



Review article

Impact of mycotoxin on immune response and consequences for pig health

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ABSTRACT

Mycotoxins are fungal secondary metabolites detected in many agricultural commodities, especially cereals. Due to their high consumption of cereals, pigs are exposed to these toxins. In the European Union, regulations and/or recommendations exist in pig feed for aflatoxins, ochratoxin A, fumonisins, zearalenone, and trichothecenes, deoxynivalenol and T-2 toxin. These mycotoxins have different toxic effects, but they all target the immune system. They have immunostimulatory or immunosuppressive effects depending on the toxin, the concentration and the parameter investigated. The immune system is primarily responsible for defense against invading organisms. The consequences of the ingestion of mycotoxin-contaminated feed are an increased susceptibility to infectious diseases, a reactivation of chronic infection and a decreased vaccine efficacy. In this review we summarized the data available on the effect of mycotoxins on the immune system and the consequences for pig health.

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1. Introduction

Mycotoxins are toxic secondary metabolites produced by various molds, such as *Aspergillus*, *Penicillium* and *Fusarium*, which may contaminate food and feed at all stages of the food/feed chain. Despite the improvement of good agricultural and manufacturing practices, mycotoxin contamination cannot be avoided and contaminants are virtually ubiquitous at some concentrations in the average human and animal diets (Bryden, 2012). A recent study performed on 1100 samples collected worldwide showed that about 70% of samples tested was contaminated (Streit et al., 2013). This result was confirmed on a smaller study realized on 83 feed ingredients sampled in China (Guan et al., 2011a).

The biological reactions following ingestion of mycotoxins vary from acute, overt diseases with high morbidity and mortality to chronic, insidious disorders with reduced animal productivity. Different mycotoxins target different organs, inducing various toxic effects. At high doses, mycotoxins exposure leads to general cytotoxicity, often related to macromolecule synthesis inhibition (Maresca and Fantini, 2010). Mycotoxins induce primary biochemical lesions and impact on early cellular functions/events in the cascade of events leading to toxic cell injury or cellular deregulation (Bryden, 2012). At low doses, mycotoxins affect the functions of various tissues and organs, such as the gastrointestinal tract, liver or kidney tissues, as well as the nervous, reproductive and immune systems. Some mycotoxins also have genotoxic, carcinogenic and teratogenic effects (Maresca and Fantini, 2010).

Mycotoxins contamination levels in pig feedstuffs are usually not high enough to cause an overt disease but may result in economical loss through changes in growth, production and immunosuppression (Bryden, 2012; Oswald et al., 2005; Wild and Gong, 2010).

Pigs are very sensitive to mycotoxins. Due to their high consumption of cereals, they are exposed to these toxins and to a chronic contamination. In Europe, regulation and/or recommendations exist for 6 mycotoxins that may be present in pig feed:

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aflatoxins (AF), ochratoxin A (OTA), fumonisins (FB), zearalenone (ZEN) and trichothecenes (principally deoxynivalenol [DON], T-2 and HT-2 toxins) (Bennett and Klich, 2003).

This review summarizes the main effects induced by mycotoxins present in pig feed on immunity and determines the consequences of this immunomodulation in terms of susceptibility to infectious diseases, reactivation of chronic infection and vaccine efficacy.

2. Effect of major mycotoxins on the pig immune response

2.1. Aflatoxins

Aflatoxins are hepatotoxic and carcinogenic; they also display immunotoxic properties. These toxins impair both the innate and the acquired immune responses (Meissonnier et al., 2006; Weaver et al., 2013). The dysregulation of the antigen-presenting capacity of dendritic cells, which is starting from aflatoxin B1 (AFB1) low dose exposure, is deemed to be the mechanism by which the mycotoxin impairs cell-mediated immunity (Mehrzhad et al., 2014). An exposition to AF increases the T-cell proliferation-inducing capacity of porcine monocyte-derived dendritic cells, thus enhances presenting capacity of cells (Mehrzhad et al., 2015).

An alteration of the inflammatory response has been reported in pigs exposed to AF (Chaytor et al., 2011). A reduced synthesis of pro-inflammatory cytokines and an increase of anti-inflammatory ones was also demonstrated in weaning piglets fed for 4 weeks with low doses of AF (Marin et al., 2002). In utero exposure of piglets to this mycotoxin (through exposition of sows), the functional capacities of both macrophages and neutrophils were altered (Silvotti et al., 1997).

Experimentally, in a pig model vaccinated with a model antigen, which was ovalbumin (OVA), AFB1 exposure had no major effect on humoral immunity with unchanged plasma concentrations of total immunoglobulin A (IgA), IgG and IgM and the specific anti-OVA IgG. In these animals, the toxin exposure did not impair the mitogenic response of lymphocytes but delayed and decreased the OVA-specific proliferation, suggesting an impaired lymphocyte activation in pigs exposed to AFB1 (Meissonnier et al., 2008b). Similarly, in pigs vaccinated with *Mycoplasma*, the exposure to lower levels of AFB1 did not modulate the antigen-specific and total antibody response (Marin et al., 2002). Developing piglets are very susceptible to this mycotoxin. Indeed, after sows exposure to AF, the global piglets lympho-proliferative response upon mitogenic stimulation is reduced (Silvotti et al., 1997).

2.2. Trichothecenes

Type B trichothecenes, including DON, have the capacity to up- and down-regulate immune functions by disrupting intracellular signaling within leukocytes (Pestka, 2010). Depending on the dose, frequency and duration of exposure, DON will have either an immunostimulatory or immunosuppressing effect (Pestka et al., 2004). Deoxynivalenol is able to induce an inflammatory response by acting on the ribosome, inducing a Ribotoxic stress which activates the MAPK pathway, eliciting expression of inflammation-related genes as pro-inflammatory cytokines (Pestka et al., 2004; Pestka, 2010).

