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The Impact of the *Fusarium* Toxin Deoxynivalenol (DON) on Poultry

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Abstract: Deoxynivalenol (DON), a trichothecene, is prevalent worldwide in crops used for food and feed production. The presence of mycotoxins in poultry feeds is a significant factor for financial losses to animal industries. Although DON is one of the least acutely toxic trichothecenes, it should be treated as an important food safety issue because it is a common contaminant of grains. Special care must be taken in so-called "*Fusarium* years". As poultry is regarded to be less sensitive to DON compared to other species it is suspected to divert the infected cereal batches to poultry feeding. This review focuses on the ability of DON to induce toxicologic and immunotoxic effects in chickens. Chickens and laying hens respond to increasing dietary DON concentrations with a reduction in productivity only at high levels above 5mg/kg but there is no clear evidence of a dose-response relationship. The main effect at low dietary concentrations appears to be a reduction in food consumption (anorexia), while higher doses induce severe reduction in weight and impaired resistance to infection, particularly bacterial infection. One important aspect of DON toxicity is injury to the gastrointestinal tract. DON has an influence intestinal morphology of chickens, especially in the duodenum and jejunum, as evidenced by shorter and thinner villi. Additionally, DON decreased the intestinal nutrients absorption (glucose and amino acid) in the chicken small intestine *in vivo* and *In vitro*. The capacity of DON to alter normal immune function has been of particular interest. There is extensive evidence that DON impairs the immune function in broiler and Leghorn chicks. DON induced changes in the haematopoietic system of chicks and altered the mitogen-induced proliferation of lymphocytes. The feeding of DON contaminated grains decreases serum antibody titers against Newcastle disease virus (NDV) and infectious bronchitis virus (IBV) in laying hens and broilers. Other effects include superinduction of cytokine production by T helper cells (*In vitro*) and activation of T cells to produce a proinflammatory cytokine. To what extent the elevation of cytokines contributes to metabolic effects such as decreased feed intake remains to be established. Further toxicological studies on the impact of DON in the immune system and gastrointestinal tract of poultry are warranted.

Key words: Deoxynivalenol, gastrointestinal tract, nutrient absorption, immune function, chicken

Introduction

Several *Fusarium* species are considered as field fungi as they infect wheat and maize principally before harvest which results not only in a reduced crop yield by *Fusarium* head blight (scab), but also in the production of secondary metabolites, such as mycotoxins. The toxins are commonly found world-wide on cereals such as wheat, barley, oats and maize and the contamination of cereals and related products with *Fusarium* toxins causes feed-borne intoxications especially in farm animals. Deoxynivalenol (DON, Fig. 1), a trichothecene, is produced by *Fusarium graminearum* and *Fusarium culmorum*. The pattern and amount of mycotoxins varies between fungal genera and even within strains of one distinct fungal species as well as from year-to-year (Gutleb *et al*., 2002) and the toxin production depends strongly on environmental conditions such as temperature and humidity. Since *Fusarium* species are ubiquitous, a total prevention of a *Fusarium* infection and the contamination with trichothecenes seems to be unlikely. It can be predicted that food and feed are always contaminated with toxins to a greater or lesser extent with increasing accuracy of analysis (lower detection limits). Therefore, exposure to this toxin is a permanent health risk assessment issue for both humans and farm animals. DON is of outstanding importance among these contaminants because of its frequent occurrence in toxicologically relevant concentrations worldwide (Bottalico and Perrone, 2002; Logrieco *et al*., 2002; Placinta *et al*., 1999). The most data on trichothecene contamination are derived from grains and grain products destined for human consumption. Therefore, it could be suggested that poorer quality grain is probably diverted to poultry feed

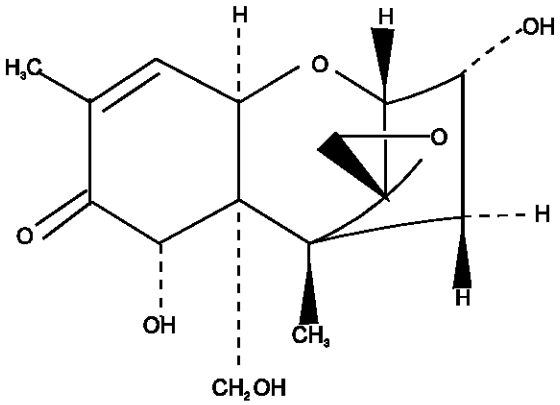

Fig. 1. Chemical structure of deoxynivalenol (EFSA, 2004)

which would probably result in a higher level of DON. Additionally, it has to be taken into account that DON is concentrated in by-products, such as bran, that often serve as animal feed (EFSA, 2004). Poultry fed low to moderate doses are able to recover from initial weight losses, while higher doses induce more long-term changes in feeding behaviour. At low dosages of DON, haematological, clinical and immunological changes are also transitory and decrease as compensatory/ adaptation mechanisms are established. Low to moderate dose of trichothecene cause gastrointestinal irritation or necrosis, haematological disorders, diarrhoea, vomiting and feed refusal, decreased body weight gain, whereas, the exposure to higher dose levels of DON are mainly expressed as severe reduction in weight, severe damage to the haematopoietic systems in bone marrow, spleen, thymus and lymph nodes and impaired resistance to infection, particularly bacterial infection (Ueno, 1984). Poultry appear to have a higher tolerance to feed refusal syndrome than pigs (Huff *et al.*, 1986). Although acute mycotoxicoses are rare in poultry production, chronic exposure to low levels of mycotoxins is responsible for reduced productivity, altered immunity and increased susceptibility to infectious diseases (Hussein and Brasel, 2001; Swamy *et al.*, 2004). Egg production and hatchability can also be negatively affected (Dänicke *et al.*, 2002; Yegani *et al.*, 2006). DON has been implicated in human mycotoxicosis, singly and in combination with T-2 toxin and other trichothecenes. It has also been reported as immunosuppressive at concentrations which are encountered naturally. Recent findings indicate some genotoxic effects of DON in human cell lines (Bony *et al.*, 2006). Apart from direct effects, the economic consequences of mycotoxin-induced poor performance and productivity are additional important factors in animal husbandry and the multiplier effect this has on other industries as a result of the reduced spending power of producers. The problems associated with mycotoxin contamination and the economic losses resulting will continue to be seen in food and agriculture industries. Therefore, the current review summarizes the toxicity and mechanisms of action of DON with special referring to poultry and will provide a clear evidence of the effects of DON on the gut and immune function even in the absence of clinical signs or impaired growth. Such changes in the gut function and immune response should be viewed as an indication for adverse DON-effects on the health status of the birds.

