High-dose copper and zinc in swine diets: applications, potential hazards, and mitigation strategies (postprint)

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Abstract

In swine production, diets supplemented with high levels of copper and zinc are widely used due to their growth-promoting effects similar to antibiotics. However, the potential hazards associated with the dietary use of high-dose copper and zinc have been frequently reported. This article reviews the current application status, potential hazards of high-dose copper and zinc, and proposes corresponding solutions.

Full Text

Application, Potential Hazards, and Solution Strategies of High-Dose Copper and Zinc in Pig Diets

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Abstract: In swine production, high-dose copper (Cu) and zinc (Zn) diets are widely used for their growth-promoting effects that resemble those of antibiotics. However, numerous studies have reported potential hazards associated with the use of high dietary levels of these minerals. This paper reviews the current application status of high-dose Cu and Zn, examines their potential hazards, and proposes corresponding mitigation strategies.

Keywords: high-dose copper; high-dose zinc; diet; pig; solution strategy

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In recent years, the proportion of intensive farming systems has increased, subjecting pigs to significant stress that compromises gastrointestinal health, particularly in piglets. Under such stress, pigs become more susceptible to disease as their nutritional metabolism and immune functions are impaired, limiting digestive and absorptive capacity while reducing their ability to resist and eliminate pathogenic microorganisms. To mitigate these adverse effects, antibiotics were initially the focus of producers and researchers. However, large-scale antibiotic use has led to problems including bacterial resistance and drug residues in animal products. Consequently, high-dose copper and zinc have been investigated and applied as prophylactic additives in pig diets as alternatives to antibiotics.

As early as 1945, Braude first discovered that dietary supplementation with high-dose copper promoted growth in pigs. Initially, researchers speculated that copper and antibiotics functioned similarly in swine production, but this proved incorrect. Subsequent studies revealed that copper' s growth-promoting effects are systemic, relating to feed intake, various enzyme activities, and neural regulation. Research on zinc in pig diets dates to the 1990s, when various zinc compounds demonstrated excellent growth-promoting effects in weaned piglet diets, showing important value in reducing diarrhea and improving survival rates.

1.1 Mechanism of Growth Promotion by High-Copper Diets

Copper is an essential trace element in pig nutrition, serving as a necessary component and cofactor for numerous enzymes and directly participating in metabolism. It plays a vital role in bone formation and hematopoiesis, while also enhancing resistance to pathogens, improving immunity and antioxidant capacity, increasing feed intake, and boosting production performance. In swine production, the growth-promoting effects of high-copper diets have been a major research focus. Adding high-dose copper (125-250 mg/kg) to early-weaned piglet diets significantly improves growth rate, feed intake, and feed efficiency, with studies confirming that different inorganic copper sources at equivalent doses produce similar growth-promoting effects.

1.1.1 High-Copper Diets and Growth Axis Regulation High-dose copper induces various growth axis regulatory factors, increasing dopamine (DA) content in the hypothalamus. DA directly acts on the pituitary to stimulate growth hormone (GH) secretion and regulates concentrations of growth hormone-releasing hormone (GHRH), somatostatin (SS), and ghrelin in the growth axis, thereby improving production performance. High-copper chyme stimulates gastric fundic glands, increasing ghrelin mRNA expression. Ghrelin shares biological functions with motilin, promoting pepsin secretion and gastric emptying while protecting gastric mucosal integrity. In vitro studies confirm that ghrelin promotes GH secretion from primary pituitary cells, stimulating animal growth. Additionally, high-dose copper increases neuropeptide Y (NPY) expression in the pig hypothalamus, which interacts with satiety signaling pathways to enhance feeding desire and stimulate saliva secretion, playing an important role in feed intake regulation and nutrient digestion.

1.1.2 Improvement of Intestinal Structure and Function by High-Copper Diets Proper use of high-copper diets not only improves digestive enzyme activities but also enhances digestive tract structure, increasing villus height and the villus height-to-crypt depth ratio. Studies show that high-copper diets improve activities of various digestive enzymes including pepsin, trypsin, pancreatic amylase, and lipase, enabling more efficient nutrient breakdown in chyme and facilitating subsequent absorption and deposition. Furthermore, copper participates in forming various antioxidant enzymes, enhancing antioxidant capacity and stress resistance while reducing environmental stress impacts on pigs.