In mice, this toxin induced a pronounced elevation in serum IgA (Pestka et al., 2004). In pigs, a similar increase of IgA in the serum of animals receiving DON contaminated feed has been observed (Drochner et al., 2004; Pinton et al., 2008; Swamy et al., 2003). In animals immunized with OVA, the specific immune response was investigated during a DON exposure inducing no feed refusal or reduced body weight gain. Ingestion of DON increased the plasma concentration of total and anti-OVA IgA titers. Deoxynivalenol did

not modulate lymphocytes proliferation after mitogenic stimulation, but the toxin had a biphasic effect on the OVA-specific lymphocyte proliferation: An up-regulation in the days after OVA immunization but a down-regulation in the weeks following (Pinton et al., 2008).

Another study on pigs immunized with OVA showed an increase of anti-OVA IgG titers, after 42 days of exposure to a DON contaminated diet. Simultaneously, the expressions of chemokines involved in inflammatory reactions (interleukin-8 (IL-8), chemokine (C-X-C motif) ligand 20 (CXCL20), interferon- γ (IFN- γ)) were up-regulated. Deoxynivalenol also up-regulated the gene of major antioxidant glutathione peroxidase 2 (GPX-2) and down-regulated expression of genes encoding enzymatic antioxidants including GPX-3, GPX-4 and superoxide dismutase 3 (SOD-3), involved in oxidative stress (Lessard et al., 2015).

Type A trichothecenes such as T-2 toxin are cytotoxic molecules and potent protein inhibitors. In pigs immunized with OVA, sub-clinical doses of T-2 toxin induced an early and transient increase of total IgA plasma concentration but a decrease in the anti-OVA IgG titer (Meissonnier et al., 2008a). For higher doses of exposure, T-2 toxin had been previously shown to decrease both the mitogenic and the antigen-specific lymphocytes proliferation following a horse globulin immunization (Rafai et al., 1995).

2.3. Fumonisins

Fumonisins induce various toxic effects depending on the animal species, and there is evidence for the carcinogenicity of these toxins (Stockmann-Juvala and Savolainen, 2008). In *in vitro* and *in vivo* experiments, fumonisin B1 (FB1) modifies the Th1/Th2 (T-helper 1/T-helper 2) cytokine balance in pigs similar to an impaired humoral response (Marin et al., 2006; Taranu et al., 2005). With pigs vaccinated against *Mycoplasma* and exposed to FB1 (8 mg/kg feed for 4 weeks), a sex-related difference in the specific immune response has also been observed. In male pigs but not for female ones, exposure to the toxin reduced the vaccine-specific antibody titer (Marin et al., 2006). However, ingestion of contaminated feed had no effect on the serum concentrations of total IgG, IgA, and IgM.

Studies have also demonstrated that FB1 influences the inflammatory response. For example, incubation of swine alveolar macrophages with FB1 led to a significant reduction of the number of viable cells and cell death by apoptosis (Liu et al., 2002). An *in vivo* experiment on pigs exposed to FB (6 mg/kg feed for 5 weeks) showed a decrease of IL-1 β and IL-6 genes expression in spleen tissue (Grenier et al., 2011).

Fumonisin B1 also impairs on the maturation of antigen presenting cells *in vivo* by reducing the intestinal expression of IL-12p40 and decreasing the upregulation of major histocompatibility complex class II molecule (MHC-II) with a reduction of T cell stimulatory capacity upon stimulation (Devriendt et al., 2009).

2.4. Ochratoxin A

Ochratoxin A is mainly toxic for kidney and liver. Gilts fed OTA-contaminated had reduced cutaneous basophil hypersensitivity response to phytohemagglutinin, reduced delayed hypersensitivity to tuberculin, decreased stimulation index for lymphoblastogenesis, decreased interleukin-2 production when lymphocytes were stimulated with concanavalin A, and decreased number and phagocytic activity of macrophages. Ochratoxin A was shown to be toxic on purified lymphocytes of pigs with an half maximal inhibitory concentration (IC50), concentration producing 50% inhibition of cell proliferation, of 1.3 μ M (Kebly et al., 2004).

Ochratoxin A show an impact on the cytokine expression. An experiment on weaned pigs that ingested an OTA contaminated

diet (181 ng/g of feed) has shown an increased level of TNF-alpha and IL-10 in plasma, with a decreased capacity to respond with cytokine expression to *ex vivo* challenge with lipopolysaccharides (LPS) (Bernardini et al., 2014). By contrast, OTA has no effect on total and specific immunoglobulin concentrations (Harvey et al., 1992).

2.5. Zearalenone

Zearalenone is best known for its toxic effect on reproduction and fertility (Zinedine et al., 2007); it induces an estrogenic activity on animal (Fink-Gremmels and Malekinejad, 2007). Pigs are particularly sensitive to ZEN, which can induce edematous swelling and reddening of vulva, prolapse of the vulva, ovarian follicle damage and abortions (Schoevers et al., 2012; Zinedine et al., 2007).

Only few papers described the effect of ZEN on immunity (Eriksen and Alexander, 1998). In pigs, exposure of intestinal epithelial cells ZEN (25 μ M) has a tendency to increase the synthesis of the inflammatory cytokines IL-8 and IL-10 (Marin et al., 2015). Sows exposed to high concentration of ZEN (5–250 mg/kg feed or 200–1000 μ g/kg BW per day) can develop a chronic inflammation of the genital tract (EFSA, 2011).