Mode of action: Trichothecenes are well-known inhibitors of protein synthesis. DON binds to the 60S subunit of eukaryotic ribosomes and impairs the function of the peptidyl transferase (Feinberg and Mclaughlin, 1989). Depending on the substituents, trichothecenes inhibit either the initiation or the elongation and termination step of protein synthesis (Ehrlich and Daigle, 1987). An increase of the amount of free ribosomes (60S + 40S) compared to polyribosomes (80S) was observed by initiation inhibitors (I-Type), while elongation (or termination) inhibitors (E-Type) stabilize polyribosome profiles (Cundliffe *et al.*, 1974; Schindler, 1974). DON is an inhibitor of elongation (Fig. 2; Ehrlich and Daigle, 1987). The trichothecenes that mainly inhibit the peptide chain initiation are several orders of magnitude more potent than are those that affect peptide chain elongation (Ehrlich and Daigle, 1985). Besides the effects on protein synthesis, trichothecenes are considered to have multiple inhibitory effects on eukaryotic cells. An inhibition of RNA and DNA synthesis, as well as adverse effects on mitochondrial function was observed (Ueno, 1977, 1985; Thompson and Wannemacher, 1986, 1990; Mekhancha-Dahel *et al.*, 1990; Charoenpornsook *et al.*, 1998; Minervini *et al.*, 2004). DON induced DNA fragmentation of chicken spleen leukocytes (Frankic *et al.*, 2006). Moreover, apoptosis was linked to alterations in cell signalling at the level of mitogen-activated protein kinases (MAPKs) (Shifrin and Anderson, 1999) induced by trichothecenes (Iordanov *et al.*, 1997; Yang *et al.*, 2000; Moon and Pestka, 2002). It has been suggested that macrophages, T cells and B cells are all highly sensitive to trichothecenes. *In vitro* and *in vivo* studies have demonstrated that trichothecenes can affect leukocytes by up-regulating cytokine production and by inducing apoptosis. Acute/subacute DON intoxications are rare in poultry production and characterized by feed refusal, weight loss and diarrhea. DON was shown to elevate serum IgA levels, as well as cytokines, chemokines and other immune related proteins by stimulation of immune associated genes at low doses. The stimulatory effects were related to the induction of immune and inflammation-associated genes by protein synthesis inhibitors (Pestka *et al.*, 2004, Fig. 3). The effect at high

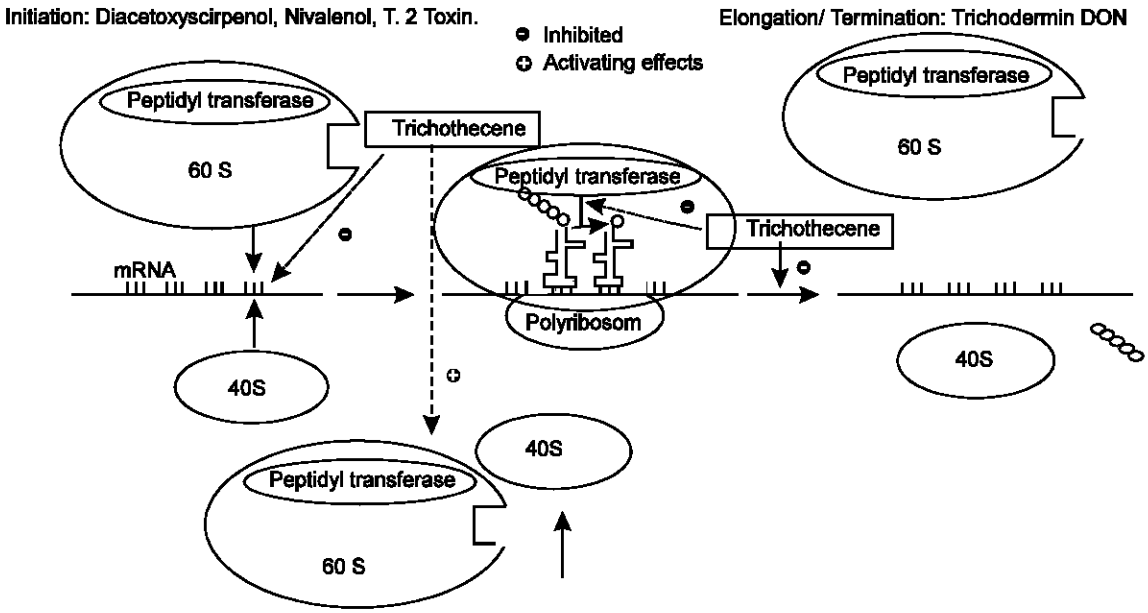

Fig. 2. Mechanism of protein synthesis inhibition by trichothecenes (Goyarts, 2006). Inhibitors of polypeptide chain initiation (I-Type) will accumulate free ribosomes (40S + 60S) as these are not able to bind to mRNA (initiation complex). Elongation and termination inhibitors (E-Type) will increase the amount of polyribosomes (80S) as the uncoupling from mRNA and release of peptide chain is inhibited inhibitory or activating effects).

doses was the induction of apoptosis in lymphoid tissue (spleen, Peyer's patches and thymus). Chronic exposure to low levels of mycotoxins is responsible for reduced productivity, lymphocyte proliferation, host resistance, cell-mediated immunity and humoral immune functions and increased susceptibility to infectious diseases (Pestka and Bondy, 1994; Bondy and Pestka, 2000; Hussein and Brasel, 2001).

