *et al.,* 1993).

In chickens, ZEN in distributed chiefly to the liver and gall bladder (Mirocha *et al.,* 1982), and is excreted mainly in feces as ZEN and α- and β- zearalenol (Olsen *et al.,* 1986). In laying hens, most is excreted in feces, but residues may occur in yolk (Dailey *et al.,* 1980).

In extensive studies with zearalenol (the commercially marketed anabolic compound used in ear implants in cattle and sheep) in rats, sheep, cattle, monkeys, dogs, rabbits and man the major route of excretion was the feces. Edible tissues of animals receiving 36 mg of zearalenol as ear implants contained no detectable quantity of the compound 65 days after administration (Hidy *et al.,* 1977).

Residues in animal products:

1-Tissues: The amount of detectable ZEN in animal tissues depends on the contamination of feed, treatment of animals with ZEN or α- zearalenol duration of exposure to the toxin, the persistence of ZEN in the animal and species variation in response to the mycotoxin (WHO, 2000).The concentration of ZEN in livers from a pig given feed containing ZEN at 40 mg/ kg for 4 weeks was 78- 128 µg/ kg (Jones and Smith, 1982) Chickens fed feed containing 100 mg/ kg ZEN for 8 days had concentrations of 59- 103 µg/ kg in muscle and up to 681 µg/ kg in liver (Mirocha *et al.,* 1982).

2-Milk: Zearalenone can be excreted into milk after lactating cows are fed it in high doses. The maximum concentrations in the milk of one cow given an oral dose of 6000 mg ZEN (equivalent to 12 mg/ kg b.wt.), were 6.1 µg/ L ZEN, 4 µg/ L α- zearalenol, and 6.6 µg/ L β- zearalenol(WHO, 2000). A dose of 544.5 mg/ day given to a cow for 21 days, yielded maximum concentrations of only 2.5 µg/ L ZEN and 3 µg/ L alpha ZEN in the milk (Prelusky *et al.,* 1990). Neither ZEN nor its metabolites were found in the milk (< 0.5 µg/ L) of three lactating cows fed 50 or 165 mg ZEN (equivalent to 0.1 and 0.33 mg/ kg b.wt.) for 21 days (Prelusky *et al.,* 1990).

Experimental studies have shown some transmission of ZEN and α- and β- zearalenol into the milk of sheep (Hagler *et al.,* 1980), cows (Mirocha *et al.,* 1981) and pigs (Kurtz and Mirocha, 1978; Palyusik *et al.,* 1980; Vanyi *et al.,* 1983) given high concentrations of ZEN. Once administration was stopped, the concentrations in milk dropped sharply, although the compound was still detectable after 5 days in sheep milk (Hagler *et al.,* 1980) and pig milk (Palyusik *et al.,* 1980).

Since very high oral doses of ZEN were required to produce detectable concentrations in milk, milk from cows fed ZEN contaminated feed should not normally pose a human health hazard (Costing *et al.,* 1990). No residue of ZEN was found in animal products after administration of lower dietary concentrations (Shreeve *et al.,* 1979; Young *et al.,* 1982). It appears also that the edible portions of chickens receiving ZEN- containing diets present little residue danger to consumer (Mirocha *et al.,* 1982)

3-Eggs: Eggs accumulated metabolites of ZEN in the yolks, even after 94% of the dose had been eliminated in excreta (Daily *et al.,* 1980) were found.

Toxicity:

Although ZEN has low acute toxicity, it exhibits marked estrogenic effects in some species. Swine are especially sensitive and experience hyperestrogenism leading to

reproductive problems and infertility following dietary ZEN exposure. Other species such as cattle and sheep seem more resistant to ZEN but may still experience some incidence of infertility, decreased milk production and spontaneous abortion after ingesting high doses. Still other species, particularly chickens, appear even less sensitive (Barrett, 2000).

Zearalenone doses that are much greater than concentrations which have hormonal effect may have genotoxic and carcinogenic effects (Mitterbaur et al., 2003). A national toxicology program study found evidence of carcinogenicity in mice but not in rats (NTP, 2002). Likewise species- specific formation of DNA adducts has been reported (Pfohl-Leszkowicz et al., 1995).

Humans:

Evidence came from Italy (Fara et al., 1979) and Puerto Rico (Saenz de Rodriguez, 1984), suggested presence estrogenic substances (Bongiovanni, 1983). especially residues of ZEN and zearalenol (Saenz de Rodriguez and Toro-Sola, 1982) in red meats and poultry, may have caused premature thelarke (development of breasts before age 8) in Italy, and premature thelarke, pubarche, gynecomastia, and precocious pseudopuberty in Puerto Rico (Hayes, 1994).

However, high levels of ZEN (up to 100 μg/L) were reported in the sera of Hungarian children exhibiting early puberty symptoms (Szuets et al., 1997, 1998), whether ZEN promotes breast cancer (Schoental, 1985; Tomaszewski et al. 1998) rather than reducing mammary tumorigenesis is also controversial (Hilakivi-Clarke et al.,1999).

Ruminants: Zearalenone was classified as a week estrogen having anabolic properties (FDA, 1979). Swine are the most commonly affected

animals. Cattle, poultry and laboratory, rodents are also affected, but to a lesser degree (CAST, 1989). The greater ZEN resistance of ruminants compared to swine can be attributed in part to ruminal degradation (Raisbeck et al., 1991).

Both bovine and ovine rumen fluid rapidly reduce ZEN to the more readily excreted α- and β-zearalenol in vitro (Kallelo and Vasenius, 1982; Kiessling et al., 1984). However, cattle also seen capable of more rapid hepatic conversion and thus elimination of ZEN and its derivations than swine (Cheeke and Shull, 1985; Kim et al., 1986).

