The ban of medicated ZnO in piglet diets: consequences & solutions

Weaning is a stressful period during swine production, which can render piglets susceptible to physiological and pathological imbalances of the gastro-intestinal functionality, and can lead to post-weaning diarrhoea (PWD). For more than 30 years, the use of zinc oxide (ZnO) has been a common practice in pig production throughout the world to prevent PWD in piglets.

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However, after all these years of use, the mechanisms by which ZnO can effectively prevent diarrhoea have still not been completely elucidated. This may be due to the polyvalent nature of the working mechanism in the gut of piglets. Microbiota modulation is thought to be one of the main pathways by which ZnO helps control PWD.

It seems ZnO acts by increasing the microbiota diversity of the gut, thereby creating competition with the colonisation of E. coli, the main cause of PWD. But other modes of action have also been described, such as the reduction of intestinal paracellular permeability, the activation of local immune cells and the regulation of anti-inflammatory cytokines.

However, these benefits also involve certain disadvantages. ZnO is unpalatable, it has a buffering effect in the stomach and it can interact with nutritional substances and enzymes, such as iron and phytase. Over the last few years, evidence has also been gathered that the use of ZnO can contribute to the selection of genes that confer bacterial resistance against both heavy metals and antibiotics.

Furthermore, as ZnO is poorly absorbed in the digestive tract of piglets, it is excreted and can cause the contamination of soil and water.

As there are no efficient mitigation strategies for this environmental risk, in 2017, the European Medicines Agency decided to impose a five-year deadline to ban the use of high levels of ZnO in swine diets. The ban of medicated ZnO came into effect in June 2022.

During these last five years, one thing has become clear to the researchers and producers that are exploring alternative solutions: although the removal of medicated ZnO involves the risk of a profitability loss (the Danish research institute Seges calculated that the removal of ZnO from piglet feed may lower the production value by around €0.26 per pig), no single solution has been identified that will be able to replace medicated ZnO in a cost-effective way.

The replacement of medicated ZnO in swine production should be achieved through a holistic approach, which should entail an increase in biosecurity, as well as animal management and dietary interventions measures in sow and piglet feeding programmes.

Some nutritional strategies that can be considered to increase the resilience of piglets against post-weaning stress are discussed hereafter.

Table 1. Performance parameters of sows fed a control diet or a diet with an appetite stimulant.

	Control	Treatment (+ Palatability product K)	Statistical significance
Body weight at weaning (kg)	214.0	214.1	
Average daily feed intake (kg/d)	5.1[a]	6.6[b]	***
Backfat thickness at weaning (mm)	14.9	14.9	
Body weight loss (%)	-7.8	-7.7	
Weaning to oestrus interval (d)	4.3	4.5	
Number of piglets weaned	12.95[a]	13.45[b]	***
Average weaning weight (kg)	5.86[a]	7.00[b]	***
Milk production (kg/d)[A]	8.59[a]	12.99[b]	***

[A]: The daily milk production was calculated considering the litter weight gain (DWG), litter size, and milk dry matter content (19%) applied to the Noblet & Etienne equation (1989). MP (kg/d) = ([0.718 × DWG – 4.9] × n. piglets)/ 0.19.
[a,b] values with different superscripts differ significantly (*** P<0.001) (Silva et al 2018).

From sow to piglet: stimulating feed intake

Achieving the target piglet weight at weaning is important to ensure a good performance in the nursery phase. Lighter pigs are more likely to eat less at weaning or even not at all in the first days in the nursery, thus leading to poor development of the gut. This will increase the likelihood of the piglets developing diarrhoea, as the pig adapts to dry feeding, and this will have a negative effect on their growth and viability.

Several different nutritional interventions are used to support piglets during the suckling period and these include milk replacers, as well as liquid and solid creep feeds. However, most of the piglet growth comes from the sow's milk.

Achieving a high weaning weight therefore starts with the sow: the lactation feed intake needs to be optimal to maximise milk production and the growth of the litter.

Using specifically designed palatability products to stimulate a sow's feed intake has been shown, in numerous trials, to benefit both the sow and the piglets. In a recently published study, a significant increase in intake of sows offered a diet containing such a palatability supplement led to a greater milk production and a subsequent significant improvement in litter uniformity and piglet weight at weaning, with no additional cost to the body weight or the condition of the sow (Table 1).

