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In vivo and in vitro effects of the mycotoxins zearalenone and deoxynivalenol on different non-reproductive and reproductive organs in female pigs – a review

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Abstract

This review summarizes the toxicological data on the effects of the mycotoxins zearalenone (ZON), its metabolites, and deoxynivalenol (DON) on different parameters relating to reproductive and non-reproductive organs in female pigs. In vivo 22 mg ZON kg⁻¹ in the diet cause alterations in the reproductive tract of swine such as in the uterus, on the follicular and embryo development. ZON and its metabolites have been shown to competitively bind to estrogen receptors in an in vitro system. The feeding of pigs with 9 mg DON kg⁻¹ diet contaminated diet can act on protein synthesis, humoral and cellular immune response depending on dose, exposure and timing of functional immune assay, and on liver and spleen cell structures. Beside these effects, reproductive alterations were observed in pigs, too. Both in vivo and in vitro exposure to DON decreased the oocyte and embryo development. In vitro application of DON to uterine cells inhibits their proliferation rate and modulates the process of translation at a different molecular level when compared with the in vivo application. The histopathological results provide evidence of spleen and liver dysfunction in the absence of clinical signs, especially in pigs fed higher concentrations of Fusarium toxin-contaminated wheat. Prepuberal gilts react more sensitively to DON>ZON feeding compared to pregnant sows. In the liver, histopathological changes such as glycogen decrease and interlobular collagen uptake were observed only observed in prepuberal gilts, whereas enhancement of haemosiderin was found in both perpuberal gilts and pregnant sows. This review presents some of the current knowledge on the biological activities of ZON and DON in pig.
Altogether, ZON affects reproduction of pigs most seriously because it possesses estrogenic activity. Whereas DON affects reproduction in pigs via indirect effects such as reduced feed intake, resulting in reduced growth or impairment of function in vital organs like liver and spleen.

**Keywords:** Fusarium toxins, zearalenone, deoxynivalenol, reproductive and non-reproductive organs, female pig

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Introduction

Mycotoxins are biologically active secondary fungal metabolites found as contaminants of feedstuffs and exert toxic effects in animals and human beings (Fink-Gremmels, 1999).

Fusarium toxins, such as deoxynivalenol (DON) and zearalenone (ZON), contaminate wheat, maize, and barley worldwide (Abouzied et al. 1991; Chelkowski, 1998; EFSA, 2004a,b). These mycotoxins are produced mainly by F. graminearum, F. culmorum, and F. roseum under predisposing environmental conditions during cereal flowering and include humidity and fungus specific optimum temperature range (Oldenburg et al., 2000). Fusarium species are probably the most prevalent toxin-producing fungi of the northern temperate regions and are commonly found in cereals grown in America, Europe and Asia. They cause a variety of toxic effects in experimental animals and livestock. Different effects were described for Fusarium toxins ZON (Kuiper-Goodman et al. 1987; Wood, 1992) and DON (reviewed by Pestka and Casale, 1990; Rotter et al. 1996).

Zearalenone is biologically potent, but hardly toxic; rather, it sufficiently resembles 17β-estradiol, the principal hormone produced by the human ovary, to allow it to bind to estrogen receptors in mammalian target cells (Katzenellenbogen et al. 1979). ZON is better classified as a non-steroidal estrogen or mycoestrogen. Metabolism of ZON in monogastric animals takes place in the liver and intestinal mucosa where it is reduced to α- and β-zearalenol (α-ZOL and β-ZOL) (Olsen et al., 1987; Olsen, 1989), a reaction that competes with glucuronidation of the parent molecule. Examination of excretory products indicated that in pig the α-epimer predominates (Farnwoth and Trendholm, 1983; Olsen et al., 1985a,b; Biehl et al., 1993; Zöllner et al., 2002; Döll et al., 2003; Dänicke et al., 2005b). Biotransformation studies with pig liver sub-cellular fractions indicated that α-ZOL is the main hepatic metabolic of ZON in pigs (Malekinejad et al. 2005). Additionally, the authors could detect that another extrahepatic
Biotransformation of ZON into α-ZOL exists in porcine granulosa cells (Malekinejad et al. 2006). Alpha-ZOL binds more effectively to the receptor than the parent toxin (ZON) and might therefore explain the sensitivity of pigs to this mycotoxin.

