A deep dive into the mode of action of copper

Copper, like zinc, can be highly beneficial to pigs but can also be toxic if levels become too high for either the pigs or the environment. It is crucial to select the right source and amount to ensure it performs its intended function effectively. Therefore, understanding its specific role and requirements is essential for producers.

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Copper has long been used at high dietary levels as a growth promoter in production animals. It is thought there are two modes of action – both hypotheses will be discussed in further detail.

First, copper acts **locally** in the gastro-intestinal tract with antimicrobial effects, potentially modulating gut microbiota to enhance gut health and nutrient absorption. Second, after absorption, copper is thought to influence **hormone synthesis** and regulation, impacting growth and feeding efficiency.

What does the literature say about these two mechanisms? Do all copper sources have the same effect?

A local effect?

The antimicrobial effect of copper occurs once dietary copper passes through the stomach, dissociates into copper ions (Cu+ or Cu2+) and reaches the intestine in its ionic form.

The hypothesis behind it is that, prior to absorption, high levels of copper reduce bacterial populations, resulting in a positive modulation of the intestinal microbiota and reduce diarrhoea.

Studies reported that high copper supplementation (>150 mg/kg) can modulate the microbiota (e.g., increasing the abundance of *Lachnospiracea*), which helps degrade carbohydrates. It is also thought to reduce *Escherichia coli*, which is one of major causes of post-weaning diarrhoea, while improving average daily gain (at least in 5%, versus a negative control), as presented in *Table 1*.

In one of three studies, the source effect of copper was observed, but the dose effect (copper supplementation versus control) was consistent across all studies, influencing both growth and bacteria. The resulting microbiota modulation positively impacts gut health and enhances the metabolism and utilisation of energy and protein, potentially providing more nutrients and energy for the animal.

A systemic effect?

Conversely, high dietary copper levels have also been associated with increased feed intake in swine, potentially due to the release of neuropeptides, like somatostatin, and growth hormone-releasing hormone. There are also other nutrient-related signals, as is shown in *Table 2*.

Those studies underscore the connection between copper,

Table 1 – Summary of studies assessing Cu supplementation, antibacterial effect and piglet performance.

Reference	Initial BW (kg)	Duration (days)	Supplemented Cu level (mg/kg)	Copper source	Effect on bacteria	Effect on growth
Ao et al., 2019	22.7	42	150	Cu chloride	↓ *E. coli* count vs NC	↑ 5% ADG vs NC
Roméo et al., 2019		35	15, 80, 160	$CuSO_4$ Cu_2O	↓ *E. coli* count vs $CuSO_4$	↑ 4% ADG vs $CuSO_4$ ↑ 21% ADG vs 15 mg/kg
Forouzandeh et al., 2022	11.5	28	250	$CuSO_4$ Cu_2O	↑ abundance of *Lachnospiraceae* and *Peptostreptococcaceae* ↓ abundance of the *Rikenellaceae* family, *Campylobacter* and *Streptococcus*	↑ 7% ADG vs NC Not significant for source effect
Lei et al., 2023	21.6	14	60	$CuSO_4$ Cu-Gly"	↑ abundance of *Lachnospiraceae* ↓ abundance of *Peptostreptococcaceae* family	Not significant for source effect

hormones and growth performance, but the nature of this relationship remains unclear. Is copper directly influencing the brain and hypothalamus to produce systemic effects, or is it primarily modulating the gut microbiota, leading to improved gut health and enhanced feed intake, which then indirectly stimulates nutrient-specific signals (i.e., ghrelin)? This idea of a systemic effect would be related to the bio-availability of copper, as it implies in its absorption by the enterocyte and its release in the blood. However, there is no clear relationship between copper bio-availability and growth performance. First, according to the NRC (2012), the copper requirement for piglets is around 5-6 mg/kg. Secondly, those amounts are already covered by the basal diet, which provides around 8-13 mg copper/kg.
A recent study done at Wageningen University & Research in the Netherlands zoomed in on the effects of growth-promoting copper levels on the expression of growth hormone genes in the brains of weaned piglets, comparing dietary copper levels of 15 ppm and 160 ppm. The findings showed no significant impact on the mRNA levels of somatostatin or somatotropin in the hypothalamus. The authors suggested that dietary copper does not directly affect the hypothalamus but, instead, may help in reducing biological stress response in pigs.

Local vs systemic

Although some studies suggest that copper can reduce inflammation and stress, thereby enhancing overall growth performance, most evidence points to its impact on gut microbiota as the primary driver of these benefits. Consequently, we can conclude that copper sources with stronger antibacterial properties are more effective in promoting growth. The antibacterial effects of copper however vary significantly, depending on its redox state or, in simple terms, in which ionic form the copper is at any given time. Literature shows that the monovalent form (Cu^{+}) demonstrates a stronger efficacy in anaerobic conditions, compared to the divalent form (Cu^{2+}). In a recent study (2024), a team from the University of Berlin, Germany, found that monovalent copper was more effective than divalent copper at acidic pH in inhibiting both gram-positive and gram-negative bacteria. The minimum inhibitory concentration (MIC) for *E. coli* and *Staphylococcus aureus* being half that of divalent copper – meaning that half the concentration of the monovalent form is needed, compared to the divalent form, in order to prevent the growth of *E. coli* and *S. aureus.* Similarly, a recent study reported that the MIC of monovalent copper (CoRouge, Animine) for *Streptococcus suis* at neutral pH was 64 µg/mL, significantly lower than the 256 µg/mL MIC observed for three divalent copper sources ($CuSO_4$, TBCC, Cu-chelate).
In-vivo studies have shown that post-weaning piglets supplemented with 150 mg/kg of monovalent copper demonstrated a 10.7% increase in body weight compared to those receiving divalent copper (e.g. $CuSO_4$). Additionally, growing pigs fed 250 mg/kg of monovalent copper had about 7.0 kg higher final body weight than those fed divalent copper ($CuSO_4$). Monovalent copper was also more effective in reducing pathogenic bacterial populations, such as the *Rikenellaceae* family and *Holdemanella* genus, suggesting improved intestinal health, which likely contributed to the observed body weight gains.

Table 2 – Summary of studies evaluating the effect of copper supplementation on piglet hormones and performance.

Reference	Cu dose, ppm	Hormone	Growth
Zhu et al., 2011	175, 250	↓ LeptinRb, Proopiomelanocortin, ↑ neuropeptide Y	↑ ADFI, ADG
Yang et al., 2011	125	↑ somatoliberin ↓ somatostatin	↑ ADG ↓ FCR
Wang et al., 2016	150, 200, 300	↑ growth hormone	↑ ADG
Gonzales-Esquerra et al., 2019	50	↑ ghrelin, growth hormone	↑ ADG, ADFI ↓ FCR
Van Baal et al., 2024	15, 160	Not significant (somatostatin, somatotropin)	↑ ADFI, ADG ↓ FCR

Take home message

Copper supplementation at growth-promoting levels significantly enhances body weight gain in piglets. This effect is primarily due to modifications in the intestinal microbiota. However, a synergistic impact via systemic pathways and on stress responses cannot be ruled out. While the exact mechanisms remain unclear, it is evident that the source and ionic state of copper are critical factors in the overall performance and health of piglets.

*References available upon request.**

Figure 1 – The hypothesis of the mode of action of copper.