The success of this palatability product in sow feeds led us to explore it as a part of a programme used to provide a sensorial link to the starter feed of piglets. Piglets in a farrowing pen copy the feeding behaviour of the sow and will often congregate around the sow feeder, where they investigate and sample any lactation feed material that is on the floor/ground.

This is an example of observational learning, a common characteristic that involves one animal watching the actions of another and learning from those actions. Incorporating a taste that is already familiar to the pig into the starter feed helps to stimulate early consumption at weaning. This concept has been proven to be extremely effective in stimulating early feed intake and growth at weaning, thereby avoiding the need for growth checks and further capitalising on the benefit of a higher weight at weaning.

From sow to piglet: increasing the anti-oxidative buffer

The qualitative production of sow milk is not only important because of its nutritional value: colostrum and milk contain IgG and IgM antibodies, which provide a way of passively transferring immunity to newborn piglets, whose immune system is still not completely developed.

An insufficient colostrum intake or poor colostrum quality can therefore predispose newborn piglets to increased morbidity and mortality as a result of microbial infections. In addition to antibodies, the transfer of selenium (Se) from sows to piglets is another way of increasing the natural defence status of piglets. The periods immediately after birth and post weaning are critical in terms of antioxidant protection, and young piglets are especially prone to oxidative stress reactions.

Se is an essential trace element with known functions in the antioxidant and immune system. The immune system depends on a well-

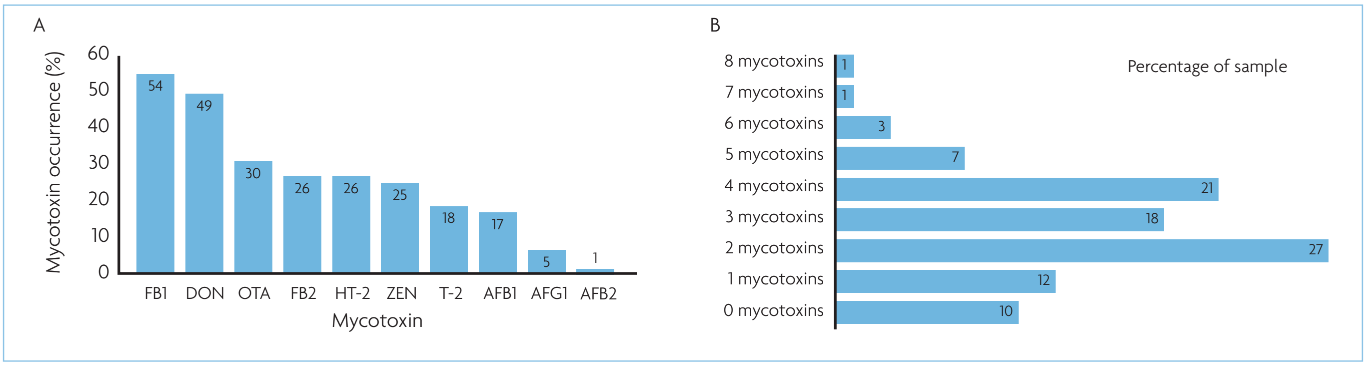

Fig. 1. (A) Mycotoxin occurrence in feeds for piglets (Spain 2021) and (B) average number of mycotoxins per sample.

maintained Se status to combat bacterial and viral infections, deal with oxidative damage, and regulate inflammation. Furthermore, antioxidant nutrition can play a major role in the gastrointestinal functionality and health of young pigs.

Organic Se sources, with a high selenomethionine (SeMet) content, such as hydroxy-selenomethionine (OH-SeMet), are able to build up a stock of Se in the body, which is then mobilised and metabolised in moments of stress. Under such challenging conditions, the Se requirements increase to support the activity of the selenoproteins that act in oxidative stress and immune modulation.

Feeding sows with pure sources of organic Se helps them to deal with gestation stress, and to improve their reproduction performance, but also to support the health of newborn piglets.

Building Se reserves in the sow increases the possibility of transferring Se to piglets during gestation and lactation, which in turn results in improved immune responses to challenges and the alleviation of oxidative stress. It was found that when sows were provided with high antioxidant diets, containing organic Se, their piglets received an increased concentration of IgM in the colostrum and milk.

The piglets from those sows were affected less than others when exposed to a pathogenic challenge in the suckling environment. They were also more capable of resisting a challenge due to reduced acute inflammation.

