Copper metabolism and growth promotion: is there a relation?

Copper (Cu) at high dietary levels has been used for a long time as a growth promoter in different production animals. Two possible modes of action have been proposed: a pre (antimicrobial and local) and a post (systemic) absorption effect.

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In the feed, Cu is usually provided as a sulphate source ($CuSO_4$), although other sources are also available. Increasing $CuSO_4$ supplementation to supra nutritional levels is well recognised to significantly enhance the growth performance of piglets, as shown in Fig. 1 where the improvement in body weight (BW) is of 3.4kg when 160ppm of Cu is compared to 15ppm.

Hypothesis of pre absorption effect of Cu

The antimicrobial effect has been recognised since Ancient Egypt, where Cu was used to sterilise chest wounds and drinking water.

In the pig, this antimicrobial effect occurs once dietary Cu passes through the stomach, dissociates into Cu ion, and reaches the intestine in its ionic form.

Some authors reported that the supplementation of high Cu (250ppm from $CuSO_4$) reduced the caecal Enterobacteriaceae population by 23% and improved the average daily gain in piglets by 37% when compared to a basal diet.

The improvement in pig performance following supra nutritional addition of Cu in the diet was also observed in a recent feeding trial performed at Wageningen University & Research with 200 weaned piglets.

Copper was supplemented from $CuSO_4$ at two levels (15 or 160ppm) in the diets.

The significant increase in the final BW by Cu supplementation was accompanied by a decrease in E. coli population in the colon (Fig. 2).

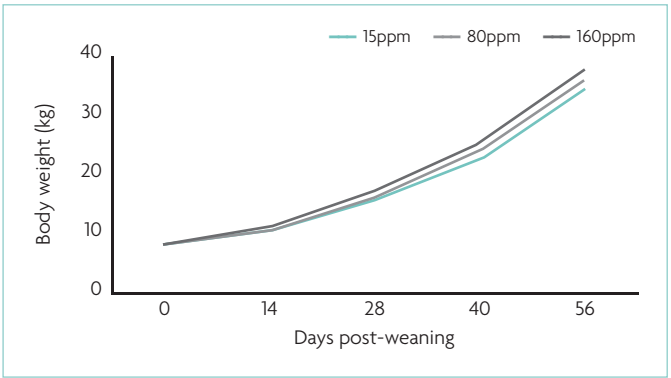
These results suggest that prior to absorption, high levels of Cu reduce bacterial populations, resulting in a positive modulation of the intestinal microbiota. Other studies have also shown that high Cu dosages by $CuSO_4$ supplementation significantly inhibited potential pathogenic coliforms in the caecum and the colon of piglets.

This regulation positively affects the intestinal health and reduces the incidence of diarrhoea in piglets. Besides this, the modulation of microbiota also has an effect on the dietary utilisation and metabolism of energy and protein, which may render more energy and nutrients available to the host animal.

In the small intestine, for example, bacteria can produce the bile salt hydrolase (BSH) enzyme, which alters lipid metabolism and energy release. A reduction of this enzymatic activity has been reported as effective to enhance feed efficiency and body weight gain in monogastric animals.

As Cu is one of the main BSH inhibitors, a modulation of the intestinal microbiota composition may be one mechanism by which Cu improves growth performance in piglets. This may explain why some recent studies demonstrated that Cu supplementation seems to enhance pigs' ability to utilise fat after absorption, resulting in increased energy utilisation of the entire diet.

Fig. 1. Body weight of piglets fed with different doses of Cu (15, 80 and 160ppm) from $CuSO_4$, from weaning to 56 days after weaning.



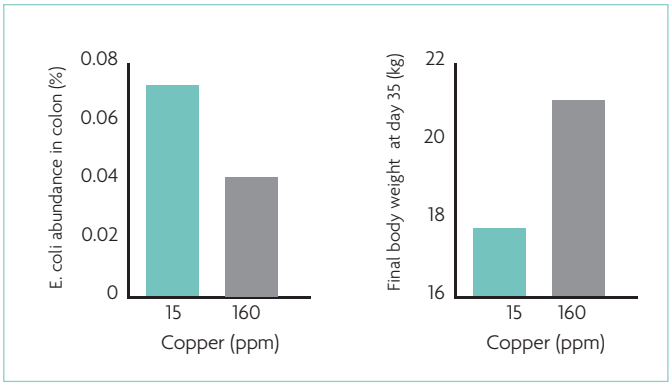


Fig. 2. Relative E. coli abundance in the colon of piglets, and final body weight after 35 days of supplementation.

Hypothesis of post absorption effect of Cu

Once Cu is in the intestine, the Cu(II) form must be reduced at membrane level to the Cu(I) form, so it can be absorbed by the enterocytes. Then, it is bound to chaperone proteins and/or metallothionein (MT) to avoid cellular toxicity and to further transport copper outside the enterocyte.

Cu is exported via the portal venous system to the liver, which is the central regulatory organ of copper homeostasis; but it can be then taken up by other tissues (brain, kidney, heart).