Cattle: Estrogenism in swine and dairy cows is usually more prevalent in the winter and early spring because, once the fungus is established in the grain, it generally requires a period of relatively low temperatures to produce biological significant amounts of ZEN (Jacobsen et al., 1993). Infertility, reduced milk production, and hyperestroginism in cows have been reported in association with ZEN (Diekman and Green 1992). Zearalenone causes estrogenic effects in dairy cattle, and large doses of the toxin are associated with abortions. Other responses of dairy animals to ZEN may include reduced feed intake, decreased milk production, vaginitis, vaginal secretions, poor reproductive performance and mammary gland enlargement in virgin heifers (Jones et al., 1994). On the other hand Schoental (1983) suggested that a "cold cow" syndrome characterized by decreased body temperature, diarrhea and swelling of the vulva, among other symptoms, may be the result of exposure to excessive levels of ZEN and possible, other secondary metabolites of common field microfungi, such as Fusarium culmorum.

Heifers fed equivalent 15 mg ZEN/ kg diet dry matter for 63 days had reduced conception rates (Weaver et al., 1986). However, administration of 25 and 100 ppm ZEN to

Holstein cows (one cow on each dosage rate) for 42 consecutive days had no effect on the hematocrit, hemoglobin, total erythrocyte count, total white blood cell count, or differential white cell count. Both dosages resulted in swollen and hyperemic external genitalia within one week after treatment began. Both cows come into estrus normally on day 21 of the cycle, and `ovulated (Mirocha *et al.,* 1978; FDA, 1979).

Dairy cattle fed ration that contained 0.385 to 1.925 ppm of ZEN for 7 weeks had normal milk production. No. ZEN were found in milk, urine, serum or tissues. Corn contaminated with 0.500 ppm of ZEN had no effect on milk or butterfat production (Diekman and Green 1992). The effects of zearalenol on bulls appear to be most pronounced when given before puberty. These effects may include decreased scrotal circumference and surviving ability, degenerative lesions in the genital epithelium and accessory sex glands, and poor semen quality (Deschamps *et al.,* 1987a). These effects were attributed to decreased gonadotropin secretion resulting from estrogenic effects of zearalenol (Raisbeck *et al.,* 1991).

Implanting young bulls (104 days- old) with 36 mg of zearalenol, decreased circulating testosterone concentrations and the responsiveness of Leydig cells to endogenous LH. However, testicle weights and sperm concentrations were similar to those of control animals after a 168 days recovery period, apparently as a result of compensatory growth (Juniewics *et al.,* 1985). Implantation of older bulls (267 days of age) with either 36 mg or 72 mg zearalenol had no effect upon either spermatogenesis or testosterone production (Juniewics *et al.,* 1985; Raisbeck *et al.,* 1991).

Conversely, bull calves implanted with 36 mg zearalenol (every 3 months) from birth through 6 months of age, secreted less LH and more FSH in response to gonadotrophin releasing hormone and less testosterone in response to LH (Deschamps *et al.,* 1987b).

Sheep: Estrogenic disturbances are also suspected in sheep. Abortion is suspected to result and mild vulvovaginitis and hypertrophy of the uterus are recorded (Radostitis *et al.,* 1994). Reduction in the incidence of ovulation and in fertilization were seen in ewes dosed with ZEN (12 and 24 mg per ewe per day) for 10 days before mating (Smith *et al.,* 1990). There are no effects of the toxin on embryo survival or lambing performance when 12 ppm ZEN was fed 10 days immediately post- mating (Smith *et al.,* 1986). Intakes of ZEN as low as 3 mg per ewe per day for a period of 10 days before mating reduced ovulation rate, while concentrations of 12 mg per ewe per day were needed to reduce fertilization rates (Smith *et al.,* 1987)

However, ZEN may exert its toxic effects by accumulating in body when low levels are fed long-term or as a result of short- term exposure to high concentrations. For instance reduced ovulation rate was evident in ewes exposed to 1.5 ppm of the toxin in diet for 10 days premating, and ewes exposed to 0.5 ppm for 20 to 40 days premating (Smith *et al.,* 1986). Apparently, only ewes are affected by ZEN when dosed prior to mating. On the country rams fed 2.5 ppm ZEN for 30 days had normal semen production and fertility (Vencelli and Parker, 2003). Rams dosed with ZEN (6 mg/ ram/ day) for 42 days, had no discernable effect on quality and lipido (Smith *et al., 1*987).Rams dosed also with ZEN (12 mg/ram/day) for 8 weeks had no effect on the volume of ejaculate and its concentration and the mobility and abnormalities in the spermatozoa (Milano *et al.,* 1991).

Experimental feeding of ZEN to lactating ewes does result in minor contamination of their

milk sufficient to produce hyperstrogenism in a lamb suckling a poisoned ewe (Hagler *et al.,* 1980).

Pigs: Swine are the most susceptible to the effects of ZEN (Vencelli and Parker, 2003). In swine the clinical manifestations of ZEN toxicosis include primarily the reproductive tract (Wyatt, 1991). In gilts, the vulva becomes extremely reddened, swollen and oedematus. This swelling can become so severe that the vulva may rupture and hemorrhage, although this is most often observed in chronic intoxications. Vaginal prolapse, enlargement of the uterus and uterine horns, and ovarian atrophy are also typical signs of the disease (McNutt *et al.,* 1928; Kurtz and Mirocha, 1978; Wyatt, 1991).

In the prepubertal gilts, the vulva bevomes swallen and edmatus, and in severe cases may led to the vaginal or rectal prolapse. The uterus of affected animals becomes enlarged, edematous and tortus with atrophy of the ovaries (Chang *et al.,* 1979; Mirocha *et al.,* 1979). In an outbreak of ZEN mycotoxicosis on two farms in Northern Queensland, most prepubertal gilts in the herds displayed enlarged teats and signs of oestrus such as red, swallen vulvas. In several cases both rectal and vaginal prolapses occurred. On one of the farms 25 pigs died as a direct result of prolapses. Postmortem examination of a 3- months- old gilt revealed apparently enlarged ovaries and uterine horns. Sows and boars seemed to be unaffected (Blaney *et al.,* 1984).