1.1.3 Relationship Between High-Copper Diets and Intestinal Microbiota Copper exhibits antibacterial effects against Gram-positive bacteria, leading some researchers to attribute its growth-promoting properties to this characteristic. Interestingly, intravenous copper injection also promotes growth performance in weaned piglets, indicating that high-copper diets possess both growth-promoting and antibacterial properties. Højberg et al. found that dietary supplementation with 175 mg/kg copper sulfate reduced populations of lactic acid bacteria, *Lactobacillus*, and *Streptococcus* in the gastrointestinal tract—bacteria considered important for maintaining intestinal homeostasis. This may occur because reduced total bacterial populations decrease nutrient consumption from the diet, making more nutrients available for pig growth.

1.2 Mechanism of Growth Promotion by High-Zinc Diets

Zinc is an essential trace element that primarily participates in forming various enzymes and acts as a metal enzyme activator. It is involved in protein and RNA synthesis, playing crucial roles in animal growth, development, reproduction, and immunity. In pig production, zinc serves as a prophylactic additive, significantly improving diarrhea and edema in weaned piglets. Initially, zinc oxide (ZnO) was commonly used as a zinc source in weaned piglet diets. Research indicates that ZnO effectively reduces diarrhea rates while improving growth performance and feed efficiency, showing antibiotic-like effects in improving piglet health and production performance. Consequently, therapeutic doses of ZnO (2,000–3,000 mg/kg) have been widely adopted as prophylactic additives in the swine industry.

1.2.1 High-Zinc Diets and Improved Pig Immunity Zinc’ s preventive functions primarily manifest in improving immunity, stress resistance, and intestinal structure and function. Pig immunity and stress resistance are reflected by antioxidant capacity, immunoglobulin content, and T-lymphocyte transformation rate. Studies show that high-zinc diets significantly increase antioxidant enzyme activities in piglet tissues, such as metallothionein and copper-zinc superoxide dismutase, while elevating serum immunoglobulin levels including IgG, IgM, and IgA.

1.2.2 High-Zinc Diets and Improved Intestinal Health Zinc nutrition is closely related to small intestine health—the most important digestive organ and the largest immune organ. Zinc promotes secretion of insulin-like growth factors (IGFs) from small intestinal epithelial mucosa, stimulating villus growth to rapidly establish a complete intestinal barrier during early weaning and improving small intestinal structure and function. Research demonstrates that high-zinc diets significantly increase villus height and the villus height-to-crypt depth ratio in weaned piglets while enhancing intestinal cytokine and tight junction protein expression. Additionally, zinc regulates ghrelin secretion to improve feed intake and modulate the growth axis, thereby enhancing growth performance. High-zinc diets also regulate intestinal microbiota diversity and reduce nutrient fermentation in the small intestine.

2.1 Adverse Effects of High-Copper and High-Zinc Diets on Pigs

While high-copper diets demonstrate good growth-promoting and disease-preventing effects in weaned piglets, long-term use shows limited benefits and may even produce negative effects including organ oxidative stress, increased inflammatory factor expression, intestinal microbiota imbalance, reduced growth rate, and deteriorated meat quality. Studies show that high-copper diets catalyze Fenton reactions in the intestine, generating anions and hydroxyl radicals that damage, detach, or kill intestinal cells, causing oxidative stress and barrier damage. Additionally, high copper content in chyme reduces total bacterial populations in the digestive tract, inhibiting both harmful and beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*. Therefore, long-term high-copper diets disrupt intestinal microecological balance and severely impair intestinal function. Regarding meat quality, prolonged high-copper diets increase unsaturated fatty acid content in pork, making it more susceptible to lipid oxidation, resulting in softer texture and reduced flavor.

Although high-zinc diets improve piglet performance, high dietary zinc may cause toxic reactions and disrupt intestinal microbiota balance. Excess zinc directly affects various membrane structures, altering membrane permeability, reducing ATP production, and decreasing active transport capacity. As one of the first organs exposed to zinc stimulation, the small intestine suffers epithelial cell membrane damage from long-term high-dose zinc exposure, reducing digestive and absorptive capacity and inhibiting pig growth. Long-term high-zinc feeding not only suppresses immune organ development but also affects T-lymphocyte transformation and leukocyte phagocytosis rates, causing significant decreases in serum immunoglobulin levels.