The effect of ZON and its metabolites depends upon the reproductive status (pre-puberal, cycling or pregnant) of the affected animal (Lopez et al. 1988; Diekman and Green, 1992). Pigs, especially gilts before the first oestrus, are the most susceptible to intoxication with higher ZON doses (50-100 mg kg\(^{-1}\)) and they can develop symptoms such as vulvae oedema and erythema, impairment of ovulation, conception, implantation, fetus development, and newborn’s viability (Mirocha et al. 1977; Weaver et al. 1978; Chang et al. 1979; Long and Diekman, 1986; Price et al. 1993; Dacasto et al. 1995; Yang et al. 1995; Gajecki, 2002). The amount of 22.09 mg kg\(^{-1}\) of ZON in the ration of breeding gilts had an obvious harmful effect on their reproductive performance: a decreased number of corpora lutea, a decreased weight of ovaries, a decreased number of live embryos, an increased number of dead-born piglets, and the occurrence of aborts. These effects were less pronounced in gilts fed mash containing 2.2 mg kg\(^{-1}\) ZON (Kordic et al. 1992). New guidance values recommended not to exceed 0.1 mg ZON kg\(^{-1}\) for piglets and gilts, 0.25 mg ZON kg\(^{-1}\) for sows and fatting pigs, and 0.9 mg ZON kg\(^{-1}\) diet for pigs in order to avoid adverse effects on reproductive traits (EU, 2006). EFSA (2004b) concluded from a recent literature evaluation that safe levels of ZON in feed for pigs can not reliably established at present.

Deoxynivalenol, a *Fusarium* toxin belonging to the trichothecene group, has been reported to produce a variety of adverse health effects in farm animals, such as inhibition of protein synthesis, reduction of feed intake, and alteration of the immune system. The upper critical concentrations in Germany was set at 0.9 mg DON kg\(^{-1}\) diet for all pigs, as a guideline level in
prevention or minimizing strategies (EU, 2006). EFSA (2004a) recommended the collection of more data for refining or establishment of safe dietary DON levels, including the effects of DON on the immune system.

Macrophages, T cells, and B cells of the immune system are central targets of DON that can be immunostimulatory or immunosuppressive depending on dose, exposure and timing of functional immune assay (Rotter et al., 1996; Bondy and Pestka, 2000; Pestka et al. 2004). The presence of DON in pig diets decreases feed intake, causes feed refusal, and induces occasional vomiting (Diekman and Green, 1992). Beside these effects, reproductive alterations were observed in humans and pigs (Hussein and Brasel, 2001; Alm et al. 2006).

Effects of a *Fusarium* toxin contaminated diet containing DON and/or ZON on the fertility/reproduction of female pigs need to be viewed in the general context of the toxin effects on porcine health and performance. Before the toxins are able to modify metabolic processes they need to be consumed voluntarily by the pig. Data reported in the literature indicate that the adverse effects of DON contaminated diets on growth performance of growing pigs is primarily caused by depressing the voluntary feed intake (Rotter et al., 1994; Swamy et al., 2002; Goyarts et al., 2005). The mycotoxins obviously act in a concerted manner with regard to metabolic processes and consequently influence the health and fertility/reproduction (Figure 1).

This review aims to give an overview about the effects of feeding with DON>ZON contaminated diet on non-reproductive and reproductive organs which can influence metabolism, health, and fertility/reproduction of female pigs. Figure 1 demonstrates a scheme of the investigations on specific organs and parameters dealt with in the current study.
Furthermore, we have focused on the comparison of *in vivo* and *in vitro* effects of DON and ZON on different parameters.

### Protein synthesis

Deoxynivalenol is known to be a potent protein synthesis inhibitor according to research in different *in vitro* and *in vivo* systems (Feinberg and McLaughlin, 1989). However, the significance of this toxic feature was not yet evaluated for the pig. Therefore, an experiment was carried out by Dänicke et al. (2006) to measure porcine tissue protein synthesis employing the so-called flooding dose technique using $[^2\text{H}_5]$-phenylalanine as a tracer in dependence on different exposition of DON to pigs exposed to a DON-contaminated diet for ~ 4 wks (chronic) or just uniquely (acute oral) to reflect different feeding scenarios. Moreover, an additional group of pigs was injected with a single intravenous DON-dose (acute intravenous) representing a complete systemic DON-availability. Protein synthesis expressed as fractional synthesis rate (FSR) was significantly reduced in kidneys, spleen and ileum of DON-exposed pigs. FSR of liver, skeletal and heart muscle, mesenteric lymph nodes, duodenum, jejunum, jejunal mucosa cells, pancreas and lung were not affected by DON. Goyarts et al. (2006a) have shown that DON decreased the FSR of albumin as the main protein exported from the liver and as the predominant plasma protein. Pigs exposed to DON 5.7 mg kg$^{-1}$ diet showed an increased protein synthesis capacity (RNA to protein ratio) caused by an elevated liver RNA-concentration (Dänicke et al. 2006).