Toxicokinetics of deoxynivalenol: Laying hens and broilers are regarded as tolerant to the *Fusarium* mycotoxin DON. The difference in sensitivity may be explained by differences in absorption, distribution, metabolism and elimination of DON (Pestka and Smolinski, 2005) and by the hypothesis of a protective effect of the renal first pass effect known to exist in chickens (Rotter *et al*., 1996). Since exposure to DON has been associated with a number of toxic effects in farm animals (i.e. feed refusal, emesis, anorexia), this has resulted in concern about potentially toxic residues in food products intended for humans, not only contaminated grains but also from contaminated products (meat, eggs) obtained from poultry previously exposed to DON-contaminated feeds. But this is probably not significant in view of the relatively low consumption of eggs on dietary weight basis, compared with other sources of exposure such as cereals and cereal based products. DON seems to be rapidly and efficiently absorbed, most probably from the upper parts of the small intestine and little appears in the excreta of hens (Lun *et al*., 1988), with no significant accumulation in tissues (Prelusky *et al*., 1988; Eriksen *et al*., 2003). Human and animal contamination occurs mainly orally and the toxin must traverse the intestinal epithelial barrier before inducing potential health effects. Awad *et al*. (2007a) suggested that the major part of DON transport across the intestinal epithelium is likely due to simple diffusion. This passive diffusion is probably via the paracellular route and found that the DON absorption were time and concentration-dependent in chicken. Fowl appear to cope with ingested DON by altering the molecule shortly after absorption such that it has reduced toxicity, does not express affinity for body tissues and can rapidly be removed from the vascular system by the kidney (Lun *et al*., 1989). Lun *et al*. (1988) have shown that DON as such largely disappears from the GIT between the crop and jejunum. This disappearance is presumed to have occurred because of its absorption by the enterocyte and conversion to its metabolite. High radioactivity in the liver and bile in birds given labelled DON suggests that the metabolite is being excreted in association with bile back into the small intestine. Short-term DON consumption can induce phase I and II liver biotransformation enzymes (Gouze *et al*., 2005). DON is conjugated to glucuronides in liver and the metabolites found in animal tissue and excreta (Gareis *et al*., 1987). The principal DON metabolite detected in urine and faeces of chicken is de-epoxy DON (DOM-1) (He *et al*., 1992). In chickens, absorption of DON from the GIT was found to be very

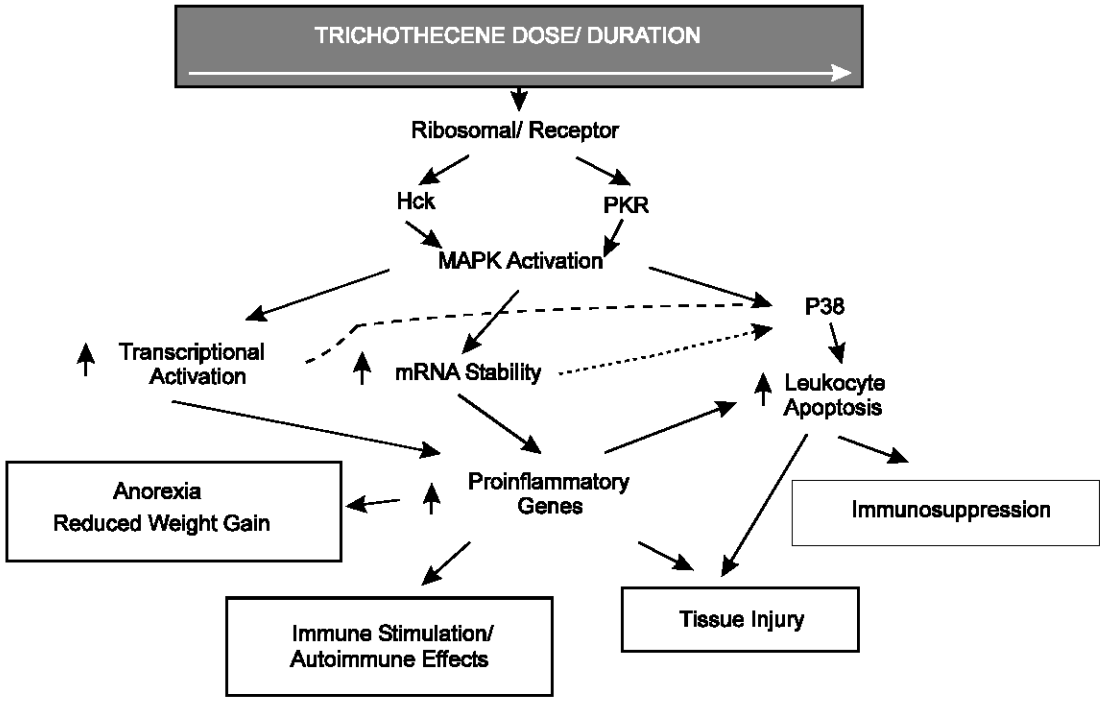

Fig. 3. Depiction of interactive molecular and cell-signaling mechanisms involved in trichothecene-induced toxicity. PKR (double-stranded RNA-activated protein kinase), HCK (Haematopoetic cell kinase) and MAPKs (Mitogen-activated protein kinases) potentially function as molecular rheostats and define whether an immunostimulatory or immuno suppressive response will result (Pestka *et al*., 2004).

rapid, as DON could be detected in plasma within 15-30 min after oral dosing (Prelusky *et al*. 1988; Awad *et al*., 2007a) and peak plasma concentrations occurring at 2.0-2.5 h after administration of ^{14}C-DON (Prelusky *et al*., 1986). The quantity of DON present in plasma at peak plasma concentration accounted for less than 1% of the administered dose. The radioactivity in the tissues (not including gastrointestinal tract and bile) was only marginally detectable. Based on high specific activity measured in bile samples and the relatively low systemic absorption of DON, these authors suggested biliary excretion played an important role in the elimination of DON from the body. They found the clearance rate of DON by chickens to be high; estimated recoveries of DON in excreta were 58, 78, 90 and 99% at 12, 24, 48 and 96-h after intubations, respectively. A rapid plasma clearance and excretion due to an efficient hepatic or renal first-pass effect (Rotter *et al*., 1996) as well as a rapid intestinal transit time (Prelusky *et al*., 1986) and the intestinal microflora which plays a major role in DON detoxification (He *et al*., 1992) might explain the relative tolerance of poultry. Prelusky *et al*. (1986) orally administered ^{14}C-DON to chickens and observed high radioactivity in the liver and bile with over 90% of the original label accruing in the excreta before 48-h. No significant accumulation was found in tissues and eggs of poultry (El Banna *et al*., 1983, Kubena *et al*., 1985, 1987). However, traces amount of DON below 1 µg/kg were detected in eggs of laying hens which were fed a diet containing DON at 5-0 mg/kg (Sypecka *et al*., 2004). Low levels of radioactive residues were transmitted to eggs of laying hens following a single oral dose of ^{14}C-DON (2.2 mg/bird) (Prelusky *et al*., 1987) or of ^{3}H-DON (0.1 mg/kg body weight) (Lun *et al*., 1989) or during prolonged administration of a diet containing 5.5 mg/kg ^{14}C-DON (Prelusky *et al*., 1989). In the study by Prelusky *et al*. (1987) only 10% of the radioactivity in yolk could be identified as the parent toxin DON.