In fact, the antioxidant status prior to weaning improves the robustness of pigs via immunomodulatory mechanisms, which benefit the piglets when challenges appear during the weaning transition period.

Studies have also shown that including OH-SeMet in the diet of piglets after weaning continues to support their ability to cope with challenges. Animals that receive diets rich in antioxidants have demonstrated a better immune response when submitted to challenges.

Healthy weaned piglets are the result of a proper sow feeding that not only involves a high milk yield but is also part of a nutrition programme that will boost their immune system for the challenges to come.

Using low protein diets

When not fully absorbed in the mid-gut, proteins that reach the hindgut can be a substrate for the growth of potentially harmful bacteria that can produce potentially toxic metabolites, such as cadaverine, putrescine, ammonia, and acetic acid, and this can lead to intestinal inflammation and PWD.

A simultaneous reduction in the dietary crude protein (CP) level with the supplementation of essential amino acids could therefore be an effective alternative to the use of ZnO to control the intestinal microbial composition of animals.

This strategy has proven to be successful in trials where low (18%) and high (21%) CP diets were supplemented with a medicinal dose of ZnO or with amino acids (glycine and glutamine). No difference in growth performance was found for 21% of CP when medicinal ZnO was removed from the diet.

However, the reduction of CP by three percentage points significantly reduced the performance, in comparison to a standard CP level. This demonstrated that the removal of ZnO did not impair the performance but rather the decrease of CP to 18%, and that performance loss could be limited by non-essential amino acids.

The supplementation of non-essential amino acids mechanically increased the CP level to 20% and improved the performance of the animals.

Other studies have indicated that lowering the dietary CP can reduce diarrhoea while ensuring a similar feed efficiency, if it is applied over a short period of time. Different dietary protein strategies were tested considering different amino acid profiles, from 7-30kg of body weight, and it was found that a diet with low CP levels from weaning to about 15kg BW reduced the incidence of diarrhoea but decreased the weight gain, without affecting the feed conversion ratio.

Overall, low protein diets can be part of a dietary solution adopted to avoid an increase in diarrhoea in piglets when medicinal ZnO is removed during the post-weaning period.

Nevertheless, a great deal of attention should be paid to the dietary levels of essential and non-essential amino acids as they are known to impact the performance and gut health of such animals.

The impact of mycotoxins

Mycotoxins are prevalent in most feedstuffs and in complete feeds fed to piglets. The presence of mycotoxins in feeds contributes to the total stress of weaning, thereby adding to the negative impact on gut health, and on the immune and antioxidant systems of piglets.

They have been found to be pre-disposing factors for intestinal diseases as they increase the permeability of the intestinal epithelial layer of pigs and affect the viability and proliferation of intestinal epithelial cells.

Mycotoxins impair protein synthesis, can cause oxidative and inflammatory stress, damage intestinal cells, alter microbiota, and reduce energy and nutrient digestibility.

As such, they pose a risk by increasing the susceptibility of animals to E. coli, PWD and other health problems. In 2021, we analysed 105 samples of piglet feeds in Spain (Fig. 1) and found that 90% of the feed samples were contaminated by mycotoxins. Moreover, 87% of the contaminated samples had from two to eight mycotoxins at the same time, that is, multiple contamination with a possible synergism between low doses of mycotoxins.

About half of the samples (54% and 49%, respectively) were contaminated with fumonisins (FUM) and deoxynivalenol (DON), which, even at low levels, has been shown to increase susceptibility to pathogens.

Most mycotoxins, including DON, T-2, aflatoxins and FUM, are known to negatively impact the immune system by decreasing the activity of immune cells and antibody titers after vaccination.

A case study conducted in France showed that, despite vaccination, low levels of mycotoxins (DON, mainly T-2 and nivalenol) in weaner feeds increased the incidence of PWD and weaners' oedema disease (ED) caused by E coli. However, the use of mycotoxin control strategies significantly decreased the cases of PWD and ED among the weaners.

A holistic approach, based on the binding of polar mycotoxins (aflatoxins, ergots), the stimulation of a natural bio-inactivation process in the body by the liver, intestinal cells, microbiota etc for non-polar mycotoxins (DON, T-2, FUM etc) should be applied to obtain mycotoxin deactivation.

Furthermore, such an aid to immune and antioxidant systems, and to organ support in piglets, would help them to deal with mycotoxicosis more efficiently during the weaning period.