### Humoral and cellular immune response

DON affects the humoral immunity (Bondy and Pestka, 2000). An overview on the mechanisms of IgA production induced by DON is given by Pestka (2003). The effects of DON on immunoglobulin levels of serum in swine are rather inconsistent. After feeding of...
grains naturally contaminated with DON>ZON for 5 wk the serum IgA concentration of prepuberal pig increased significantly, while serum IgM and IgG concentrations were not altered (Goyarts et al. 2006b; Tiemann et al. 2006a). Similarly, Swamy et al. (2002) observed such effects in pigs fed with DON contaminated corn and wheat. Drocher et al. (2004) demonstrated an IgA elevation in pigs fed a semisynthetic diet without grain components with pure DON (600 µg kg⁻¹) under highly standardized conditions. In contrast, some investigators were not able to show interaction between DON and IgA serum concentrations (Bergsjø et al. 1992, 1993; Döll et al. 2003; Swamy et al. 2003; Dänicke et al. 2004a,b). No differences were observed in serum level of IgA between the pregnant sows fed 9.6 mg DON/0.358 mg ZON kg⁻¹ diet and the controls for 35 days (Tiemann unpublished data). Table 1 summarized the data and it can be notable that the in vivo effects of DON on humoral immunity are rather inconsistent. The reason may be methodological differences in the experiments carried out by several investigators. In vitro, the IgA concentration in the supernatant of ConA stimulated porcine peripheral lymphocytes was dose-dependently inhibited with increasing DON concentrations (Goyarts et al. 2006b).

Mitogen-induced proliferation is a common technique to assess immunotoxicity. The immunosuppressive effect of DON is primarily associated with cellular immune response. Øvernes et al. (1997) observed a significant higher response to phytohemagglutinin in the high DON group compared to the low DON group in growing pigs. In contrast, no effect of DON-contaminated feed on peripheral lymphocyte mitogen response was reported by Rotter et al. (1994); Tiemann et al. (2006a, unpublished data). Compared to bloods lymphocytes, splenocytes were more sensitive to ConA-induced response in perpuberal pigs fed the DON contaminated diet compared to pregnant sows. The DON>ZON feeding of pregnant sows
reduced the proliferative response in splenocytes in approximately the same manner, as
observed in prepuberal gilts (Tiemann et al. 2006a, unpublished data).

Mitogen-induced proliferation was impaired at low concentrations after \textit{in vitro} exposure to
porcine lymphocytes or splenocytes (Goyarts et al. 2006b; Tiemann et al. 2006a). Both
authors found a reduced proliferative response which may be due to the capacity of DON to
inhibit protein synthesis (Ueno, 1983; Thompson and Wannemacher, 1986; Ehrlich and
Daigle, 1987). The latter assumption is supported by the findings of Goyarts et al. (2006a)
who measured the overall protein synthesis of porcine peripheral blood lymphocytes \textit{in vivo}
by using a stable isotope labelled amino acid. Other toxic mechanisms that have been
associated with trichothecenes include impaired membrane function (Bunner and Morris,
1988), altered cellular communication (Jone et al. 1987), deregulation of calcium homeostasis
(Yoshino et al. 1996), and such as described above.

The capacity of DON to affect porcine neutrophils, critical mediators between innate and
acquired immunity (Ellis and Beaman, 2004), at pharmacological concentrations was
investigated by Takayama et al. (2005).

\textbf{Histopathology of spleen and liver}

After 5 weeks of feeding, the histopathological effects on spleens and livers in gilts (Tiemann
et al. 2006a,b) and pregnant sows (unpublished data) can be mostly observed at a dietary DON
concentration of 9.57 mg kg\(^{-1}\), originating from naturally contaminated wheat containing only
minor traces of ZON (0.358 mg kg\(^{-1}\) diet), but in absence of clinical signs (Dänicke et al.
2005a, unpublished data). The authors observed the appearance of a dysfunction in porcine
liver and spleen which can be seen as hemosiderosis. Pre-puberal gilts react more sensitively
to DON>ZON feeding. In the liver, histopathological changes such as glycogen decrease and
interlobular collagen uptake were observed only in prepuberal gilts. In both animals an
enhancement of haemosiderin in liver and spleen was found. These results were supported by
ultrastructural investigations and can be due to a dysfunction in both spleen and liver cell
circulation. Because there was a statistically significant, but only a modest elevation of the
liver enzyme activities for aspartate aminotransferase (AST), alanine aminotransferase (ALT),
the authors suggest that the doses of mycotoxins used did not cause hepatic fibrosis. The
observed histological alterations in liver and spleen, however, were not clinically manifested.
There were no adverse effects on liver and spleen of piglets when their mothers consumed
diets containing up to 9,570 and 358 µg DON/ZON kg\(^{-1}\) diet (unpublished data).