Toxicity of deoxynivalenol:

Effects on performance and feed intake: Prolonged dietary DON exposure of animals was described to cause anorexia, decreased live weight gain and altered nutritional efficiency (Pestka and Smolinski, 2005). Regarding livestock production these adverse effects of DON on performance resulted in great economic losses. Most experimental studies with poultry show a highly variable effect of DON on performance. In addition to the rarely observed intoxication with high DON concentrations, the chronic exposure to lower amounts of DON is of major interest, where DON-caused economical losses in animal production due to reduced feed intake and live weight gain. However, direct effects of DON on haematology, clinical-chemical parameters

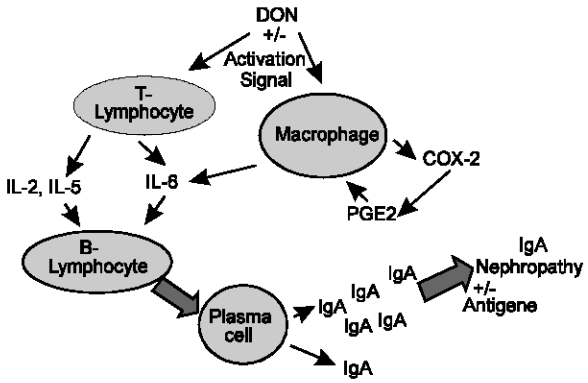

Fig. 4. Cellular mechanism involved in DON-induced IgA production and IgA nephropathy (Pestka, 2003.

and immunity are as yet poorly defined since most investigations could not separate the effect of feed intake from DON contamination (Rotter *et al.*, 1996). Dänicke *et al.* (2001) reviewed the literature regarding the effects of DON on the performance of broilers and came to the conclusion that dietary concentrations greater than 5 mg/kg are necessary to cause detrimental effects. Even higher concentrations did not consistently induce detrimental effects and in fact, even growth promoting effects were observed especially at moderately high concentrations of DON. The authors concluded that it is not possible to establish a simple dose-response relationship between growth depression and the dietary concentrations of DON for broilers compared to that of pigs. A review of the literature (Table 1) indicates that dietary concentrations of DON below 15 mg/kg had no adverse effect on body-weight gain, feed consumption or feed efficiency of broilers (Hulan and Proudfoot, 1982; Bergsjo and Kaldhusdal, 1994; Kubena *et al.*, 1997; Harvey *et al.*, 1997; Leitgeb *et al.*, 1999, 2000; Swamy *et al.*, 2002; Li *et al.*, 2003; Awad *et al.*, 2004, 2006a, b). Feed refusal and reduced weight gain were found when the dietary concentration of DON reached 16-20 mg/kg (Kubena *et al.*, 1987, 1988, 1989; Kubena and Harvey, 1988; Harvey *et al.*, 1991). Dänicke *et al.* (2003) found that an increase in dietary *Fusarium* mycotoxin concentrations (major toxin was DON) resulted in a linearly related decrease in feed intake, slight decrease in weight gain, an improvement in feed conversion and linear decrease in serum antibody titres to Newcastle disease virus after vaccination in broilers. Chowdhury and Smith (2004) and Dänicke *et al.* (2002) concluded that layer performance, immune response and metabolism were adversely affected by chronic intake of *Fusarium* mycotoxins. The highly variable effect of DON on performance of poultry indicating that zootechnical traits might not be a sensitive indicator of toxicity of this *Fusarium* toxin. However, feed refusal, reduced weight gain, reduced immune function and changes in haematology and serum chemistry could be found when the dietary concentration of DON reached 16-20 mg/kg (Harvey *et al.*, 1991; Dänicke *et al.*, 2003). Differences in toxic effects may be because some of those studies used artificially contaminated grain or a single source of contaminated grain. Artificially contaminated diets with purified DON seem to be less toxic than naturally contaminated diets (Canady *et al.*, 2002). The use of a blend of naturally contaminated grains would increase the potential for toxicological synergies arising from interactions between multiple mycotoxins (Smith *et al.*, 1997).

Effects of DON on the gastrointestinal tract and other organs: The gastrointestinal tract is the first barrier against ingested chemicals, feed contaminants and natural toxins. Following ingestion of mycotoxin-contaminated food or feed, intestinal epithelial cells can be exposed to high concentrations of toxins (Prelusky *et al.*, 1996). Deoxynivalenol intoxication results in cytotoxicity and inhibition of protein synthesis, lesions of the gastrointestinal tract, bone marrow and lymphoid tissues as well as kidney and heart lesions. Small erosions of the gizzard mucosa were observed in birds fed a highly contaminated diet containing 82.8 mg DON/kg for 27 days (Lun *et al.*, 1986). Increased absolute and relative gizzard weights and lesions of the proventriculus were interpreted to be a consequence of an irritation of the upper gastrointestinal tract. Moreover, DON and several other toxins were found to decrease the trans-epithelial electrical resistance (TEER) of a human epithelial cell line (Maresca *et al.*, 2002). These disaggregating effects of mycotoxins on epithelial intestinal cells may at least in part explain the intestinal lesions observed in humans and animals. In any case, alterations of the gastrointestinal tract, such as corrugation of the mucosa in the stomach, duodenitis, jejunitis, intestinal bleeding and necrosis, have been associated with the exposure to DON and other *Fusarium* toxins (Arnold *et al.*, 1986; Forsell *et al.*, 1987; Rotter *et al.*, 1994; D´Mello *et al.*, 1999). However, Moran *et al.* (1982) and Huff *et al.* (1981) did not observe any lesions in the upper gastrointestinal tract or haemorrhage when DON levels of less than 49 mg/kg of diet or 140 mg/kg body weight were fed to broilers, respectively. Harvey *et al.* (1997) found no histopathological lesions in kidneys from broiler chicks fed a diet containing 16 mg DON /kg for 21 days. Bergsjo and Kaldhusdal (1994) observed that when DON at a concentration of 3.4 mg/kg was fed to broilers for 35 days, there were no effects on heart weight, furthermore, microscopical examination of organs did not reveal pathological changes. The weights of liver, kidney, spleen and bursa of Fabricius of broilers, expressed as a percentage of body weight, were not altered by dietary inclusion of *Fusarium* contaminated grains (Swamy *et*

