Jennifer Maurin
Animine France

Dr. Denise Cardoso
Animine France

ZNO WILL NOT BE BANNED IN ANIMAL NUTRITION IN 2022 IN EU

"After the decision to ban the medicinal use of zinc oxide in piglet diets, feed formulators are seeking feed ingredients and additives which can reduce the risk of digestive disorders in critical phases like the post-weaning period. Specific potentiated form of zinc oxide can be used in premixes at nutritional levels without prescription and showed efficacy to modulate intestinal bacterial populations and to improve gut barrier function."

WHICH FORMS OF ZNO TO BE BANNED?

It is needed to remind everyone that only the pharmacological usage of zinc oxide in piglet diets is currently under pressure. This means that the ban of ZnO in the European Union is restricted to medicated feeds which are prescribed by qualified veterinarians. This does not apply to the nutritional usage of zinc oxide which is routinely included in premixes and remains the dominant source of zinc utilised by the feed industry.

Medicated zinc oxide was diversely utilised in European countries for more than 15 years. On the contrary to feed regulation, veterinary regulation is country specific. Thus, pig producers, nutritionists and veterinarians face very heterogeneous regulatory situations.

As example, Dutch feed manufacturers were never authorised to use pharma ZnO in piglet diets. In France, it was only in 2016 that the French authorities gave permission for medicated use of ZnO. Since that authorisation, less than 20% of pig farmers have adopted it. This was a temporary period as in January 2021 the only product authorisation available expired, preceding the ban at EU scale of 18 months. In Germany, the end of the use of ZnO at medical dosage is scheduled for June 2021, so 1 year before the European deadline.

Outside EU, the situation is accelerating too. China has already implemented in 2018 a drastic reduction of authorised Zn supplementation level (from 2250ppm Zn to 1600ppm) in piglet diets. Pharmacological ZnO is as well under scrutiny in

many other countries in Asia (e.g Korea) and Americas (e.g: Canada).

WHY BANNING PHARMACOLOGICAL ZNO?

1. Zinc and microbial resistance

Intensive usage of zinc in animal diets favours the development of bacterial resistance. Bacteria regulate intracellular zinc concentration with a system of efflux pumps. These pumps can be specific to zinc or can evacuate other molecules like antibiotics. High levels of zinc tend to increase their synthesis; thus, the use of zinc oxide at pharmacological dosages reduces the sensitivity of bacteria to antibiotics.

2. Negative nutritional interactions

Studies about interactions between zinc and phytase suggest that pharmacological dosages of zinc have a negative effect on phytase activity and consequently on phytate-phosphorus liberation. This implies a reduced efficacy in phytase functions and possible phosphorus deficiency for affected animals.

The acid binding capacity of zinc oxide is the greatest among feedstuffs. Thus, high levels of zinc oxide appear to be antagonistic with feed acidifiers, like organic acids.

Moreover, high levels of zinc results in overproduction of metallothionein. This intestinal transporter binds preferentially to copper and consequently may lead to a sub-deficiency of this trace mineral.

3. Environmental concerns

Using 3 kg ZnO / ton of feed during the first two weeks after weaning increases by almost 30% the total quantity of zinc excreted in the pig's growing life. Technological treatments of pig slurry accentuate the problem as they concentrate the zinc in the solid fraction, and the level in the by-product may then exceed the maximal zinc level authorized for organic fertilizers in the EU.

4. Contamination by heavy metals

Impurities in commercial zinc oxide are a real problem when zinc quality is not strictly controlled. A study from the French institute IFIP indicated that cadmium concentration in kidneys exceeds the regulatory limit (1 mg/kg) for human consumption when pigs are fed with contaminated diets (0.5 mg Cd/kg diet) between 42 and 160 days. Cadmium is known for its organ toxicity and long elimination period; consequently, if tissues are contaminated during the post-weaning period

it is possible to have elevated levels of cadmium in tissues at slaughter time.

UNDERSTANDING ZNO MODE OF ACTION TO DESIGN SUITABLE ALTERNATIVES

According Prof. Zentek (Univ. of Berlin) interviewed in December 2020 by Animine regarding the state-of-the-art research on ZnO, he said: "The mechanisms of action are manifold and refer on the one hand to the intestinal microbiota, but then also to numerous processes in the intestinal mucosa. High doses of zinc oxide have a functional impact on the intestine, they can reduce the secretion of chloride and thus of water. Furthermore, it is increasingly shown that also the intestinal barrier and the gut associated and also the general immune system is affected. Further on, numerous regulatory mechanisms react on different levels of zinc intake. Therefore, these interesting findings are extremely valuable to narrow down the mechanisms of action more precisely and thus to develop considerations on alternatives to the pharmacological dosage of zinc oxide"

ZINC: AN ESSENTIAL DIMENSION WHEN CONSIDERING PHARMA. ZNO REPLACEMENT

ZnO is the most common source of Zn used in pig feeding. ZnO is known to be variable in the different parts of the world. In North America, the most common source of ZnO used is a dark-brownish powder; in Europe standard ZnO is more of a light-brownish product. In Asia, however, ZnO is known as a white powder. These differences go beyond the color and aspect of the powder, it is highly related to their quality, purity and bioavailability (see picture 1). The quality of raw material and the method by which ZnO is produced affects they composition (including the presence of heavy metals) and also their physicochemical properties. Particle size and specific surface area, among other characteristics are important in the fate of ZnO in gastrointestinal tract of animal.