3. Consequence of mycotoxin induced immunomodulation for pig health

3.1. Susceptibility to infectious diseases

The broad immunosuppressive effect of mycotoxins may decrease host resistance to infectious diseases (Antonissen et al., 2014). Table 1 summarizes the data obtained in pigs.

Table 1
Influence of mycotoxins on susceptibility to infectious diseases in pig.

Mycotoxin	Exposure dose	Exposure period	Pathogen	Effect compared with negative control	References
AFB1	0.07 and 0.14 mg/kg	32 days	<i>Brachyspira hyodysenteriae</i>	↓ of incubation period for dysentery, ↑ diarrhea and dysentery time, ↑ death, visible clinical signs and lesions of dysentery at necropsy	Joens et al., 1981
AF	1.3 mg/kg feed	25 days	<i>Erysipelothrix rhusiopathiae</i>	↑ the severity of bacterial infection	Cysewski et al., 1978
DON	2.5 mg/kg feed	3 weeks	PCV2	↑ viremia and lung viral load no clinical effect	Savard et al., 2015b
DON	3.5 mg/kg feed	3 weeks	PRRSV	↓ weight gain, ↑ lung lesions and mortality, no effect on viral replication	Savard et al., 2014
DON	1 μ g/mL	6 h	<i>Salmonella typhimurium</i>	synergistic ↑ gene expression <i>IL-12, TNF-α, IL-1β, IL-8, MCP-1 and IL-6</i>	Vandenbroucke et al., 2011
T-2 toxin	15 and 83 μ g/kg feed	23 days	<i>Salmonella typhimurium</i>	↓ colonization of the cecum	Verbrugghe et al., 2012
FB1	10 mg/kg feed	3 days	<i>Bordetella bronchiseptica</i> & <i>Pasteurella multocida</i> (type D)	↑ extent and severity of the pathological changes	Posa et al., 2011
FB1	0.5 mg/kg BW	6 days	<i>Escherichia coli</i> (SEPEC)	↑ intestinal colonization; ↑ translocation to the mesenteric lymph node, lung, liver and spleen	Oswald et al., 2003
FB1	1 mg/kg BW	10 days	<i>Escherichia coli</i> (ETEC)	intestinal infection prolonged; impaired function of intestinal antigen presenting cells	Devriendt et al., 2009
FB1	25.4 mg/kg feed	42 days	<i>Mycoplasma hyopneumoniae</i>	↑ severity of the pathological changes	Posa et al., 2013
FB1	0.5 mg/kg BW	7 days	<i>Pasteurella multocida</i> (type A)	↓ growth rate and ↑ coughing; ↑ total number of cells, number of macrophages and lymphocytes in BALF; ↑ gross pathological lesions and histopathological lesion of lung	Halloy et al., 2005
FB1	12 mg/kg BW	18 days	PRRSV	↑ histopathological lesions of lungs	Ramos et al., 2010
FB1	11.8 mg/kg feed	9 weeks	<i>Salmonella typhimurium</i>	Modification of the microbiota profiles	Burel et al., 2013
OTA	3 mg/kg feed	3 weeks	<i>Brachyspira hyodysenteriae</i> & <i>Camphylobacter coli</i>	Salmonellosis arises spontaneously in animals fed the contaminated diet, clinical and patho-morphological changes (typical of salmonellosis), change of hematological and biological parameters	Stoef et al., 2000
OTA	75 μ g/kg feed	42 days	PCV2	↑ PCV2 replication in serum and tissues	Gan et al., 2015

AFB1 = aflatoxin B1; AF = aflatoxins; DON = deoxynivalenol; FB1 = fumonisin B1; OTA = ochratoxin A; BW = body weight; PCV2 = porcine circovirus type 2; PRRSV = porcine reproductive and respiratory syndrome virus.

In pigs, the consumption of feed contaminated with AF increases the severity of infection with *Erysipelothrix rhusiopathiae* (Cysewski et al., 1978). Similarly, during an experimental infection with *Brachyspira hyodysenteriae*, the consumption of AF reduced the incubation time and increased the severity of diarrhea (Joens et al., 1981).

In presence of porcine circovirus type 2 (PCV2) virus, DON increases the severity of the viral infection, and in presence of the porcine reproductive and respiratory syndrome virus (PRRSV) it also increases the infection with more tissue lesions induced (Savard et al., 2014, 2015b). During a bacterial infection, DON enhances the inflammatory reaction with an increased production of pro-inflammatory cytokines (Vandenbroucke et al., 2011). The elevation of circulating IgA in presence of low quantity of DON may, by contrast, increase the resistance to certain pathogens. Indeed, IgA initiates rapid and transient up-regulation of many immune related genes (Pestka et al., 2004).

In pigs, FB1 ingestion can induce intestinal infections, with some intestinal functions affected (Burel et al., 2013; Devriendt et al., 2009; Oswald et al., 2003). The ingestion of FB1-contaminated feed was also associated with an increased susceptibility to pulmonary infection and an increase of the severity of the pathological changes with bacterial or viral pathogens (Devriendt et al., 2009; Halloy et al., 2005; Oswald et al., 2003; Posa et al., 2011, 2013; Ramos et al., 2010).

Ingestion of OTA contaminated feed also increases susceptibility to natural infectious disease. Indeed, salmonellosis arose spontaneously in all piglets receiving an OTA contaminated diet, and when the animals were vaccinated against salmonellosis, the consumption of contaminated feed leads to spontaneous *Brachyspira*

hyodysenteriae and *Campylobacter coli* infections (Stoev et al., 2000). During a PCV2 infection, OTA increases the viremia in sera and tissues (Gan et al., 2015).