**Follicle development, oocyte maturation, and embryo development**

Edwards et al. (1987) reported that pre-pubertal gilts fed zearalenone displayed first estrus
later than controls; however, in other investigations, pre-pubertal gilts consuming a milo diet
contaminated with zearalenone exhibited puberty at a younger age without an alteration in
conception rates, ovulation rates, or embryonic survival (Rainey et al., 1990).

Zwierzchowski et al. (2005) observed that the amount of ZON to a dose of 200 µg kg\(^{-1}\) body
weight in immature gilts leads to distribution in the development and maturation of the largest
follicles through the activation of an apototic-like process in the granulosa layer of single
mature follicles. In contrast, Alm et al. (2006) found that the size distribution of follicles was
not affected by feeding of gilts with different *Fusarium*-toxin contaminated diets. In these
animals the cumulus cell morphology was not changed by increasing dietary concentrations of
both toxins up to 9,570 and 0,358 mg kg\(^{-1}\) for DON and ZON, respectively. The authors
recovered oocytes from pig ovaries by follicle aspiration after ovario-hysterectomy. At the
concentration named above, at the time of recovery, oocytes with compact cumuli showed a
significantly reduced proportion with immature chromatin. Here, the proportion of oocytes
having degenerated meiotic chromatin was significantly higher compared to lower
concentrations. The oocyte quality was significantly reduced by feeding of a DON>ZON
contaminated diet to gilts. The competence of oocytes in compact cumulus oocyte complexes
for *in vitro* maturation was likewise significantly reduced by high concentrations of *Fusarium*
toxin in feed; this is probably directly related to the reduced proportion of normal germinal
vesicle-stage oocytes, i.e., oocytes capable of maturation, in the high toxin groups. These
results are in agreement with data reported by Kordic et al. (1992) who observed a doses-
dependent effect of ZON on reproductive performance in breeding gilts, with decreased
numbers of live embryos as well as other reproductive problems including increased number
of dead-born piglets. Little information is available about effects of indirect (i.e., from mother
to young) exposure to DON/ZON on the health of piglets. Placenta transfer of mycotoxins can
indicate a potential risk for direct effects in the fetus. Long and Diekman (1984) reported that
gilts fed 5 to 30 mg kg\(^{-1}\) ZON from d 2 to 15 postmating had normal embryonic development,
but no fetuses were present in gilts fed 60 or 90 mg kg\(^{-1}\) ZON when killed d 40 to 43 post-
mating. Embryos recovered on d 14 from gilts fed 60 mg kg\(^{-1}\) of ZON from d 7 to 10 post
breeding were fragmentous, while those from control gilts were filamentous (Diekman and
Long, 1989). Degeneration in blastocysts, affecting both embryonic membranes and the
embryonic disk occurring in ZON-treated sows were observed by Long et al. (1992). In
contrast, the authors observed no deleterious effects of DON on fetal development when feed
containing 8 mg kg\(^{-1}\) of purified DON was consumed (summarized Diekman and Green,

*In vitro*, the maturation of porcine oocytes was investigated after addition of \(\alpha\)- and \(\beta\)-ZOL
and DON. All three substances negatively affected oocyte maturation and degeneration rates
in a dose-dependent manner, but to different extents (DON>α-ZOL>β-ZOL). In addition, α-ZOL directly affected the early embryonic development in vitro of in vivo-derived porcine embryos (Alm et al. 2002).

Intrafollicular steroid synthesis

The feeding of wheat contaminated naturally with DON and ZON to gilts at increasing proportions did not influenced the activity of enzymes involved in progesterone synthesis. In vivo-derived porcine granulosa cells were analyzed for the mRNA expression of the mitochondrial enzyme cytochrome P450, cholesterol side-chain cleavage (P450scc) and microsomal enzyme 3β-hydroxysteroid dehydrogenase/isomerase (3β-HSD) by RT-PCR, and additionally for P450scc protein by Western blotting. Neither the expression of the P450scc nor of the 3β-HSD mRNA, nor the abundance of the P450scc protein was significantly influenced by the mycotoxin feeding (Alm et al. 2006).