Table 1: Summary of the toxicity of deoxynivalenol in broiler

Species, strain, sex, age	Length of study (days)	Effect	LOEL (mg/kg bw per day)	NOEL (mg/kg bw per day)	Reference
Broiler chicks, male, 1 day of age at beginning	21	Reduced feed efficiency	1.3		Kubena *et al.* (1989)
Broiler chicks, male, female, 1 day of age at beginning	35	No effect on feed intake, weight gain, carcass weight, heart, or histological parameters		0.21, 0.34	Bergsjo and Kaldhusdal (1994)
Broiler chicks, male, female, 1 day of age at beginning	21	No effect on body-weight gain, feed conversion; decrease small intestine weight; slight villus atrophy and irregular crypts especially in the duodenum and jejunum, as evidenced by shorter and thinner villi	0.5		Awad *et al.* (2006a, b)
Broiler chicks, male, 1 day of age at beginning	21	No effect on feed intake, body-weight gain, haematological, serum and histological parameters		1.5	Harvey *et al.* (1997)
Broiler chicks, male, 1 day of age at beginning	21	No effect on feed intake, body-weight gain, haematological or serum parameters; increased relative weight of heart, bursa and gizzard	1.3		Kubena *et al.* (1997)
Broiler chicks, 1 day of age at beginning	37	No effect on body-weight gain, feed conversion, or serum parameters; increased heart weight: dose-related, significant at highest dose	0.46	0.3	Leitgeb *et al.* (1999)
Broiler chicks, male, female, 1 day of age at beginning	42	No effect on body-weight gain, feed conversion, decrease glucose absorption	1		Awad *et al.* (2004)
Turkey poults, female, 1 day of age at beginning	21	No effect on feed intake, body-weight gain, haematological, most serum parameters, histology, heart or kidney weights; reduced serum calcium	1.6		Morris *et al.* (1999)
Mallard duck, male, female, 1 year old	14	No effect on serum, haematological, or histological parameters		1.5	Boston *et al.* (1996)
laying Leghorn hens, 1 day old	168	No effect was found on feed intake, body weight, egg production, egg yield, or the number of cracked eggs, or egg fertility	1.8		Kubena *et al.* (1987)
White Leghorn laying hens, 20-23 weeks old	70	No effect on food intake, weight gain, egg production, fertility, hatchability, perinatal mortality, chick viability, body weight; developmental anomalies: delayed ossification, cloacal atresia, cardiac anomalies	0.12		Bergsjo *et al.* (1993)

al., 2004). Dänicke *et al.* (2002) found that liver, spleen, or heart weights of hens were not affected by dietary treatments with *Fusarium* contaminated maize, but the weight of small intestine slightly decreased. Awad *et al.* (2006a) found also that the weight of small intestine decreased in broilers fed the DON contaminated wheat. Feeding of naturally contaminated grains did not alter the gross weight of lymphoid organs such as the bursa and spleen in turkeys (Chowdhury, *et al.*, 2005). The absolute and relative weight of liver were decreased in growing chicks fed DON-contaminated grains (Kubena *et al.*, 1985). Furthermore, Kubena *et al.* (1988) observed no changes in organ weights (liver, spleen, kidney and bursa of Fabricius). In another study, Kubena *et al.*

(1989, 1997) reported increased weights of gizzard, heart and bursa of Fabricius. In these studies the chickens fed 16 mg/kg DON from contaminated wheat for 21 days. The outcome of these studies was highly variable indicating that organ weights might not be a relevant indicator of toxicity of DON. Conversely, Swamy *et al.* (2004) postulated, that the time of toxin exposure may be a significant factor as the organ initially swells with toxin exposure followed by shrinkage. It was observed that DON may alter the stomach epithelial cell layer, as the fundic region of the stomach appeared thicker and the degree of folding higher (Rotter *et al.*, 1994). Fairchild *et al.* (2005) who found that feeding both fusaric acid and diacetoxyscripenol for 18 days to poults decreased enterocyte height at mid-villus by 59%. This is supported by Sklan *et al.* (2003) who indicated that feeding of T-2 toxin or diacetoxyscripenol at levels up to 1 mg/kg for 32 days to poults did not depress but enhanced growth and did not influence antibody production but caused changes in small intestinal morphology, especially in the jejunum where villi were shorter and thinner. Ayral *et al.* (1992) observed that diacetoxyscripenol and DON exert similar effects on the immune system and these mycotoxins could lead to enhanced susceptibility to infections in various species. Awad *et al.* (2006a, b) found mild intestinal changes such as slight villus atrophy and irregular crypts by the dietary inclusion of naturally or artificially contaminated diets with DON. Furthermore, DON altered small intestinal morphology, especially in the duodenum and jejunum, as evidenced by shorter and thinner villi. The decrease in enterocyte height is highly indicative that DON altering digestive and absorptive functions.