To the best of our knowledge, there are no data available concerning the effect of ZEN on *in vivo* analysis on mice which were fed 10 mg/kg ZEA (1.5 mg/kg BW per day) during 2 weeks, infected with *Listeria monocytogenes*, and showed a decreased resistance to *Listeria* with an increasing trend of the splenic bacterial counts, compared with control animals (Pestka et al., 1987).

3.2. Reactivation of chronic infection

The effect of mycotoxin intoxication on the reactivation of chronic infection was also investigated. However, the experiment was not performed with pigs but with rodents. In the immunocompetent host, *Toxoplasma gondii* infection progresses to a chronic phase characterized by the presence of encysted parasites. Cyst rupture may occur, but infection remains latent and reactivation is prevented. In immunosuppressed animal and human subjects, such as patients infected with the human immunodeficiency virus, rupture is associated with the formation of new cysts and disease. Low and repeated doses of either AFB1 or T-2 toxin are able to accelerate *Toxoplasma* cyst rupture in previously infected mice (Venturini et al., 1996).

3.3. Vaccination efficacy

Immunity acquired through vaccination can also be impaired by mycotoxin ingestion (Table 2). For example, AFB1 interferes with the development of acquired immunity in swine following erysipelas vaccination with bacterin preparation (a suspension of killed bacteria) of *E. rhusiopathiae* (Cysewski et al., 1978). As already mentioned, ingestion of feed contaminated with AFB1 or T-2 Toxin reduced the vaccine response to the model antigen, ovalbumin, acting on the cellular and the humoral response respectively (Meissonnier et al., 2008a, 2008b). Ingestion of low

doses of another mycotoxin, FB1, decreases the specific antibody response mounted during *Mycoplasma* vaccination in pigs (Taranu et al., 2005). In pigs exposed to OTA or FB1 and vaccinated against Aujeszky disease (Suid Herpesvirus 1 [SuHV1]), the humoral immune response was greatly disturbed, with a strong decrease in antibody observed (Stoev et al., 2012). In diet contaminated with DON or FB1, pigs showed an alteration of the specific immune response upon vaccination with OVA (Grenier et al., 2011).

Likewise, feeding pigs a DON-contaminated diet was shown to inhibit the vaccination efficiency of PRRSV modified live vaccine by severely impairing viral replication (Savard et al., 2015a).

It should also be mentioned that the vaccine immune response is altered at mycotoxin doses that do not alter the global immune response (Meissonnier et al., 2008a, 2008b; Taranu et al., 2005). The breakdown in vaccine immunity and may lead to the occurrence of disease even in properly vaccinated flocks. These reactions are of considerable consequence in animals for which we rely on an effective vaccination program for disease prevention.

4. The problem of mycotoxins co-contamination

In the above paragraphs, the effects of single mycotoxin on immunity were described. However, mycotoxins often co-occur and animals are exposed to several mycotoxins at the same time. Indeed, raw materials can be contaminated by several fungi, which are able to simultaneously produce several mycotoxins, and in addition the diet of animal is composed of several commodities (Allassane-Kpembi et al., 2015, 2016). A worldwide survey on 7049 samples reported that 48% of feed and feedstuff samples are contaminated by 2 or more mycotoxins (Rodrigues and Naehrer, 2012). Other studies showed that 75%–100% of animal feed samples are contaminated with more than one mycotoxin (Guan et al., 2011a; Streit et al., 2012).

The toxicity of mycotoxins mixtures cannot always be predicted based upon their individual toxicities. It can be antagonistic,

Table 2
Influence of mycotoxins on vaccination efficacy in pigs.

Mycotoxin	Exposure dose	Antigen	Effect compared with negative control	References
AF	1.3 mg/kg feed	<i>Erysipelothrix rhusiopathiae</i>	Interfered on the development of acquired immunity,	Cysewski et al., 1978
AFB1	385–1807 µg/kg feed	OVA	Decreased and delayed cell-mediated immunity	Meissonnier et al., 2008b
DON	3.5 mg DON/kg feed	OVA	Increased OVA-primary IgG antibody response	Lessard et al., 2015
DON	2.5–3.5 mg/kg BW	PRRSV	Decreased PRRSV post-vaccinal viremia and reduced vaccinal efficacy	Savard et al., 2015b
DON	2.2–2.5 mg DON/kg feed	OVA	Increased concentration of OVA specific IgA and IgG	Pinton et al., 2008
DON	0.6–4.7 mg DON/kg	Human serum albumin, sheep red blood cells, paratuberculosis vaccine, tetanus toxoid and diphtheria toxoid	Significant dose-dependent reduction in secondary antibody response to tetanus toxoid	Overnes et al., 1997
DON + ZEN	2.1–3.2 mg DON/kg diet and 0.06–0.25 mg ZEN/kg diet	Parvovirus	No effect	Gutzwiller et al., 2007
DON or FB1	3 mg DON/kg feed or 6 mg FB1/kg feed	OVA	Reduced anti-OVA antibody production with a decrease of lymphocytes proliferation	Grenier et al., 2011
T-2 toxin	1324–2102 µg/kg feed	OVA	Reduced anti-OVA antibody production without significant alteration to specific lymphocyte proliferation	Meissonnier et al., 2008a
FB1	8 mg/kg BW	<i>Mycoplasma agalactiae</i>	Decreased specific antibody titer	Taranu et al., 2005
OTA	1 mg/kg feed	<i>Salmonella choleraesuis</i>	Immunosuppression and delayed response to immunization	Stoev et al., 2000
OTA or FB1	0.5 mg OTA/kg feed or 10 mg FB1/kg feed	Suid Herpesvirus 1 (Aujeszky disease)	Decreased anti-SuHV1 antibody production after vaccination	Stoev et al., 2012