In other outbreak involving 62 suckling piglets of both sexes, the clinical signs included oedematous swelling and reddening of the vulva,sometimes associated with reddening and/ or necrosis of the tail. Sex female piglets had congenital lesions of the external genitalia while in the remainder, clinical signs appeared 2 to 3 days after birth. No sows ingesting the contaminated feed had signs of hyperestrogenism (Dacasto *et l.,* 1995).

Reproductive insufficiency including infertility, stillbirths, fetal mummification, reduced letter size, and weakened piglets with higher than- normal piglet mortality have been noted (McNutt *et al.,* 1928; Kurtz and Mirocha, 1978; Wyatt, 1991).

Vanyi *et al.* (1994) studied the toxicity of ZEN in 8 large pig herds and in animal experiments and recorded that the mycotoxin markedly lowered the conception rate of sows and gilts, and increased the number of repeat breeder, fitter size decreased and the number of stillbirths increased. Both newborn piglets and the stillborn fetuses showed swelling of the vulva and teats and oedematous infiltration of the perineal region, ventral part of the abdomen and umbilicus, often accompanied by exudative-crusted inflammation, then necrosis of the teats. The number of piglets with splaying and congenital tremor increased. Gross and histopathological examination, revealed enlargement of the ovaries and uterus, with signs of follicle maturation in the ovary, glandular proliferatiom in the endometrium and epithelial proliferation in the vagina in addition to oedema and hyperaemia.

Young males may undergo a feminizing effect (hyperestrogenism) characterized by testicular atrophy, swollen prepuce and mammary gland enlargement, decreased lipido may be a variable sequela, but mature boars apparently have enough testicular reserve to avoid decreased spermatogenesis (CAST, 1989). The ZEN does reduce serum progesterone levels in sows but the administration of progesterone to affected gilts does not counteract the estrogenic effects (Green *et al.,* 1991). At high doses the toxin is passed through the milk of sows in sufficient dose rates to produce clinical

signs of vulvar enlargement in the suckling pigs (Radostits *et al.,* 1994).

Dose related effect in pigs:
Zearalenone has been found to mimic effects of female hormone estrogen and it induces feminization at dietary concentrations of less than 1 ppm (Lawlor and Lynch, 2001). Young gilts are most sensitive: concentrations as low as 0.5 to 1 ppm can cause pseudoestrus and vaginal or rectal propapse (Blaney and Williams, 1991). However, mild forms of hyperestrogenism have been observed in pigs exposed to ZEN levels as 250 μg/ kg in their diet.

In the prepubertal female, classic field observation of animals ingesting 1 to 5 ppm ZEN include vulval reddening and or swelling, which may progress to vaginal or rectal prolpse. The teats or mammary glands become enlarged. These outward changes are accompanied by an enlarged, potentially twisted uterus and shrunken ovaries. On withdrawal of contaminated feed, clinical signs disappear within three to four weeks. There is little evidence of permanent changes interfering with subsequent reproductive processes (Vencelli and Parker, 2003).

Levels of 3 to 10 ppm ingested by mature females have induced pseudopregnancy. The females do not cycle and can not be mated successfully, and the breeding programme is disrupted. Also, placental membrane weights can potentially be reduced affecting fetal development (Vencelli and Parker, 2003). While, Goihl (1990) suggested that dietary levels up to 5 ppm are unlikely to cause serious reproductive problems in sows, but level of 10 ppm in a sow diet may increase weaning to service interval and reduce the litter size.

When cycling gilts are administered either 20 mg ZEN/ or estradiol benzoate in he feed on days 6 to 10 or days 11 to 15 of the estrus cycle, the interval between estrus is extended. Usually these gilts will return to estrus within 30 days after ZEN is removed from the diet and can be rebred and produce normal litters (Diekman and Green, 1992). Continuous feeding of diet containing 25 to 100 ppm ZEN from weaning to rebreeding produce constant estrus, pseudopregnency and ultimately infertility (Diekman and Green, 1992).

Zearalenone at a concentration of 100 ppm in the ration consumed by sows for one week resulted in the development of degenerative lesions in the ovary and in the mid part of the uterine horn. Ovulation was suppressed and the degeneration of the uterine glands in the mucosa of the uterus contributed to infertility by not supporting the nidation and nourishment of the fertilized ovum (Vanyi *et al.,* 1974). On the other hand Osweller (1992) described that young boars may have reduced libido and decreased testicular size but mature boars are unaffected by concentrations of ZEN as high as 200 ppm.

Histopathological changes include ductal hyperplasia and increased mitotic index in the mammary glands, hypoplasia and follicular atrasia in the ovary, edema and cellular proliferation with increased thickness of the myometrium, metaplasia of the mucosal and squamous epithelium of the cervix, and squamous metaplasia of the vagina (Kurtz *et al.,* 1969). As described by FDA (1979); Bristol and Djurickovic (1971) investigating a natural outbreak of estrogenism swine in Canada, reported vaginal epithelium 10- 15 layers thick, with squamous metaplasia of superficial cells, and many epithelial investigation of the stratum germinativum of affected sows.

Horse:
A natural outbreak of ZEN mycotoxicosis in horse was recorded by Gimeno and Quintanilla (1983). Symptoms in exposed

mares were enlarged edematous vulva, prolapsed vagina, oversized uterus and internal hemorrhage. Severe flucidity of the genitals was observed in males. The food was found contaminated with 2- 3 mg ZEN/ kg and the previous symptoms appeared after feeding period of 30 days.

Poultry: Broiler chicks and laying hens, unlike swine and dairy cows are affected very little by dietary ZEN even when fed massive doses (Jacobsen *et al.,* 1993). When graded levels of dietary ZEN from 10- 800 ppm were fed to day-old chicks for 21 days, no effect on weight gain, feed consumption, or feed: gain ratio was recorded. No prominent lesions were observed at postmortem examination except for hypertrophy of the oviduct in some birds receiving 800 ppm ZEN (Chi *et al.,* 1980).