Effects on the intestinal nutrient absorption: The movement of ions responsible for the electrical current across the epithelium are mainly due to the absorption of Na^+ and the secretion of Cl^- (Skadhauge, 1981; Grubb, 1991). The electrophysiological parameters of epithelia such as the transmural potential difference (PD), short-circuit current (Isc) and electrical tissue resistance (Rt) can be measured by using Ussing chambers. Transepithelial electrical potential (PD) constitutes an important electrophysiological parameter which reflects the functional state of a tissue. The current induced by ion transport is recorded as changes in PD (Wright, 1983; Boucher, 1994). There is a little information available regarding the effects of DON on the electrical properties of the intestine of chickens. A study carried out by Grubb *et al.* (1987) showed that the avian intestine has a regional electrical profile different from that of mammals. In the chicken, the region with the highest electrical resistance is the duodenum, whereas in the rat and the rabbit the region of highest resistance is the colon (Powell, 1987). The small and large intestines of birds are known to have high absorptive capacities for water and electrolytes. It seems likely that the morphological changes in the intestine and the decreased feed conversion are linked to an impaired absorption of nutrients. Intestinal absorption of sugars and amino acids occurs mainly actively through cellular pathways and small quantities passively through a paracellular or a cellular route. Cotransporters are specialized membrane proteins transporting sugars, amino acids and ions, utilizing electrochemical gradients across the membrane. Glucose is transported by carrier systems usually co-transported with Na^+ via the sodium glucose-linked transporter SGLT1. Amat *et al.* (1999) and Awad *et al.* (2004, 2007b) showed that the addition of glucose on the mucosal side produced increases in the current (Isc) in different parts of small and large intestines of chickens relative to basal values. The higher Isc after glucose addition is due to a stimulation of the Transepithelial Na^+ transport. Furthermore, most amino acids are cotransported with sodium. Laverty (1997), Galietta *et al.* (1998) and Jiang *et al.* (2000) reported that the addition of amino acids increased the Isc compared with the baseline values. Awad *et al.* (2005) found that the addition of L-proline on the luminal side of the isolated mucosa of chicken increased the Isc. Scharrer (1972) and Lerner *et al.* (1976), in studies comparing the jejunum and the ileum of chicken, demonstrated that the former is characterized by relatively higher transport rates of several nutrients. Studies comparing the jejunum and the proximal caecum indicated that the jejunum had a higher total transport capacity for sugar than the proximal caecum (Moreto *et al.*, 1991). The Na^+-coupled glucose uptake across SGLT1 is present in all regions of the small and large intestine of chicken (Obst and Diamond, 1989; Ferrer *et al.*, 1994; Awad *et al.*, 2007b). Maximal transport capacity values for methyl-D-glucose showed that the jejunum is the segment that is best suited for Na^+-mediated uptake (Ferrer *et al.*, 1986; Amat *et al.*, 1996, Awad *et al.*, 2007b). DON decreased the current (Isc) after addition of D-glucose in broilers (Awad *et al.*, 2004) and suggested that DON decreased the absorption of glucose. In fact, this can be taken as an indirect indication that DON interferes with SGLT1 activity and decreased the absorption of glucose in the chicken intestine. However, Awad *et al.* (2007a) studied the direct effects of DON on the glucose transport capacity in chickens' jejunum by using radiolabelled glucose in the Ussing chamber technique. Results provided clear evidence that glucose uptake is decreased by DON. The effect of DON was similar to the effect of phlorizin (SGLT1 inhibitor). The similarity between the effects of phlorizin and DON on glucose uptake evidences their common ability to inhibit Na^+-D-glucose co-transport. Also, it was found that L-proline absorption was decreased by DON (Awad *et al.*, 2005). This finding also indicates that the inhibition of Na^+ co-transport systems

is an important mechanism for DON toxicity in chickens. Dose-efficacy studies on sugar and amino acids uptake in human intestinal epithelial cells with DON showed that DON inhibited the uptake of α-methyl-glucose resulting in 50% decrease at 10 µmol/L and a maximal effect at 100 µmol/L (76±1.6% of inhibition). DON selectively modulated the activities of intestinal transporters. The SGLT1 was strongly inhibited by DON (50% inhibition at 10 µmol/L), followed by active and passive L-serine transporters. On the other hand, passive transporters of D-glucose (GLUT) were only slightly inhibited by DON (15 % inhibition at 1µmol/L) (Maresca *et al.*, 2002). Previous studies have often ascribed the functional consequences of mycotoxin action on the intestinal absorption to their inhibitory action on RNA and protein synthesis (Rotter *et al.*, 1996). Accordingly, the shortening and thinning of villi in the small intestine of chickens observed in previous investigations after DON feeding (Awad *et al.*, 2006a, b) may suggest that the decrease in glucose absorption is a consequence of a general impairment of epithelial protein synthesis and function. However, Maresca *et al.* (2002) reported that DON selectively modulates the activities of specific intestinal transporters in human intestinal epithelial cells. Based on this study and previous investigations, the DON-sensitive transport in chicken intestine comprises sodium-glucose cotransport by SGLT1. It is not clear at present whether the interference with these specific intestinal transport pathways occurs mainly at the level of RNA transcription and/or protein synthesis. Given the profound effects of DON on nutrient absorption in the small intestine, it is astonishing that poultry performance is often not or only moderately affected by the DON contamination of feedstuffs (Dänicke *et al.*, 2002; Sypecka *et al.*, 2004). One plausible explanation could be that under normal circumstances the major absorption of nutrients occurs in the duodenum and proximal jejunum and the small intestine apparently has surplus absorptive capacity (Noy and Sklan, 1995, 1996). Feeding of DON decreases the absorption of some nutrients such as D-glucose and amino acids in the proximal small intestine (Awad *et al.*, 2004, 2005) and this could displace some of the uptake to more distal intestinal sites. It is known, that chicken are able to absorb D-glucose and amino acids efficiently even in the large intestine (Bindslev *et al.*, 1997). The absorptive functions in the large intestine may be better protected against the deleterious effects of DON, whereas DON has been reported to be completely transformed to de-epoxy-DON after incubating for 96 h with the content of the large intestine of hens (He *et al.*, 1992). Therefore, DON appeared to alter the gut function but overall compensatory capacity is so high that this may not impair performance.