Supporting gut health

Apart from mycotoxins, several other factors have a well-described disruptive effect on the health and functioning of the digestive tract. A healthy gut status in the small and large intestine depends on three pillars: the gut mucosa, the (local) immune system and the gut microbiota.

However, these three foundations of gut health are very susceptible to imbalances, especially during the weaning period. The villi, for example, can show signs of atrophy. Furthermore, disruption of the integrity of the epithelial lining can cause a 'leaky gut' phenotype.

The composition of the gut microbial is labile and sensitive to the opportunistic overgrowth of potentially pathogenic bacteria, such as F4+ or F18+ E. coli, which are

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associated with PWD. Lastly, during weaning, the intestine temporally goes through an inflammatory status.

In this context, organic acids, such as short- and medium-chain fatty acids (SCFA and MCFA, see Fig. 2) are a family of feed supplements that have been studied extensively as a way of mitigating the negative effects of weaning.

They can have distinct effects, depending on the exact nature of the molecule.

For example, acids such as SCFA and lactic and citric acid have been used for decades as acidifying molecules, both as feed preservatives and a means to overcome high gastric pH during weaning.

They are often supplemented as a mixture of pure acids, or acids and their buffered salts, depending on the application.

Butyric acid plays a specific role as a signalling molecule, as it is one of the SCFA that is produced endogenously in the hindgut of monogastrics, where they instigate mechanisms that are key to gut health.

Butyrate, in the intestine of weaned piglets, has been shown to dampen inflammation, to increase tight junction formation and to upregulate the expression of antimicrobial peptides.

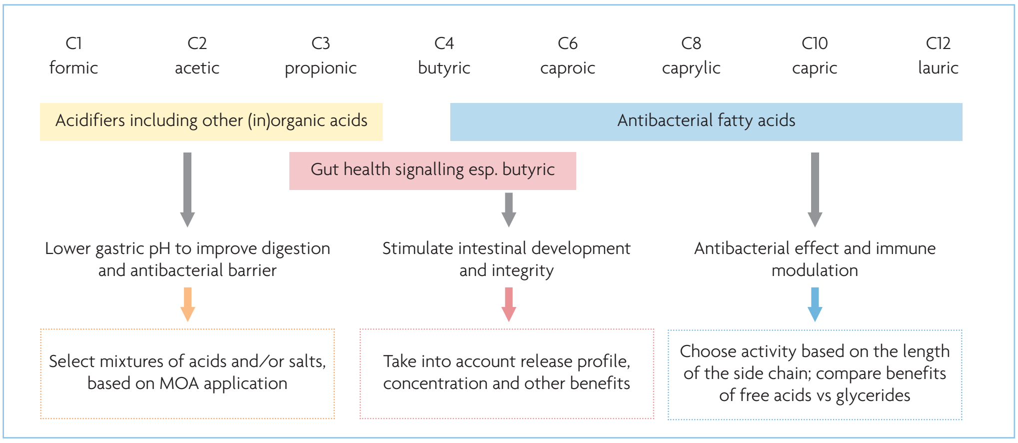

Fig. 2. Different short- and medium chain fatty acids can have distinct effects as feed supplements.

However, its effect depends to a great extent on where it is delivered in the gastrointestinal tract.

Commercial products, such as fat-embedded butyrates or butyric glycerides, have a distinct butyrate release profile and trigger different physiological responses. For example, precision delivery coated butyrate in a strong E. coli challenge model has proven to be more effective in improving the morphology and performance of the gut than unprotected butyrate.

On the other hand, medium-chain fatty acids (MCFA) are best known for their antimicrobial activity, even against several swine pathogens. These characteristics can be attributed to their molecular structure, which can interfere with the membranes of bacteria.

To use MCFA optimally, two considerations should be made. The first is the length of the side chain: for activity against Gram-positive bacteria (e.g. Streptococcus suis), lauric acid (C12) has typically emerged as the 'best in the class' in in vitro screening assays when comparing the antibacterial effect of SCFA and MCFA.

On the other hand, certain Gram-negative bacteria (e.g. E. coli) are more sensitive to shorter MCFA and SCFA (C3-C10). The second consideration is the choice between free MCFA or MCFA-glycerides: free MCFA are rapidly absorbed in the first part of the GIT, and are pH-dependent, while MCFA-glycerides are pH-independent and can be enterically delivered.

In addition, the antimicrobial effect of glycerides (especially alpha-monoglycerides) is much more pronounced than that of free fatty acids. ■