In another trial, dietary feed containing 300 ppm of ZEN in chicks resulted in increased weight of the bursa of Fabricius, increased comb weight and increased in number of cysts in the genital tract (Meronuck *et al.,* 1970). Older broiler chickens (6 to 9 weeks- old) receiving graded levels of dietary ZEN (50- 800 ppm) showed no difference in performance parameters, relative organ weight and selected blood parameters when compared with control (Allen *et al.,* 1981a).

In laying hens, no significant effects were observed with regard to body weight, egg production, feed consumption or plasma concentrations of calcium, phosphorus and cholesterol when the birds were fed 250 or 500 ppm pure ZEN or the *F. roseum* contaminated ration (505 to 637 ppm of ZEN). The specific gravity of eggs from hens fed the *F. roseum-* contaminated rations was significantly reduced. On necropsy, the macroscopic appearance of the internal organs appeared normal (Speers *et al.,* 1971). This data indicate that a possible

effect of ZEN on the health of young chicks, however laying hens appear to be tolerant to the presence of ZEN or other toxic factors related to the use of *F. roseum-* contaminated corn in the diet (Wyatt, 1991).

Consumption of feed containing 100 ppm of ZEN by mature geese had no effect on egg production or fertility (Palyusik *et al.,* 1975). Turkeys when eating feed containing 300 ppm developed enlarged vents within four days. However no other gross effects were noted (Jacobsen *et al.,* 1993; Vincelli and Parker, 2003).

Studies conducted with mature male and female chickens indicate that dietary ZEN up to 800 ppm is without effect on reproductive performance. Zearalenone did not affect egg production, egg size, egg shell thickness, fertility, hatchability of fertile eggs, feed intake, body weight or the relative weight of comb, oviduct heart, liver and spleen. Postmortem and histological examination of tissues from these birds revealed no effect of ZEN feeding (Allen *et al.,* 1981b; Lesson *et al.,* 1995). Even though ZEN appears to be non- toxic for poultry species, the detection of this mycotoxin in poultry feed has been suggested to be used as a "biomarker" for other yet unknown Fusarium toxins (Romer, 1990). The type B trichothecene deoxynivalenol is another example of a potential biomarker for poultry feed. The presence of biomarkers whether toxic or not, indicate that the feed was exposed to conditions favorable for mold growth. This increases the possibility that feed is contaminated with mycotoxins (Romer, 1990; Lesson *et al.,* 1995).

Regulatory control:

The scientific committee on food of the European Commission on Health and Consumer Protection arrived at a temporary tolerable daily intake for ZEN of 0.2 µg/kg

b.wt., while the joint FAO/WHO expert Committee on Food Additives recommended a provisional maximum tolerable daily intake of 0.5 ug/ kg b.wt. (Mitterbauer *et al.,* 2003).

Several countries have proposed guideline levels for ZEN in foods (Table 1). The maximum acceptable levels are ranged from 0 to 0.1 mg/ kg. Other action levels for ZEN in livestock diets were proposed by Jones *et al.,* (1994) and Vincelli and Parker (2003) in United States of America, and Murphy (1996) and Charmley and Trenholm (2000) in Canada (Table 2). These suggested levels are: 0.1 mg/ kg for horse, 0.25- 5.0 mg/kg for sheep, 0.25-10.0 mg/ kg for cattle, and 0.1- 5.0 mg/ kg for pigs.

Table (1): Maximum recommended levels for ZEN in human foodstuffs.

Commodity (products)	Maximum recommended levels (mg/ kg)	Country
All foods	0.030 0.050	Romania Hungary
Cereal products	0	The Netherland
Cereals, flour, wheat bran, legumenous, protein isolators vegitable oil, nut (kernel)s	1.00	Russia
Cereals, vegitable oils	0.20	France
Maize, barley	0.20	Brazil, Uruguay
Wheat, rye, durum wheat	0.060	Austria

Table (2): Maximum recommended levels of ZEN in animal feeds.

Species of animal	Maximum recommended levels (mg/ kg)	Reference
Diet for: Horse, mature,.nonbreeding,	0.10	Jones *et al.,* (1994)
Beef cattle	0.25	
Pigs	0.20	
Sow hard, breeding males	0.10	
Heifers, feeder cattle	5.00	Vencelli and Parker (2003)
Cattle, mature, dairy	10.00	
Sheep	0.5	
Pigs, nursery, grower, finisher	1.00	
Sow herd, breeding males	2.00	
Pigs, nursery, breeding	0.50	Murphy (1996)
Grower, finisher pigs	2.00	
Cows	10.00	
Cows (if other mycotoxin present)	1.50	Charmley and Trenhom (2000)
Sheep and pigs	0.25- 5.00	
gilts	1.00- 3.00	

REFERENCES :

Allen, N.K.; Mirocha, C.J.; Weaver, G.; Aakhus- Allen, S. and Bates, F. (1981a):"Effect of dietary zearalenone on finishing broiler chickens and young turkey poults." Poult. Sci., 6: 124- 131.

Allen, N.K.; Mirocha, C.J.; Aakhus- Allen, S.; Bitgood, J.J.; Weaver, G. and Bates, F. (1981b):"Effect of dietary zearalenone on reproduction of chickens." Poult. Sci., 60: 1165- 1174.

Barrett, J.R. (2000):"Mycotoxins of molds and maladies. Environmental health Perspectives." 108 (1): 2000.

Biehl, M.L.; Prelusky, D.B.; Koritz, G.D.; Hartin, K.E.; Buck, W.B. and Treholm, H.L. (1993): "Biliary excretion and enterohepatic cycling of zearalenone in immature pigs." Toxicol. Appl. Pharmacol., 121: 152-159.

Blaney, B.J.; Bloomfield, R.C. and Moore, C.J. (1984): "Zearalenone intoxication of pigs." Austr. Vet. J., 61 (1): 24-27.