Gastrointestinal transformation of DON to the de-epoxy metabolite: The micro-organisms in faeces from chicken possess the de-epoxidation ability (He *et al.*, 1992). This de-epoxidation is the most important step in the detoxification of trichothecenes. The 12, 13 epoxide rings has been considered to be essential for the toxicity of the trichothecenes (Wei *et al.*, 1974; Ehrlich and Daigle, 1987; Betina, 1989; Rotter *et al.*, 1996). The de-epoxides of DON were 24 times less toxic in the cell toxicity test than the corresponding toxin (Eriksen *et al.*, 2003). It has been shown that the de-epoxides are considerably less acutely toxic than the corresponding trichothecenes (Swanson *et al.*, 1987). A review of the literature revealed that DON is degraded by *Eubacterium* sp. in the GIT which transforms DON into its metabolite DOM-1 the non- toxic de-epoxide of DON (Binder *et al.*, 1997, 1998). Since the de-epoxidation is a detoxification reaction, any differences in the ability to transform trichothecenes to their corresponding de-epoxy metabolite may influence the toxicity of trichothecenes. De-epoxy metabolites of trichothecenes have been found in the excreta of chicken (Lun *et al.*, 1988). It has therefore been assumed that the deepoxidation reaction occurs in the gastrointestinal tract of monogastrics before the absorption (Swanson and Corley, 1989; Rotter *et al.*, 1996). If a significant proportion of the trichothecenes is de-epoxidised prior to absorption or before any damage occurs on the epithelial layer in the gastrointestinal tract, this ability may significantly reduce the toxicity of trichothecenes. A gastrointestinal de-epoxidation in the gut before absorption in some species could contribute to species-differences in sensitivity towards trichothecenes, which might explain the relative high tolerance of poultry.

Effects of DON on the immune system: Studies of DON immunotoxicity have focused primarily on the mouse model, with few investigations on possible effect in humans or domestic animals. These studies have shown that DON and other trichothecenes can suppress or stimulate immunity, sometimes even when present at identical dosages (Rotter *et al.*, 1996). Most of the immunotoxic effects were short term, whereas prolonged consumption of purified DON sometimes resulted in the disappearance of adverse effects, which were mainly attributed to feed refusal rather than to systemic toxicity. In chickens, humoral immunity can be either stimulated or impaired by DON. Chicken fed 50 mg/kg DON had reduced antibody responses to Newcastle disease vaccine (Harvey *et al.*, 1991). Dänicke *et al.* (2002) found a decreased antibody titer against the Newcastle disease virus in laying hens consuming a diet containing 17.6 mg of DON/kg. Harvey *et al.* (1988) reported decreased immune function in broiler and leghorn chicks that were fed DON-contaminated diets. The feeding of contaminated diets with *Fusarium* mycotoxins to chickens did not cause significant changes in serum or bile immunoglobulin concentrations (Swamy *et al.*, 2004). However, Swamy *et*

al. (2002) controversially observed that the feeding of contaminated grains with *Fusarium* mycotoxins caused significant declines in the biliary IgA but not in serum IgG and IgM. Moreover, the immunological and haematological effects of long-term feeding of *Fusarium* mycotoxins have not been well characterized (Sharma, 1993). Oral exposure to *Fusarium* mycotoxins may alter gut mucosal immunity because of local effect of mycotoxins in the gut. Serum IgA mediates the transport of antigens from the circulation into the bile (Russell *et al.,* 1981). It has also been suggested that the hepatobiliary transport of IgA from blood serves to reinforce the intestinal supply of secretory IgA, which protects the mucosal surface against infection and prevents penetration of antigens from the gut lumen. Secretory IgA provides an important line of defense against bacteria, such as Salmonella, Vibrio cholera and Neisseria gonorrhoea and viruses such as polio, influenza and reovirus (Goldsby *et al.,* 2000). Trichothecenes bind to ribosomes and inhibit protein synthesis. Therefore, it is possible that *Fusarium* mycotoxins decrease biliary IgA concentrations, despite maintenance of serum IgA concentrations, by inhibiting the synthesis of secretory component proteins required for IgA transport into the bile. In addition, Chowdhury *et al.* (2005) reported that the chronic feeding of *Fusarium* mycotoxins reduced biliary IgA concentration; however, IgG and IgM antibody titers to sheep red blood cells were not affected by diet.

Altered immune cells in tissues: DON at low levels could slightly stimulate *in vitro* B-cell proliferation in a cloned B-cell line (Minervini *et al.,* 1993), but it did not enhance Ig secretion in purified B-cell cultures (Warner *et al.,* 1994). Feeding diets with a high level of grains contaminated with *Fusarium* toxins to broiler chickens reduced the percentage of lymphocytes, but did not alter serum immunoglobulin concentrations (Swamy *et al.,* 2004). In another study, the consumption of grains naturally contaminated with *Fusarium* mycotoxins decreased the number of blood leukocytes as well as the numbers of blood B-lymphocytes, $CD4^+$ and $CD8^+$ T-helper cell (Chowdhury *et al.,* 2005). It was suggested that the DON related up-regulation of pro-inflammatory cytokines (e.g. IL-6) produced by T-lymphocytes and macrophages is essential for the differentiation of B-cells to IgA secreting plasma cells (Pestka 2003; Fig. 3). Hence, it is important to determine cell function in terms of cell-mediated or antibody-mediated immune competence. T-lymphocyte-mediated hypersensitivity reaction is characterized by T-lymphocyte activation in the lymph nodes draining the site at which antigen is applied (Kimber and Dearman, 1991). The early increase in response in birds fed mycotoxin-contaminated grains may be due to an increased migration of macrophages with consequent elevation in phagocytic capacity or to altered T-cell regulatory activity (Corrier, 1991), through upregulation of the expression of many immune related genes such as those coding for cyclo-oxygenase-2 (COX-2), cytokines (Th1 and Th2) and chemokines. The induction of gene expression is under transcriptional and post-transcriptional (increased mRNA stability) control. Regarding immunostimulation, COX-2 induction is critical in driving the production of IL-6 by macrophages. IL-6 from macrophages and T-cells is probably the crucial cytokine in mediating the differentiation of B-cells to IgA producing plasma cells. However, consumption of DON (5.8 mg/kg of diet) arising from grains naturally contaminated with *Fusarium* mycotoxins did not affect the cell-mediated response of pigs (Swamy *et al.,* 2003). The reasons for these discrepancies might be due to differences in species sensitivity or to the concentrations of toxins. It appears that feeding of grains naturally contaminated with *Fusarium* mycotoxins containing up to 12 mg of DON/kg is not immunotoxic to poultry. In contrast, high dose trichothecene exposure severely injures actively dividing tissues including bone marrow, lymph nodes, spleen, thymus and intestinal mucosa resulting in immunosuppression evidenced by depression of circulating blood leukocytes, reduced serum IgM and IgG levels, decreased resistance to pathogens, inhibition of antibody responses to model antigens and impaired delayed type hypersensitivity responses. The suppressing effect on leukocyte function is linked to induction of apoptosis demonstrated *in vivo* and *in vitro* in macrophages, T-cells and B-cells (Pestka *et al.,* 1994, 2004). DON sequentially induces mitogen-activated protein kinases (MAPKs) phosphorylation (activation), transcription factor activation and COX-2 mRNA expression. The process in which compounds bind to ribosomes and rapidly activate MAPKs and apoptosis is known as "ribotoxic stress response". The MAPKs, extracellular signal regulated protein kinases 1 and 2 (ERK 1 and 2) and p38 contribute to upregulation of inflammatory genes and cytokines. However, the effect on a given cytokine may differ between individual trichothecenes. Double-stranded RNA-(dsRNA)-activated protein kinase (PKR) and haematopoietic cell kinase (Hck) are upstream transducers of MAPKs and their activation contributes to leukocyte apoptosis via sequential activation of p38, p53 and caspase 3. Payer's patch and, to a lesser extent, splenic lymphocyte cultures prepared from DON-fed mice produced significantly more IgA than cultures derived from mice receiving *ad libitum* or restricted control diets. These results indicate that in mice DON enhances premature differentiation of IgA secreting cells at the level of Payer's patch within the gut, which was reflected in the systemic immune compartment (Pestka *et al.,* 1989, 1990a, b; Bondy and Pestka, 1991). Pestka and Dong (1994) suggested that d DON enhances differentiation to IgA-secreting cells at the Payer's patch level and subsequently affects the systemic compartment.