Cultured primary porcine granulosa cells have been used to test the toxic potential of xenobiotics on reproduction (Haney et al. 1984). In vitro addition of α- and β-ZOL at concentrations of 15 and 30 µmol l⁻¹ inhibited the FSH-stimulated progesterone synthesis in porcine granulosa cells. The inhibitory effect at a concentration of 30 µmol l⁻¹ of both mycotoxins could mainly be due to cell death. The antisteriodogenic effect of 15 µmol l⁻¹ α-ZOL or β-ZOL was not due to cytotoxic effects. The enzyme activity of 3β-HSD and the abundance of P450scc protein were reduced by both mycotoxins as well (Tiemann et al. 2003a).
Estrogenic effects and alterations in uterus

After 5 wk feeding of pre-puberal pigs with a diet containing a concentration of DON which was more than nine times, and of ZON only 0.43 times, higher than the upper critical concentrations, hyperestrogenism, uterotrophic effects (Tiemann et al. 2006b) or an impairment of several enzymes on endometrial cell metabolism were not observed (Wollenhaupt et al. 2006a). The data was supported by the fact that the quantity of progesterone and estradiol receptors in the uterus was not affected by DON>ZON feeding. In agreement to these results, Döll et al. (2004) reported that after 5 wk feeding of prepuberal piglets with the concentrations of ZON up to 0.42 mg and DON up to 3.9 mg kg⁻¹ originating from Fusarium toxin contaminated maize, the mean weight of the uteri of animals receiving the most highly contaminated diet was significantly increased at the time of slaughtering. Although an uptake in uterus weight occurred the surface epithelium of the uterus, the uterine glands and the vaginal epithelium were not altered by the treatment (Döll et al. 2004).

Enhancement of ZON (56 mg kg⁻¹) and DON (4.99 mg kg⁻¹) in the diet of pigs caused histopathological changes of uterine tissue such as hyperplasia, hypertrophy, and metaplasia of the myometrium (Lopez et al. 1988). Application of ZON in crystalline form in the dose of 200–400 µg kg⁻¹ body weight day⁻¹ for a period of 7 days to immature gilts caused an intensified cell proliferation which was expressed with the increase of PCNA (Proliferating Cell Nuclear Antigen) index. This can be due to estrogenic effects and was observed in the oviduct and uterus (Obremski et al. 2003). Higher concentrations of ZON, 2.2 mg kg⁻¹ and 22.09 mg kg⁻¹ in the ration of breeding gilts had an obvious harmful effect on their reproductive performance, and the uterotropic effect of ZON was obvious in both groups (Kordic et al. 1992).
In vitro, the affinity of ZON to uterine and oviduct estrogen receptors is greatest in pigs compared to rats and chickens (Fitzpatrick et al. 1989). The relative binding affinities to the pig uterine cytoplasmic receptor for ZOL show that α-ZOL is more potent than β-ZOL (Tiemann et al. 2003b). Responsible for the higher binding affinity of α-ZOL to estrogen receptor is the reduction of the 6-keto and also vinyl groups in its molecule, while the β-epimer is much less active in this regard (Kuiper-Goodman et al. 1987). The mechanism by which α-ZOL inhibits the formation of a hormone-receptor complex can be explained by the fact that α-ZOL exerts its effect by competing with estrogen for cytosolic receptor on cells in target tissue and this fact might upset the delicate balance necessary for normal reproductive activity (Guilette et al. 1996). In contrast to the natural hormones, α-ZOL does not bind the carrier protein (Shrimanker et al. 1985), and consequently may exhibit elevated unbound serum concentrations, thereby increasing its ability to activate the estrogentic pathway (Martin et al. 1978). Compared to α-ZOL, a strong anti-proliferative effect of β-ZOL and DON in porcine endometrial cells was observed by Tiemann et al. (2003b). This finding corresponds to changes in the substructure and to a reduction in viability caused by apoptosis at β-ZOL (Wollenhaupt et al. 2004) or necrosis at DON (Tiemann et al. 2003b). It can be assumed that β-ZOL and DON modulate the process of translation at different molecular level. A molecular target of DON in proliferating eukaryotic cells is the 60 S ribosomal subunit (Middlebrook and Leatherman, 1989; Witt and Pestka, 1990). Following binding of DON to the ribosomal RNA, a rapid activation of mitogen-activated protein kinases (MAPKs) could be observed in a process that has been termed the “ribotoxic stress response” (Zhou et al. 2003; Pestka et al. 2004). The results of Wollenhaupt et al. (2004, 2006a, summerized 2006b) indicated that β-ZOL and DON showed a pronounced impact on MAPKs, which are in mRNA translation, and different signalling pathways can be modulated resulting in the inhibition of cell proliferation after β-ZOL and DON exposure.
Conclusions