Blaney, B.K. and Williams, K.C. (1991): "Effective use in livestock feeds of moldy and weather damaged grain containing mycotoxins- case histories and economic assessments pertaining to pig and poultry industries of Queensland." Austr. J. Agric. Res., 42: 993- 1012.

Bongiovanni, A.M. (1983):"An epidemic of premature thelarche in Puerto Rico." J. Pediatr., 103: 245- 246.

Boyd, P.A. and Wittliff, J.L. (1978): "Mechanism of Fusarium mycotoxin action in mammary gland." J. Toxicol. Eviron. Health, 4:1.

Bristol, F.M. and Djurickovic, S. (1971): "Hyperestrogenism in female swine as the result of feeding moldy corn." Can. Vet. J., 12: 132- 135.

Caldwell, R.N.; Tuite, J.; Stob, M. and Baldwin, R. (1970): "Zearalenone production by Fuarium species."Appl. Microbiol., 20: 31.

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

Chang, K.; Kurtz, H. and Mirocha, C.J. (1979): "Am. J. Vet. Res., 40: 1260- 1267, In: C.J. Mirocha (1983) Fusarium toxins, Proc. Int, Symp. Mycotoxins, PP. 71-79".

Charmley, L.L. and Trenholm, H.L. (2000): "Fact sheet- mycotoxins." Canadian Food Inspection Agency- Feed Section, 59 Camelot Dr. Nepean, On K1AOY9.

Cheeke, P.R. and Shull, L.R. (1985): "Natural toxicants in feeds poisonous plants." AVI Publishing, Westport, CT, 422.

Chi, M.S.; Mirocha, C.J.; Kurtz, H.J.; Weaver, G.A.; Bates, F.; Robison, T. and Shimoda, W. (1980):"Effect of dietary zearalenone on growing broiler chicks." Poult. Sci., 59: 531- 536.

Christensen, C.M.; Mirocha, C.J. and Meronuck, R.A. (1988): "Molds and mycotoxins in feeds." Minn. Ext. Serv. Bull. AG- FO- 3538, P. 14.

Costing, D.C.; Steinhart, C.E. and Cochrene, B.A. (1990): "Food safety 1990- An annotated bibliography of the literature." P. 351, Food Research Institute, University of Wisconsin-Madison, Butter-worth-Heinemann, Boston, London, Oxford, Singapore, Sydney, Toronto, Wellington.

Daily, R.E.; Reese, R.E. and Brouwer, A. (1980):"Metabolism of [^{14}C] Zearalenone in laying hens." J. Agric. Food Chem., 28: 286-291.

Dacasto, M.; Rolando, P.; Nachtmann, C.; Ceppa, L. and Nabbia, C. (1995): "Zearenone mycotoxicosis in piglets suckling sows fed contaminated grain." Vet. Human. Toxicol., 37 (4): 359-361.

Deschamps, J.C.; Ott, R.S.; McEntee, K.; Heath, E.H.; Heinrichs, R.R.; Shanks, R.D. and Hixon, J.E. (1987a): "Effects of zeranol on reproduction in beef bulls: scrotal circumference, serving ability, semen characteristics, and pathologic changes of the reproductive organs." Am. J. Vet. Res., 48: 137.

Deschamps, J.C.; Ott, R.S.; Weston, P.G.; Shanks, R.S.; Kesler, D.J., Bolt, D.J. and Hixon, J.E. (1987b): "Effects of zeranol on reproduction in beef bulls: Luteinizing hormone, follicle- stimulating hormone and testosterone secretion in response to gonadotropin-releasing hormone and human chronic gonadotropin." Am. J. Vet. Res., 48: 31.

Diekman, M.A. and Green, M.L. (1992): "Mycotoxins and reproduction in domestic livestock" J. Anim. Sci., 70: 1615- 1627.

Eugenio, C.P.; Christensen, C.M. and Mirocha, C.J. (1970): "Factors affecting production of the mycotoxin F.2 by *Fusarium roseum*." Phytopathology, 60: 1055.

Elasasser, T.H.; Bolt, D.J.; Bradly, B.D. and Roper, H. (1983): "Lutinizing hormone, follicle stimulating hormone and prolactin secretion in ewes and wethers after zeranol or estradiol injection." J. Anim. Sci., 57: 443.

Fara, D.; DelCorvo, G. and Bernuzzi, S. (1979): "Epidemic of breast enlargement in an Italian school." Lancet, 2: 259- 297.

FDA, Food and Drug Administration (1979): "Conference on mycotoxins in animal feeds and grains related to animal health. "June, 8, 1979, Rockville, Maryland.

Gentry, P.A. (1986): "Comparative biochemical changes associated with mycotoxicosis other than aflatocicosis and trichothecene toxicosis." In: Diagnosis of mycotoxicosis, edited by J.R. Richard and J.R. Thurston, PP. 125-139, Martinus Nijhoff, Dordrecht, Netherlands.

Gillepsie, A.M. and Schenk, G.M. (1977): "Fluorescence and phosphorescence of ochratoxins, sterigmatocystins, patulin and zearalenone: quantitation of ochratoxins." Analytical Litters, 10 (2): 161- 172.

Gimeno, A. and Quintailla, J.A. (1983): "Analytical and mycological study of a natural outbreak of zearalenone mycotoxicosis in horses. "Proc. Int. Symp. Mycotoxins, Pp. 387- 392.

Goihl, J. (1990): "Zearalenone in sow diets can affect performance." Feedstuffs Match 12th: Pp. 12- 13.

Green, M.L. et al., (1991): " Am. J. Vet. Res., 52: 1871. In: Radostits *et al.* (1994)".

Hagler, W.M.; Mirocha, C.J.; Pathre, S.V. and Behrens, J.C. (1979): "Identification of the naturally occurring isomer of zearalenol produced by *Fusarium roseum* Gibbosum in rice culture." Appl. Environ. Microbiol., 37: 849.