AF = aflatoxins; AFB1 = aflatoxin B1; DON = deoxynivalenol; ZEN = zearalenone; OTA = ochratoxin A; BW = body weight; OVA = ovalbumin; PRRSV = porcine reproductive and respiratory syndrome virus; OVA = ovalbumin.

additive or synergistic and increase the impact of each mycotoxin. The studies concerning the toxicity of mycotoxins mixture on pig immune response are scarce. Reduction of lymphocyte proliferation has been investigated in several pig *in vivo* studies, and different type of interaction were observed: additivity (co-exposure to AF and FB [0.05 and 30 mg/kg feed] for one month; co-exposure to OTA and T-2 toxin [2.5 and 8 mg/kg feed] for 30 days) or synergy (co-exposure to FB and DON [50 and 4 mg/kg feed] for 28 days) (Grenier and Oswald, 2011). In animals co-exposed to DON and FB (6 and 3 mg/kg of feed) for 35 days, synergistic interaction was observed on lymphocytes proliferation upon mitogenic stimulation, additive interaction on cytokines expression (IL-8; IL-1 β , IL-6 and macrophage inflammatory protein 1 β) and antagonistic interaction on levels of specific IgA and cytokine expression (Grenier et al., 2011).

In animals co-exposed to DON and FB (6 and 3 mg/kg of feed) for 35 days, additive interaction on specific IgG, on lymphocytes proliferation upon mitogenic stimulation and on cytokines expression (IL-8, IL-1 β , IL-6 and macrophage inflammatory protein 1 β) was observed, and antagonistic interaction on levels of specific IgA was observed (Grenier et al., 2011).

5. Conclusion

Mycotoxins can contaminate many raw materials and cause significant health risk to animals. Numerous strategies are used to minimize mycotoxins contamination throughout the feed chain. In the fields, resistant crops associated as well as agronomic control measures can be used. Similarly, during feed storage and processing, physical, chemical and biological methods can reduce mycotoxin contamination. However once mycotoxins are present in feed, it's difficult to reduce their concentrations and their toxicity due to the stability of these compounds (Bryden, 2009). The simultaneous presence of several mycotoxins, not sensitive to the same detoxification procedure, also increases the difficulty to control animals' exposure to mycotoxins (Bryden, 2012). Recently, new detoxification biological methods showed that the use of bacteria (Grenier et al., 2012, 2013; Guan et al., 2011b), feed additives such as arginine or glutamate were effective to decrease the toxic effects of mycotoxins in young pigs (Duan et al., 2014; Wu et al., 2013, 2015), even for exposition to mycotoxins mixtures (Yin et al., 2014; Grenier et al., 2013).

Pig, a species very sensitive to mycotoxins, is really exposed due to a cereal rich diet. At the European level, regulation or recommendations exist for 6 mycotoxins that are often present in pig feed. They are FB, AF, OTA, DON, T-2/HT-2 toxins and ZEN. Exposure to these toxins induces several toxic effects on pig, including a modulation of the immune response. This later effect increases the susceptibility and severity of infectious diseases, and reduces the efficacy of vaccines. This is of particular note for animal husbandry because during infection, nutrients are used for the immune system instead of growth and development (Klasing, 2007). Consequently, mycotoxin contamination also has an indirect effect on animal productivity (Klasing, 2007; Oswald et al., 2005).

The presence of new mycotoxins (emerging, masked, modified toxins, etc.) revealed by new analytical methods can also increase the risk for pig health. Currently, very few studies document the occurrence and toxicity of these toxins, thus there is a need to determine the risk they represent in pig production (Broekaert et al., 2015; Pierron et al., 2016).

Conflict of interest

The authors declare that they have no competing interests.