A recent study at Ghent University, Belgium, scrutinized the effect of a particular source of potentiated zinc oxide manufactured in Europe (commercialised under the brand HiZox®, picture in the middle below). Using a patented manufacturing technology, the physicochemical properties of this nutritional ZnO source are modified to give it a "porous" particle with a very large surface area, 10 to 15 times greater than conventional zinc oxide sources. This larger surface area drastically increases the contact

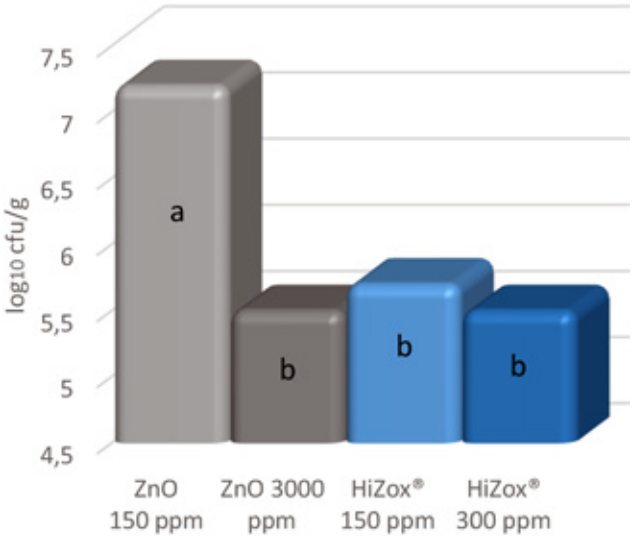

Figure 1- Coliform count in distal small intestine (P<0.05). Ghent University (Belgium)

Picture 1: from left to right: Asian ZnO source, EU potentiated ZnO (HiZox(r)) and American ZnO source.

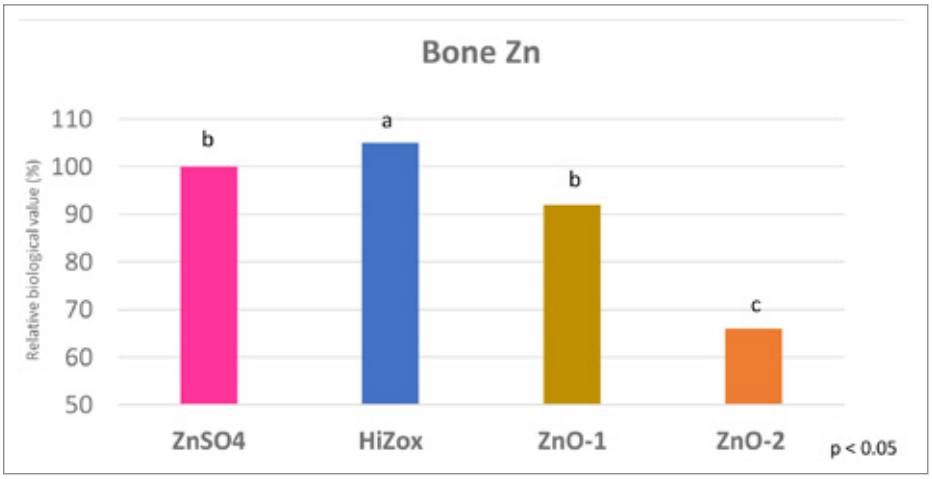

Figure 2: Relative bioavailability (%) of different sources of ZnO compared to ZnSO4

area with gut bacteria and the high porosity amplifies the antibacterial activity of this potentiated zinc oxide (see figure 1).

This potentiated zinc source is already represented widely on worldwide market and showed its efficacy to replace partially or totally pharmacological dose of ZnO.

The use of ZnO at pharmacological levels also answers the challenge of nutritional supply and bioavailability. Although the Zn requirements are established, the complexity of the period after weaning seems not to supply adequate amount of Zn. It is questionable if the requirements for this mineral should be defined as mg /day instead of mg /kg diet, so the feed intake in this early stage does not compromise the Zn supply. Among the different sources used to supply in the diets, ZnO is the most known one.

A recent study using sources of ZnO with different physicochemical properties was performed at INRA, France (Cardoso et al., PSA 2020) with the objective to determine their bioavailability. The study confirmed what previous studies have demonstrated; that ZnO bioavailability is variable and highly connected to the properties of the different sources. Additionally, the experiment also showed that when compared to ZnSO4, ZnO can have a lower, similar, but also superior bioavailability depending on the source of ZnO (see figure 2)

CONCLUSION

Misleading market information might suggest that all ZnO sources will be banned in EU, this is not correct and only its veterinary use is under legal constraints. Nutritional supplementation of zinc under oxide form remains authorized, recommended and one of the top sources used by formulators nowadays. Any strategy replacing pharmacological ZnO should integrate a zinc dimension that cannot be avoided. This zinc appropriate supply can sometimes kill 2 birds with 1 stone as certain European sources of ZnO also provide high antibacterial properties when supplemented at 150ppm Zn (according to regulation 2016 / 1095).