Hagler, W.M.; Danko, G.; Horvath, L.; Palyusik, M. and Mirocha, C.J. (1980): "Transmission of zearalenone and its metabolite into ruminant milk." Acta Vet. Acad. Sci. Hung., 28: 209-216.

Hagler, W.M.; Tyczkowska, K. and Hamilton, P.B. (1984): "Simultaneous occurrence of deoxynivalenol, zearalenone and aflatoxin in 1982 scabby wheat from the Midwestern United States." Appl. Environ. Microbiol., 47: 151.

Hayes, A.W. (1994): "Principles and methods of toxicology." 3rd ed., P. 343, Raven press, New York.

Hidy, P.H.; Baldwin, R.S.; Greasham, R.L.; Keith, C.L. and McMullan, J.R. (1977): "Zearalenone and some derivatives, production and biological activities." Adv. Appl. Microbiol., 22: 55-82.

Hilakivi-Clarke, L.; Onojafe, I.; Raygada, M.; Cho, E.; Skaar, T.; Russo, I. and Clarke, R. (1999): "Prepubertal exposure to zearalenone or genistein reduce mammary tumorigenesis." Br. J. Cancer, 80: 1682- 1688.

Humphreys, D.J. (1998): "Veterinary Toxicology." 3rd ed. Pp. 305-307. Bailliere Tindall, London, Philadelphia, Toronto, Sydney, Tokyo.

Jacobsen, B.J.; Bowen, K.L.; Shelby, R.A.; Diener, U.L.; Kemppainen, B.W. and Floyd, J. (1993): "Mycotoxins and mycotoxicosis circular ANR- 767." Aubern Univ., Aubern, Alabama.

Jones, L.J. and Smith, T.K. (1982):"Effect of dietary alfalfa on zearalenone toxicity and metabolism in rats and swine." J. Anim. Sci., 55: 110-118.

Jones, F.; Genter, M.; Hagler, W.; Hansen, J.; Mowrey, B.; Poore, M. and Whitlow, L. (1994):"Understanding and coping with effects of mycotoxins in livestock feed and forage." Electronic publication No. DRO-29. NCCES, North Carolina State Univ., Raleigh.

Juniewicz, P.E.; Welsh, T.H. and Johnson, B.H. (1985):"Effects of zeranol upon bovine testicular function" Theriogenology, 23: 565.'

Kallelo, K. and Vasenius, L. (1982):"The effects of lumen fluid on the content of zearalenone in animal fodder." Nord. Vet. Med., 34: 336.

Kawabata, Y.; Tashiro, F. and Ueno, Y. (1982): "Synthesis of a specific protein induced by zearalenone and its derivatives in rat uterus." J. Biochem., 91: 801.

Kiessling, K.H.; Patterson, H.; Sandholm, K. and Olsen, M. (1984): "Metabolism of aflatoxin, ochratoxin, zearalenone and three trichothecenes by intact rumen fluid, rumen protozoa and rumen bacteria." Appl. Environ. Microbiol., 47: 1070.

Kim, H.L.; Ray, A.C. and Stipanovic, R.D. (1986):"Rapid separation and identification of urinary metabolites of Zeranol by HPLC- UV spectrophotometry." J. Agric. Food Chem., 34: 312.

Kuiper-Goodman, T.; Scott, P.H. and Watanabe, H. (1987): "Risk assessment of the mycotoxin zearalenone." Regul. Toxicol. Pharmacol., 7: 253- 306.

Kurtz, H.J. and Mirocha, C.J. (1978): "Zearalenone (F-2) induced estrogenic syndrome in swine." In: Sillie, T.D. and Morehouse, L.G. (Eds.), Mycotoxic fungi, Mycotoxins, Mycotoxicosis. An Encyclopedic Handbook, New York: Marcel Dekker, Vol. 2, Pp. 260- 265.

Kurtz, H.J.; Nairn, M.E.; Nelson, G.H.; Christensen, C.M. and Mirocha, C.J. (1969):"Histologic changes in the genital tracts of swine fed estrogenic mycotoxin." Am. J. Vet. Res., 30: 551- 556.

Lawlor, P.G. aand Lynch, P.B. (2001): "Mycotoxins in pig feeds." 2: clinical aspects. Irish Vet. J., 54 (4): 172- 176.

Leeson, S.; Diaz, G.J. and Summers, J.D. (1995): "Poultry metabolic disorders and mycotoxins." Pp. 326- 332, University Books, Guelph, Ontario, Canada.

McMillan, W.W.; Wilson, D.M.; Mirocha, C.J. and Widstrom, N.M. (1983): "Mycotoxin contamination in grain sorghum from fields in Georgia and Mississippi." Cercal. Chem., 60:226.

McNutt, S.H.; Purwin, P. and Marray, C. (1928): "Vulvovaginitis in swine." J. Am. Vet. Med. Assoc., 73: 484.

Meronuck, R.A.; Garren, K.H.; Christensen, C.M.; Nelson, G.H. and Fern Bates (1970): "Effects on turkey poults and chicks of rations containing corn invaded by Penicillium and Fusarium species." Am. J. Vet. Res., 31: 551- 555.

Milano, G.D.; Odriozola, E. and Lopez, T.A. (1991): "Lack of effect of a diet

containing Zearalenone on spermatogenesis in rams. " Vet. Rec., 129 (2): 33-35.

Miller, J.K.; Hacking, A.; Harrison, J. and Gross, V.J. (1973): "Stillbirths, neonatal mortality and small litters in pigs associated with the ingestion of Fusarium toxin by pregnant sows." Vet. Rec., 93: 555.

Mirocha, C.J.; Christensen, C.M. and Nelson, G.H. (1971):"F-2 (zearalenone) estrogenic mycotoxin from Fusarium In: Microbial toxins." Vol. 7, Kadis, S.; Ciegler, A. and Ajl, S.J. (Eds.), Acadamic Press, New York, 7: 107- 138.

Mirocha, C.J.; Schauerhamer, B. and Pathre, S.V. (1974): "Isolation, detection and quantitation of Zearalenone in maize and barley." J. Assoc. Off. Anal. Chem., 57: 1104.