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References

- Alassane-Kpembi I, Puel O, Oswald IP. Toxicological interactions between the mycotoxins deoxynivalenol, nivalenol and their acetylated derivatives in intestinal epithelial cells. *Arch Toxicol* 2015;89:1337–46.
- Alassane-Kpembi I, Schatzmayr G, Taranu I, Marin D, Puel O, Oswald IP. Mycotoxins co-contamination: methodological aspects and biological relevance of combined toxicity studies. *Crit Rev Food Sci Nutr* 2016. <http://dx.doi.org/10.1080/10408398.2016.1140632>.
- Antonissen G, Martel A, Pasmans F, Ducatelle R, Verbrugge E, Vandenbroucke V, et al. The impact of Fusarium mycotoxins on human and animal host susceptibility to infectious diseases. *Toxins (Basel)* 2014;6:430–52.
- Bennett JW, Klich M. Mycotoxins. *Clin Microbiol Rev* 2003;16:497–516.
- Bernardini C, Grilli E, Duvigneau JC, Zannoni A, Tugnoli B, Gentilini F, et al. Cellular stress marker alteration and inflammatory response in pigs fed with an ochratoxin contaminated diet. *Res Vet Sci* 2014;97:244–50.
- Broekaert N, Devreese M, De Baere S, De Backer P, Croubels S. Modified Fusarium mycotoxins unmasked: from occurrence in cereals to animal and human excretion. *Food Chem Toxicol* 2015;80:17–31.
- Bryden WL. Mycotoxins and mycotoxicoses: significance, occurrence and mitigation in the food chain. In: Ballantyne B, Marrs T, Syversen T, editors. *General and applied toxicology*. 3rd ed. Chichester, UK: John Wiley & Sons Ltd; 2009. p. 3529–53.
- Bryden WL. Mycotoxin contamination of the feed supply chain: implications for animal productivity and feed security. *Animal Feed Sci Technol* 2012;173:134–58.
- Burel C, Tanguy M, Guerre P, Boilletot E, Cariolet R, Queguiner M, et al. Effect of low dose of fumonisin on pig health: immune status, intestinal microbiota and sensitivity to Salmonella. *Toxins (Basel)* 2013;5:841–64.
- Chaytor AC, See MT, Hansen JA, de Souza AL, Middleton TF, Kim SW. Effects of chronic exposure of diets with reduced concentrations of aflatoxin and deoxynivalenol on growth and immune status of pigs. *J Anim Sci* 2011;89:124–35.
- Cysewski SJ, Wood RL, Pier AC, Baetz AL. Effects of aflatoxin on the development of acquired immunity to swine erysipelas. *Am J Vet Res* 1978;39:445–8.
- Devriendt B, Gallois M, Verdonck F, Wache Y, Bimczok D, Oswald IP, et al. The food contaminant fumonisin B(1) reduces the maturation of porcine CD11R1(+) intestinal antigen presenting cells and antigen-specific immune responses, leading to a prolonged intestinal ETEC infection. *Vet Res* 2009;40:40.
- Drochner W, Schollenberger M, Piepho HP, Gotz S, Lauber U, Tafaj M, et al. Serum IgA-promoting effects induced by feed loads containing isolated deoxynivalenol (DON) in growing piglets. *J Toxicol Environ Health A* 2004;67:1051–67.
- Duan J, Yin J, Wu M, Liao P, Deng D, Liu G, et al. Dietary glutamate supplementation ameliorates mycotoxin-induced abnormalities in the intestinal structure and expression of amino acid transporters in young pigs. *PLoS One* 2014;9:e112357.
- EFSA. Scientific Opinion on the risks for public health related to the presence of zearalenone in food. *EFSA J* 2011;9:2197.
- Eriksen GS, Alexander JA. In: *Nordic Council of Ministers, editor. Fusarium Toxins in Cereal – A Risk assessment*, vol. 502. Copenhagen: Tema Nord; 1998. p. 7–58.
- Fink-Gremmels J, Malekinejad H. Clinical effects and biochemical mechanisms associated with exposure to the mycoestrogen zearalenone. *Anim Feed Sci Technol* 2007;137:326–41.
- Gan F, Zhang Z, Hu Z, Hesketh J, Xue H, Chen X, et al. Ochratoxin A promotes porcine circovirus type 2 replication in vitro and in vivo. *Free Radic Biol Med* 2015;80:33–47.
- Grenier B, Loureiro-Bracarense AP, Luciola J, Pacheco GD, Cossalter AM, Moll WD, et al. Individual and combined effects of subclinical doses of deoxynivalenol and fumonisins in piglets. *Mol Nutr Food Res* 2011;55:761–71.
- Grenier B, Oswald IP. Mycotoxin co-contamination of foods and feeds: meta-analysis of publications describing toxicological interactions. *World Mycotoxin J* 2011;4:285–313.
- Grenier B, Bracarense AP, Schwartz HE, Trumel C, Cossalter AM, Schatzmayr G, et al. The low intestinal and hepatic toxicity of hydrolyzed fumonisin B(1) correlates with its inability to alter the metabolism of sphingolipids. *Biochem Pharmacol* 2012;83:1465–73.
- Grenier B, Bracarense AP, Schwartz HE, Luciola J, Cossalter AM, Moll WD, et al. Biotransformation approaches to alleviate the effects induced by fusarium mycotoxins in swine. *J Agric Food Chem* 2013;61:6711–9.
- Guan S, Gong M, Yin Y, Huang R, Ruan Z, Zhou T, et al. Occurrence of mycotoxins in feeds and feed ingredients in China. *J Food, Agric Environ* 2011a;9:163–7.