Previously, in vivo investigations were performed to determine different non-reproductive and reproductive parameters in female pigs after feeding with DON and/or ZON contaminated diets to evaluate the risks of their metabolism, health and fertility/reproduction. From all described parameters, it is notable that the in vivo effects of DON on humoral immunity are rather inconsistent. ZON has estrogenic activity and this is reflected by alterations of fertility and reproduction in pigs. This review shows that besides the known effects of ZON on reproductive organs, ingestion of DON also causes reproductive failure showing an impairment of porcine oocyte and embryo development which may probably be related directly to the toxic effect of DON.

Table 1 indicates that in vivo effects of DON/ZON were more investigated than in vitro effects. The in vivo investigations provide information on net effects in whole animals, whereas cell specific answers result from in vitro investigations. The summarized results of in vitro studies with porcine cell cultures indicate that there are only partial agreements with that of in vivo experiments. An explanation could be the fact that sometimes the cells in vitro react more sensitively than those in vivo, because a direct interaction of chemical substances with the plasma membrane exists which may alter the membrane structure and function. Therefore, in vitro experiments may contribute to risk assessments of toxins.

Pathophysiological studies are attributable on DON/ZON feeding in pigs and can be important in understanding whether human exposure to DON/ZON may have unfavourable effects, because swine are physiologically similar to humans (Tumbleson and Schook, 1996) and are widely used as models for human disease.
Altogether, ZON affects reproduction of pigs most seriously because it possesses estrogenic activity. Whereas DON affects reproduction in pigs via indirect effects such as reduced feed intake, resulting in reduced growth or impairment of function in vital organs like liver and spleen (Figure 1).

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Legend

Figure 1. The effects of a Fusarium toxin contaminated diet containing predominantly deoxynivalenol (DON) and zearalenone (ZON) on the fertility of female pigs need to be viewed in the general context of the toxin effects on animal health and performance. Before the toxins are able to modify metabolic processes they need to be consumed voluntarily by the pig. The effects on feed intake, which are mediated by DON, not only determine the amount
of toxins entering the organism but also the metabolically available nutrients which might also markedly modulate processes involved in fertility. Although the primary molecular targets of DON (inhibition of protein synthesis) and ZON (interference with the oestrogen receptor) are different, they obviously act in a concerted manner with regard to health and fertility (further details in text).
Table 1. Effects of deoxynivalenol (DON) and zearalenone (ZON) on selected reproductive and non-reproductive parameters in pigs

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<td>+ (DON&gt;ZON)</td>
<td>+</td>
<td>Alm et al., 2002 \ Alm et al., 2006 \ Diekman and Long, 1989 \ Kordic et al., 1992 \ Long et al., 1992</td>
</tr>
<tr>
<td>Steroid synthesis</td>
<td>- (DON&gt;ZON)</td>
<td>+</td>
<td>Alm et al., 2006 \ Tiemann et al., 2003a</td>
</tr>
<tr>
<td>Uterine effects</td>
<td>- (DON&gt;ZON)</td>
<td>+</td>
<td>Döll et al., 2004 \ Fitzpatrick et al., 1989 \ Kordic et al., 1992 \ Lopez et al., 1988 \ Obremski et al., 2003 \ Tiemann et al., 2003b \ Tiemann et al., 2006b \ Wollenhaupt et al., 2004 \ Wollenhaupt et al., 2006</td>
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*'-' marked no effect; '+' marked significant effect
Figure 1. The effects of a *Fusarium* toxin contaminated diet containing predominantly deoxynivalenol (DON) and zearalenone (ZON) on the fertility of female pigs need to be viewed in the general context of the toxin effects on animal health and performance. Before the toxins are able to modify metabolic processes they need to be consumed voluntarily by the pig. The effects on feed intake, which are mediated by DON, not only determine the amount of toxins entering the organism but also the metabolically available nutrients which might also markedly modulate processes involved in fertility. Although the primary molecular targets of DON (inhibition of protein synthesis) and ZON (interference with the oestrogen receptor) are different, they obviously act in a concerted manner with regard to health and fertility (further details in text).