Mirocha, C.J.; Pathre, S.V.; Schauerhamer, B. and Christensen, C.M. (1976): "Natural occurrence of Fusariun toxins in feedstuffs." Appl. Environ. Microbiol., 32: 553.

Mirocha, C.J.; Pathre, S.V. and Christensen, C.M. (1977):"Zearlenone In: mycotoxins in human and animal health." Rodricks, J.V.; Hesseltine, C.W. and Mehlman, M. A. (Eds.), Pathotox, Park forest south. IL.

Mirocha, C.J.; Weaver, G.; Gustafsson, B.; Chi, M.; Pathre, S.V.; Robison, T.S. and Fern Bates (1978):"Pharmacological and toxicological studies on zearalenone in food producing animals. "Quarterly report II, Contract No. 233-77-7211, FDA.

Mirocha, C.J.; Schauerhamer, B.; Christensen, C.M.; Niku-Plavola, M.L. and Nummi, M. (1979): "Incidence of Zearalenone in animal feed." Appl. Environ. Microbiol., 38:749.

Mirocha, C.J.; Pathre, S.V. and Robison, T.S. (1981): "Comparative metabolism of zearalenone and transmission into bovine milk." Food Cosmet. Toxicol., 19: 25- 30.

Mirocha, C.; Robison, T.S.; Pawlosky, R.J. and Allan, N.K. (1982): "Distribution and residue determination of [^{3}H] zearalenone in broilers." Toxicol. Appl. Pharmacol., 66: 77-87.

Mitterbauer, R.; Weindrofer, H.; Safaie, N.; Krska, R.; Lemmens, M.; Ruckenbauer, P.; Kuchler, K. and Adam, G. (2003):"A sensitive and inexpensive yeast bioassay for the mycotoxin zearalenone and other compounds with estrogenic activity." Appl. and Environ. Microbiol., Vol. 69 (2): 805- 811.

Murphy, J. (1996):"Molds and mycotoxins- Feeding mold and mycotoxin contaminated wheat to swine." Ministry of Agriculture and Food, Ontario, Canada.

NTP, National Toxicology Programe, 16 December (2002):"NTP carcinogenesis bioassay of zearalenone in F344/ N rats and F6C3F1 mice. NTP Technical Report Series, Vol. 235 (online)." Dept. Health and Human Services Research Triangle Park, N.C.

Olsen, M.; Mirocha, C.J.; Abbas, H.K. and Johansson, B. (1986): "Metabolism of high concentrations of dietary zearalenone by young male turkey poults." Poult. Sci., 65: 1905.

Osweiler, G.D. (1992): "Mycotoxins." In: Diseases of swine. 7th Ed., Pp. 735- 743. Edited by A.D. Leman; B.E. Straw; W.L. Mengeling; S.D. Allaire and D.J. Taylor, London: Wolfe publishing.

palyusik, M. and Karlic- Kovacs, E. (1975): "Effect on laying geese of feeds containing the fusariotoxins T- 2 and F-2." Acta Vet. Acad. Sci. Hung., 25: 363.

Palyusik, M.; Harrach, B.; Horvath, G. and Mirocha, C.J. (1980): "Transmission of zearalenone and zearalenol into porcine milk." Acta Vet. Acad. Sci. Hung., 28: 217- 222.

Pfohl- Leszkowicz, A.; Chekir- Ghedira, L. and Bacha, H. (1995): "Genotoxicity of zearalenone, an estrogenic mycotoxin: DNA adduct formation in female mouse tissues." Carcinogenesis, 16: 2315- 2320 (Abstract).

Placenta, C.M.; D'Melo, J.P. and McDonald, A.M. (1999): "A review of worldwide contamination of cereal grains and animal feeds with fusarium mycotxoins." Animal Feed Science and Technology, 78 (1-2): 21-37.

Prelusky, D.B.; Scott, P.M.; Trenholm, H. and Lawrence, G.A. (1990): "Minimal transmission of zerealenone to milk of dairy cows." J. Environ. Sci. Health, B, 25: 87- 103.

Radostits, O.M.; Blood, D.C. and Gay, C.C. (1994): "Veterinary Medicine." 8th ed. pp. 1604- 1605, W.B. Saunders Co., Ltd.. London.

Raisbeck, M.F.; Rottinghaus, G.F. and Kendall, J.D. (1991): "Effects of naturally occurring mycotoxins on ruminants." Pp. 647- 677. In: Smith, J.E. and Henderson, R.S. (1991).

Romer, T. (1990):"Advances in mycotoxin analysis: Making fusarium." Feed Management, 41: 30- 32.

Saenz de Rodriguez, C.A. (1984): "Environmental hormone contamination in Puerto Rico (Letter)." N. Engl. J. Med., 310: 1741- 1742.

Saenz de Rodriguez, C.A. and Toro- Sola, M.A. (1982): "Anabolic steroids in meat and premature thelarche." Lancet 1: 3000.

Shoental, R. (1983): "Cold cow syndrome." Vet. Rec., 112 (25): 594.

Schoental, R. (1985): "Trichothecenes, Zearalenone and other carcinogenic metabolites of Fusarium and related microfungi. "Adv. Cancer Res., 45:217- 290.

Shotwell, O.L.; Hesseltine, C.W.; Vandegraft, E.E. and Goulden, M.L. (1971):"Survey of corn from different regions for aflatoxin, ochratoxin and zearalenone." Cereal Sci. Today, 16: 266.

Shreeve, B.J.; Patterson, D.S. and Roberts, B.A. (1979): "The :carry- over" of aflatoxin, ochratoxin and zearalenone from naturally contaminated feed to tissues and milk of dairy cows." Food Cosmet. Toxicol., 17: 151- 152.

Smith, J.E. and Hemderson, R.S. (1991): "Mycotoxins and animal foods." Pp. 553- 726, CRC press, Inc., Baco Raton, Boston, London.