- Guan S, Zhou T, Yin Y, Xie M, Ruan Z, Young JC. Microbial strategies to control aflatoxins in food and feed. *World Mycotoxin J* 2011b;4:413–24.
- Gutzwiller A, Czeglédi L, Stoll P, Bruckner L. Effects of Fusarium toxins on growth, humoral immune response and internal organs in weaner pigs, and the efficacy of apple pomace as an antidote. *J Anim Physiol Anim Nutr* 2007;91:432–8.
- Halloy DJ, Gustin PG, Bouhet S, Oswald IP. Oral exposure to culture material extract containing fumonisins predisposes swine to the development of pneumonitis caused by *Pasteurellamultocida*. *Toxicology* 2005;213:34–44.
- Harvey RB, Elissalde MH, Kubena LF, Weaver EA, Corrier DE, Clement BA. Immunotoxicity of ochratoxin A to growing gilts. *Am J Vet Res* 1992;53:1966–70.
- Joens LA, Pier AC, Cutlip RC. Effects of aflatoxin consumption on the clinical course of swine dysentery. *Am J Vet Res* 1981;42:1170–2.
- Keblyns M, Bernhoft A, Hofer CC, Morrison E, Larsen HJ, Flaoyen A. The effects of the Penicillium mycotoxins citrinin, cyclopiazonic acid, ochratoxin A, patulin, penicillic acid, and roquefortine C on in vitro proliferation of porcine lymphocytes. *Mycopathologia* 2004;158:317–24.
- Klasing KC. Nutrition and the immune system. *Br Poult Sci* 2007;48:525–37.
- Lessard M, Savard C, Deschene K, Lauzon K, Pinilla VA, Gagnon CA, et al. Impact of deoxynivalenol (DON) contaminated feed on intestinal integrity and immune response in swine. *Food Chem Toxicol* 2015;80:7–16.
- Liu BH, Yu FY, Chan MH, Yang YL. The effects of mycotoxins, fumonisin B1 and aflatoxin B1, on primary swine alveolar macrophages. *Toxicol Appl Pharmacol* 2002;180:197–204.
- Maresca M, Fantini J. Some food-associated mycotoxins as potential risk factors in humans predisposed to chronic intestinal inflammatory diseases. *Toxicol* 2010;56:282–94.
- Marin DE, Taranu I, Bunaci RP, Pascale F, Tudor DS, Avram N, et al. Changes in performance, blood parameters, humoral and cellular immune responses in weanling piglets exposed to low doses of aflatoxin. *J Anim Sci* 2002;80:1250–7.
- Marin DE, Taranu I, Pascale F, Lionide A, Burlacu R, Bailly JD, et al. Sex-related differences in the immune response of weanling piglets exposed to low doses of fumonisin extract. *Br J Nutr* 2006;95:1185–92.
- Marin DE, Motiu M, Taranu I. Food contaminant zearalenone and its metabolites affect cytokine synthesis and intestinal epithelial integrity of porcine cells. *Toxins (Basel)* 2015;7:1979–88.
- Mehrzad J, Devriendt B, Baert K, Cox E. Aflatoxin B(1) interferes with the antigen-presenting capacity of porcine dendritic cells. *Toxicol Vitro* 2014;28:531–7.
- Mehrzad J, Devriendt B, Baert K, Cox E. Aflatoxins of type B and G affect porcine dendritic cell maturation in vitro. *J Immunotoxicol* 2015;12:174–80.
- Meissonnier GM, Marin DE, Galtier B, Bertin G, Taranu I, Oswald IP. Modulation of the immune response by a group of fungal food contaminant, the aflatoxins. In: Mengheri E, Roselli M, Bretti MS, Finamore A, editors. *Nutrition and immunity*; 2006. p. 147–66.
- Meissonnier GM, Laffitte J, Raymond I, Benoit E, Cossalter AM, Pinton P, et al. Subclinical doses of T-2 toxin impair acquired immune response and liver cytochrome P450 in pigs. *Toxicology* 2008a;247:46–54.
- Meissonnier GM, Pinton P, Laffitte J, Cossalter AM, Gong YY, Wild CP, et al. Immunotoxicity of aflatoxin B1: impairment of the cell-mediated response to vaccine antigen and modulation of cytokine expression. *Toxicol Appl Pharmacol* 2008b;231:142–9.
- Oswald IP, Desautels C, Laffitte J, Fournout S, Peres SY, Odin M, et al. Mycotoxin fumonisin B1 increases intestinal colonization by pathogenic *Escherichia coli* in pigs. *Appl Environ Microbiol* 2003;69:5870–4.
- Oswald IP, Marin DE, Bouhet S, Pinton P, Taranu I, Accensi F. Immunotoxicological risk of mycotoxins for domestic animals. *Food Addit Contam* 2005;22:354–60.
- Overnes G, Matre T, Sivertsen T, Larsen HJ, Langseth W, Reitan LJ, et al. Effects of diets with graded levels of naturally deoxynivalenol-contaminated oats on immune response in growing pigs. *Zentralbl Veterinarmed A* 1997;44:539–50.
- Pestka JJ, Tai JH, Witt MF, Dixon DE, Forsell JH. Suppression of immune response in the B6C3F1 mouse after dietary exposure to the Fusarium mycotoxins deoxynivalenol (vomitoxin) and zearalenone. *Food Chem Toxicol* 1987;25:297–304.
- Pestka JJ, Zhou HR, Moon Y, Chung YJ. Cellular and molecular mechanisms for immune modulation by deoxynivalenol and other trichothecenes: unraveling a paradox. *Toxicol Lett* 2004;153:61–73.
- Pestka JJ. Deoxynivalenol: mechanisms of action, human exposure, and toxicological relevance. *Arch Toxicol* 2010;84:663–79.
- Pierron A, Mimoun S, Murate LS, Loiseau N, Lippi Y, Bracarense AF, et al. Intestinal toxicity of the masked mycotoxin deoxynivalenol-3-beta-D-glucoside. *Arch Toxicol* 2016. <http://dx.doi.org/10.1007/s00204-015-1592-8>.
- Pinton P, Accensi F, Beauchamp E, Cossalter A-M, Callu P, Grosjean Fo, et al. Ingestion of deoxynivalenol (DON) contaminated feed alters the pig vaccinal immune responses. *Toxicol Lett* 2008;177:215–22.
- Posa R, Donko T, Bogner P, Kovacs M, Repa I, Magyar T. Interaction of *Bordetella bronchiseptica*, *Pasteurella multocida*, and fumonisin B1 in the porcine respiratory tract as studied by computed tomography. *Can J Vet Res* 2011;75:176–82.