Cytokine gene expression: The capacity of DON and other trichothecenes to influence cytokine gene expression under *in vitro* conditions involves transcriptional and /or posttranscriptional mechanisms (Ouyang *et al.*, 1996, Li *et al.*, 1997) and protein synthesis appears to be mechanistically involved in effects on the immune system. DON or other protein synthesis inhibitors have been shown to super-induce cytokine secretion or mRNA abundance (Miller and Atkinson, 1987). In contrast to the studies *in vitro*, mouse exposure to DON directly enhanced mRNA expression for a wide range of cytokines including tumour necrosis factor-α (TNF- α), IL-1ß, IL-6, IL-12 p40, interferon-γ (IFN-γ), IL-2, IL-4 and IL-10 in spleen and Payer's patches, with complete recovery occurring 24 h after a single exposure (Azcona-Olivera *et al.*, 1995, Zhou *et al.*, 1997). However, information is lacking regarding the effect of chronic feeding of grains naturally contaminated with *Fusarium* mycotoxins on cytokine expression in chicken. Low doses or concentrations of trichothecenes up-regulate expression of inflammation-related genes *in vivo* and *In vitro* (Moon and Pestka, 2002), proinflammatory cytokines (Wong *et al.*, 1998; Zhou *et al.*, 1997), and numerous chemokines (Chung *et al.*, 2003; Kinser *et al.*, 2004). Human blood monocytes are also susceptible to DON-induced cytokine and chemokine expression at concentrations as low as 25 ng/mL (Islam *et al.*, 2005). Induction of these mediators might contribute to DON-induced anorexia as has been proposed for endotoxin. The ability of DON to transiently alter the expression of cytokines is important because such effects can disrupt normal regulation of a wide variety of immune functions. Deoxynivalenol can up-regulate cytokine production in murine models *in vitro* and *in vivo* (Wong *et al.*, 1998). The concentrations required for effects *in vitro* (50-1000ng/mL) are readily attained within minutes in plasma, lymph and other tissues of mice given 5 or 25 mg/kg body weight (bw) by gavage and can last for several hours (Azcona-Olivera *et al.*, 1995). The effect of DON on cytokine mRNA expression in groups of mice were investigated after a single oral dose of DON at 5 and 25 mg/kg bw. The abundance of cytokine mRNA in spleen and Payer's patches was assessed 2 h after exposure by reverse transcriptase-polymerase chain reaction in combination with hybridization analysis. At 5 and 25 mg/kg bw, DON significantly induced the mRNAs for the proinflammatory cytokines IL-1ß, IL-6 and TNF-alpha, the T-helper-1 cytokines interferon-γ (IFN-γ) and the T-helper-2 cytokines IL-4 and IL-10, whereas lower doses had no effect (Zhou *et al.*, 1997). The Peyer's patches may be particularly prone to cytokine dysregulation since they are exposed (through enterohepatic circulation) to higher levels of DON than systemic immune organs. Interestingly, IL-1, IL-6 and tumour necrosis factor-α (TNF-α) have all been experimentally shown to cause anorexia and weight loss (Schobitz *et al.*, 1994). Thus, it might be speculated that cytokine elevation contributes to the lethal toxic effects observed with DON, as well as the aforementioned chronic effects, feed refusal and reduced weight gain. Whereas, DON inhibits intestinal cell proliferation and is absorbed through the intestinal epithelium by simple diffusion (Sergent *et al.*, 2006; Awad *et al.*, 2007a). At concentrations corresponding to those found naturally, DON induced p38 ERK and JNK phosphorylation as well as concomitantly disrupted intestinal permeability.

Conclusions: DON has not generally been recognized as overtly toxic to chickens, but the results of the present review suggest that DON might be included as potentially immunotoxic substance which affects also gut function in chickens. DON was shown not only to alter gut function in chicken but also to decrease the glucose and amino acid absorption, haematocrit values, total numbers of white blood cells, $CD4^+$ and $CD8^+$ T-lymphocytes and B-lymphocytes and biliary IgA concentration. The capacity of DON to alter normal immune function has been of particular interest. Because subtle changes in haematological or immunological parameters could affect productivity or disease susceptibility, particularly in young chickens, caution should be exercised when utilizing DON-contaminated feedstuffs to formulate poultry diets.

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