On its entry to the hepatocyte, Cu is again rapidly taken up by cytosolic ligands such as MT and glutathione. The main role of MT is the storage of Cu in a 'safe compartment' and the sequestration of an intracellular excess of Cu in response to supra-physiological Cu exposure, which can generate hydroxyl radicals and be potentially toxic.

Because the liver is the main storage site for Cu, the bioavailability of Cu sources has been traditionally evaluated by using liver Cu accumulation as the key criterion. These kind of studies have been performed at nutritional dosages, to allow homeostatic regulation.

More recently, however, feeding trials with high Cu levels for pigs have also used hepatic Cu as an indicator of bioavailability. These levels, which by far exceed the requirements of pigs, demonstrate with the Cu accumulation in the liver, a way that the organ finds to avoid Cu toxicity.

Into hepatocytes, Cu is associated to different enzymes and the excess is removed from the liver through biliary excretion. The main roles of bile are to enhance the fat digestion and absorption as well as the excretion of metabolic waste products from the organism.

As around 80% of the absorbed Cu is excreted in the bile, a post absorption antimicrobial activity of Cu has been raised by some authors.

It has been reported that Cu in the bile is in the form of non-absorbable

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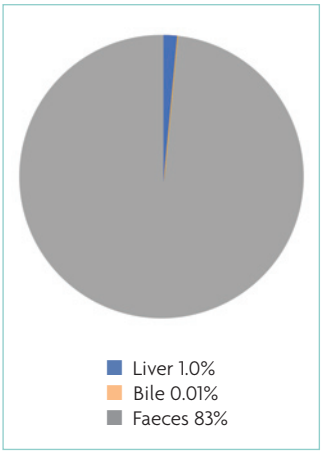
stable Cu chelates. Biliary Cu recycling can be thus, considered negligible and being mostly excreted in the faeces.

Besides, the Cu excreted by the bile (considering the Cu concentration and the bile flow during 28 days) represents less than 0.1% of total Cu intake, so it can be suggested that biliary excreted Cu would not have the same antimicrobial impact on microbiota as the dissociated Cu ion after ingestion (Fig. 3).

Fig. 3. Concentrations of Cu in liver, in the bile and Cu excreted in faeces. Results are in percentage of Cu intake. Data are from a trial with piglets from 35-63 days of age fed 250ppm of Cu from $CuSO_4$.



A recent study conducted in the United States, has shown that nursery piglets fed 250mg of Cu/kg from $CuSO_4$ presented an improved feed efficiency compared to those fed 5ppm of Cu, but without differences on inhibitory action of bile against salmonella, E. coli or Enterobacter populations.

Another trial performed at the University of Illinois with high levels of Cu showed that the hepatic Cu accumulation is not related to its effect on pig performance.

The increase of Cu supplementation from 125 to 250ppm of Cu from $CuSO_4$ for fattening pigs resulted in higher hepatic Cu accumulation, so it can be expected to have a high Cu exportation in the bile.

However, after 133 days of trial, final bodyweight did not increase accordingly (Fig. 4).

Although a plateau in the growth rate of finishing pigs was observed when Cu levels in the feed exceed 100ppm, Cu accumulation in the liver showed a dose response behaviour.

The storage of Cu in the liver is a consequence of Cu intake and not the cause of its growth promoter effect. Besides, long-term feeding with high Cu levels leads to an excess of Cu in the organism, which can cause cellular damage through the formation of free radicals and this may induce oxidative stress.

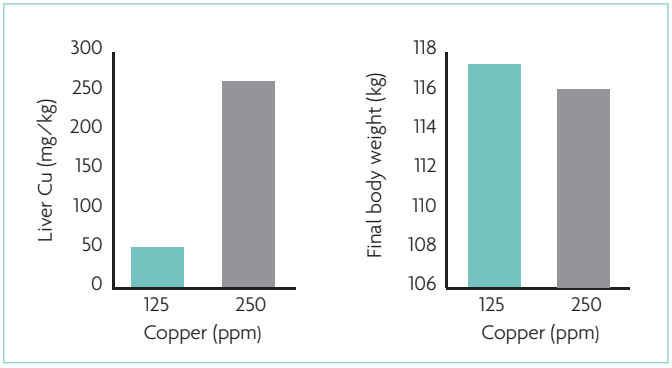


Fig. 4. Effect of dietary copper from $CuSO_4$ on its concentration in the liver and final body weight of fattening pigs after 133 days of trial.

Pre vs post absorption hypotheses

According to recent studies, copper metabolism seems to be unrelated to growth promotion. The strongest hypothesis is that its effect seems to be related to microbiota modulation resulting in the improvement of gut health, but not to Cu accumulation in the liver. Thus, a more antibacterial copper source might be more efficient to promote growth.

The effects of Cu in killing bacteria differ according to its redox state: the Cu(I), the reduced cuprous form, has a stronger antibacterial effect in anaerobic conditions than Cu(II), the oxidised cupric form.

A red source of copper(I) oxide (CoRouge, Animine), newly authorised in the EU, has shown improved pig performance and a stronger antibacterial effect than $CuSO_4$, with a lower risk of animal toxicity. ■