Smith, J.F.; DiMenna, M.E. and McGowan, L.T. (1986): "Effect of Fusarium and zearalenone on the reproductive performance of ewes." Proc. New Zealand Soc. Anim. Prod., 46: 255.

Smith, J.F.; McGowan, L.T. Menna, M.E. di; Campbell, A.G. and Menna, M.E. (1987): "Effect of zearalenone on reproductive performance." New Zealand, Ministry of Agric. and Fisheries, Agric. Res. Division, Annual Report, 1985 – 86, 1987, 33-34.

Smith, J.F.; Menna, M.E. di; McGowan, L.T. and DiMenna, M.E. (1990): "Reproductive performance of Coopworth ewes following oral doses of zearalenone before and after mating." J. Reprod. Fert., 89 (1): 99-106.

Speers, G.M.; Meronuk, R.A.; Barnes, D.M. and Mirocha, C.J. (1971):"Effect of feeding *F. roseum* contaminated corn and

the mycotoxin F- 2 on the growing chick and laying hen." Poult. Sci., 50: 627- 633.

Stob, J.; Baldwin, R.S.; Tuite, J.; Andrews, F.N. and Gillette, K.G. (1962): "Isolation of an anabolic uterotrophic compound form corn infected with Gibberella zeae." Nature (London), 196: 1318.

Szuets, P. Mesterhazy, A.; Falkay, G.Y. and Bartok, T. (1997): "Early thelarche symptoms in children and their relations to zearalenone contamination in feedstuffs." Cereal Res. Commun., 25: 429- 436.

Szuets, P.; Mesterhazy, A.; Bartok, T. and Falkay, G.Y. (1998): "Premature thelarche/mastopathy and Fusarium toxin contamination of foods: key to a mysterious disease." Pediatr. Res., 43: 86.

Tomaszewski, J.; Miturski, R.; Semczuk, A.; Kotarski, J. and Jakowicki, J. (1998): "Tissue zearalenone concentration in normal, hyperplastic and neoplastic endometrium." Ginekol. Pol., 69:363-366.

Urry, W.H.; Wehrmeister, H.L.; Bodge, E.B. and Hidy, P.H. (1966):"The structure of zearalenone." Tetrahedron Lett., 27: 3109- 3114.

Vanyi, A.; Bata, A. and Sandor, G.S. (1983): "Metabolism of zearalenone in pregnant sows." In: proceedings, International symposium on mycotoxins, September 6- 8, 1981, Cairo, Egypt, Pp. 311- 315.

Vanyi, A.; Szeky, A. and Rumvaryne, S.E. (1974): "Fusariotoxicoses. V. The effect of F- 2 toxin on the sexual activity of female swine." Magy Allatorv lapja, 29: 723- 729.

Vanyi, A.; Bata, A.; Glavits, R. and Kovacs, F. (1994):"Perinatal estrogen syndrome in swine." Acta Veterinaria Hungarica, 42 (4): 433-446.

Vincelli, P. and Paker, G. (1999): "Mycotoxins in corn produced by Fusariun fungi." ID-121- Electronic file created in 1999. Corn Growers Association, Kentucky, Frankfort.

Vincelli, P and Paker, G. (2003): "Fumonisin, Vomitoxin and other Mycotoxins in corn produced by Fusarium fungi." ID- 121-Copyright © 2003 for materials produced by University of Kentucky Cooperative extension, Frankfort.

Weaver, G.A.; Kurtz, H.J.; Behrens, J.C.; Robison, T.S.; Seguin, B.E.; Bastes, F.Y. and Mirocha, C.J. (1986):"Effect of zearalenone on the fertility of vergin heifers." Am. J. Vet. Res., 47: 1395.

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

WHO, World Health Organization (2000): "Safety evaluation of certain food additives and contaminants." WHO food additives series 44.

Wyatt, R.D. (1991):"Poultry" PP. 553-578, In: Smith, J.E. and Henderson, R.S. (1991).

Young, L.G.; King, G.J.; McGirr, L. and Sutton, J.C. (1980): "Metabolism of [14 C] zearalenone in laying hens." J. Agric. food chem.., 28: 286-291.

Young, L.G.; King, G.J.; McGirr, L. and Sutton, J.C. (1982): "Moldy corn in diets of gestating and lactating swine." J. Anim. Sci, 54: 976- 982.

السموم الفطرية فى الأغذية والأعلاف
٣ ـ الزيرالينون

بدير إبراهيم عجاج

قسم بحوث الكيمياء والنقص الغذائى والسموم
معهد بحوث صحة الحيوان- مركز البحوث الزراعية – الدقى – الجيزة

السـموم الفطريـة هـى مركبـات كيميائيـة سـامة تفرزهـا أنـواع مختلفـة مـن الفطريـات التـى تنمـو علـى الأغذيـة والأعلاف، والزيرالينون من السموم الفطرية التى يكثر تواجدها فى الحبوب خاصـة الذرة عند ارتفـاع نسبة الرطوبـة بها، وذلك نتيجة نمو بعض فطريات الفيوزاريوم.

ويؤدى ارتفاع تركيزات الزيرالينون فى الأغذية والأعلاف إلى النضج المبكر فى الأطفـال وفرط إفراز الاستروجين فى الحيوانات، ففى الحيوانات يحدث تورم الفرج، سقوط المهبل، تورم الرحم والضرع، نقص فى إنتـاج اللبن والعقم، نفوق الأجنـة، صـغر حجم المواليد، وتعتمد شدة هذه الأعراض علـى تركيز الزيرالينون فى الأعـلاف ونـوع وعمـر الحيوان ومدة تعرضه للعلف الملوث.

وقد وجد أن الخنازير أكثر الحيوانات تأثراً بالزيرالينون والخيول والأغنـام والأبقار أقل حساسية لـه، كمـا أثبتت البحوث أن الدجاج لا يتأثر إلا فى حالة وجود الزيرالينون فى الأعلاف بتركيزات عالية جداً.