- Posa R, Magyar T, Stoev SD, Glavits R, Donko T, Repa I, et al. Use of computed tomography and histopathologic review for lung lesions produced by the interaction between *Mycoplasma hyopneumoniae* and fumonisin mycotoxins in pigs. *Vet Pathol* 2013;50:971–9.
- Rafai P, Tuboly S, Bata A, Tilly P, Vanyi A, Papp Z, et al. Effect of various levels of T-2 toxin in the immune system of growing pigs. *Vet Rec* 1995;136:511–4.
- Ramos CM, Martinez EM, Carraso AC, Puento JHL, Quezada F, Perez JT, et al. Experimental trial of the effect of fumonisin B1 and PRRS virus in swine. *Vet Adv* 2010;9:1301–10.
- Rodrigues I, Naehrer K. A three-year survey on the worldwide occurrence of mycotoxins in feedstuffs and feed. *Toxins (Basel)* 2012;4:663–75.
- Savard C, Pinilla V, Provost C, Gagnon CA, Chorfi Y. In vivo effect of deoxynivalenol (DON) naturally contaminated feed on porcine reproductive and respiratory syndrome virus (PRRSV) infection. *Vet Microbiol* 2014;174:419–26.
- Savard C, Gagnon CA, Chorfi Y. Deoxynivalenol (DON) naturally contaminated feed impairs the immune response induced by porcine reproductive and respiratory syndrome virus (PRRSV) live attenuated vaccine. *Vaccine* 2015a;33:3881–6.
- Savard C, Provost C, Alvarez F, Pinilla V, Music N, Jacques M, et al. Effect of deoxynivalenol (DON) mycotoxin on in vivo and in vitro porcine circovirus type 2 infections. *Vet Microbiol* 2015b;176:257–67.
- Schoevers EJ, Santos RR, Colenbrander B, Fink-Gremmels J, Roelen BA. Trans-generational toxicity of Zearalenone in pigs. *Reprod Toxicol* 2012;34:110–9.
- Silvotti L, Petterino C, Bonomi A, Cabassi E. Immunotoxicological effects on piglets of feeding sows diets containing aflatoxins. *Vet Rec* 1997;141:469–72.
- Stockmann-Juvala H, Savolainen K. A review of the toxic effects and mechanisms of action of fumonisin B1. *Hum Exp Toxicol* 2008;27:799–809.
- Stoev SD, Goundasheva D, Mirtcheva T, Mantle PG. Susceptibility to secondary bacterial infections in growing pigs as an early response in ochratoxicosis. *Exp Toxicol Pathol* 2000;52:287–96.
- Stoev SD, Goundasheva D, Zarkov I, Mirtcheva T, Zapryanova D, Denev S, et al. Experimental mycotoxic nephropathy in pigs provoked by a mouldy diet containing ochratoxin A and fumonisin B1. *Exp Toxicol Pathol* 2012;64:733–41.
- Streit E, Schatzmayr G, Tassis P, Tzika E, Marin D, Taranu I, et al. Current situation of mycotoxin contamination and co-occurrence in animal feed—focus on Europe. *Toxins (Basel)* 2012;4:788–809.
- Streit E, Naehrer K, Rodrigues I, Schatzmayr G. Mycotoxin occurrence in feed and feed raw materials worldwide: long-term analysis with special focus on Europe and Asia. *J Sci Food Agric* 2013;93:2892–9.
- Swamy HV, Smith TK, MacDonald EJ, Karrow NA, Woodward B, Boermans HJ. Effects of feeding a blend of grains naturally contaminated with Fusarium mycotoxins on growth and immunological measurements of starter pigs, and the efficacy of a polymeric glucomannan mycotoxin adsorbent. *J Anim Sci* 2003;81:2792–803.
- Taranu I, Marin DE, Bouhet S, Pascale F, Bailly JD, Miller JD, et al. Mycotoxin fumonisin B1 alters the cytokine profile and decreases the vaccinal antibody titer in pigs. *Toxicol Sci* 2005;84:301–7.
- Vandenbroucke V, Croubels S, Martel A, Verbrugghe E, Goossens J, Van Deun K, et al. The mycotoxin deoxynivalenol potentiates intestinal inflammation by *Salmonella typhimurium* in porcine ileal loops. *PLoS One* 2011;6:e23871.
- Venturini MC, Quiroga MA, Risso MA, Lorenzo CD, Omata Y, Venturini L, et al. Mycotoxin T-2 and aflatoxin B1 as immunosuppressors in mice chronically infected with *Toxoplasma gondii*. *J Comp Pathol* 1996;115:229–37.
- Verbrugghe E, Vandenbroucke V, Dhaenens M, Shearer N, Goossens J, De Saeger S, et al. T-2 toxin induced *Salmonella typhimurium* intoxication results in decreased *Salmonella* numbers in the cecum contents of pigs, despite marked effects on *Salmonella*-host cell interactions. *Vet Res* 2012;43:22.
- Weaver AC, See MT, Hansen JA, Kim YB, De Souza AL, Middleton TF, et al. The use of feed additives to reduce the effects of aflatoxin and deoxynivalenol on pig growth, organ health and immune status during chronic exposure. *Toxins (Basel)* 2013;5:1261–81.
- Wild CP, Gong YY. Mycotoxins and human disease: a largely ignored global health issue. *Carcinogenesis* 2010;31:71–82.
- Wu L, Wang W, Yao K, Zhou T, Yin J, Li T, et al. Effects of dietary arginine and glutamine on alleviating the impairment induced by deoxynivalenol stress and immune relevant cytokines in growing pigs. *PLoS One* 2013;8:e69502.
- Wu L, Liao P, He L, Feng Z, Ren W, Yin J, et al. Dietary L-arginine supplementation protects weanling pigs from deoxynivalenol-induced toxicity. *Toxins (Basel)* 2015;7:1341–54.
- Yin J, Ren W, Duan J, Wu L, Chen S, Li T, et al. Dietary arginine supplementation enhances intestinal expression of SLC7A7 and SLC7A1 and ameliorates growth depression in mycotoxin-challenged pigs. *Amino Acids* 2014;46:883–92.
- Zinedine A, Soriano JM, Molto JC, Manes J. Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearalenone: an oestrogenic mycotoxin. *Food Chem Toxicol* 2007;45:1–18.