After absorption, dietary copper and zinc are distributed to various tissues and organs including the liver, kidneys, and brain through the circulatory system. Heavy metal deposition in the liver significantly reduces its antioxidant capacity, detoxification ability, and growth factor release. Kidney deposition of heavy metals affects glomerular filtration and tubular reabsorption by altering cell membrane permeability. Heavy metal accumulation in the pig brain affects central nervous system endocrine function, inhibiting feeding regulation, growth control, and memory. In summary, long-term use of high-dose copper and zinc diets not only reduces animal performance but also compromises animal health.

2.2 Environmental Pollution

Pigs have low absorption rates for dietary copper and zinc, with only a small portion deposited in the body while most are excreted in feces. Research data show that when pigs consume high-copper diets (250 mg/kg), fecal copper content is 14 times that of the diet. Most swine manure is composted and returned to farmland. Although China has gradually recognized the potential environmental threats from heavy metals in feed and adjusted the maximum limits for copper and zinc in pig diets in the *Feed Additive Safety Use Guidelines* (copper: $ $125 mg/kg in piglet diets; zinc: $ $110 mg/kg in piglet diets, $ $1,710 mg/kg for two weeks post-weaning, $ $100 mg/kg in sow diets, and $ $80 mg/kg in other pig diets), the large swine population produces massive amounts of manure. Since copper and zinc are difficult to degrade in soil, their deposition will increase annually with the development of China' s swine industry, eventually causing severe environmental and food chain contamination, particularly near pig farms. To protect soil and the ecological environment, China' s *Soil Environmental Quality Standards* specify maximum allowable concentrations: copper $ $50–100 mg/kg and zinc $ $200–300 mg/kg (secondary standard). High soil copper content not only affects crop yield but also impacts biodiversity and health of various organisms. Studies show soil copper content positively correlates with soil hardness; excessively hard soil is unsuitable for cropping and affects plant growth, development, and yield. Additionally, long-term work in high-copper environments may cause liver cirrhosis and jaundice. High soil zinc content inhibits plant uptake, with levels >200 mg/kg generally considered contaminated. Beyond soil pollution, copper and zinc pose greater threats to water sources, as aquatic life is highly sensitive to these metals. Research indicates that excessive copper and zinc in water pose significant threats to aquatic organisms.

2.3 Bacterial Resistance

In recent years, bacterial antibiotic resistance has attracted widespread attention from scholars worldwide, as enhanced resistance poses potential threats to human health. Hölzel et al. demonstrated that long-term use of high-dose copper as a feed additive increases resistance of intestinal bacteria in pigs. Bednorz et al. found that dietary supplementation with 2,500 mg/kg ZnO increased resistance of certain bacteria in piglet gastrointestinal tracts and enhanced multidrug resistance in *E. coli*. Slifierz et al. reported that high-dose ZnO in weaned piglet diets increased prevalence and infectivity of methicillin-resistant *Staphylococcus aureus*. Long-term high-copper diets induce copper resistance in bacteria. Current swine production often employs combined high-dose copper and antibiotic strategies for growth promotion and bacterial inhibition, with synergistic effects dramatically increasing bacterial resistance rates and creating deeper hidden dangers for future production. Studies show that long-term use of high-dose copper and zinc diets specifically selects for resistant bacteria, making these metals important factors in inducing bacterial resistance.

Furthermore, research has documented synergy between antimicrobial metals (copper, zinc, etc.) and antibiotic tolerance. Some bacteria isolated from environments already show co-resistance to antimicrobial metals and antibiotics. These resistance traits can be transmitted vertically to offspring or horizontally to other bacteria through two transmission mechanisms that jointly regulate copper resistance, zinc resistance, and enhanced antibiotic resistance. This means resistant bacteria may spread their resistance genes to different biological populations, threatening human health.

3 Solution Strategies

To ensure growth-promoting effects of copper while reducing excessive emissions and lowering the induction of resistant bacteria, more efficient feeding methods are needed in pig production. Some suggest using probiotics, acidifiers, and plant extracts to reduce environmental pollution and antibiotic resistance. Others propose changing the form of copper and zinc supplementation in diets to reduce dosage without compromising efficiency.

3.1 Alternative Strategies

Probiotic supplementation in pig diets has gained widespread industry attention, with various probiotic products emerging. Probiotics are live microorganisms that regulate host microbial balance. They compete with pathogens for nutrients and binding sites on intestinal walls, activate the immune system, and produce substances harmful to pathogens. Wang et al. reported that *Enterococcus faecium* promotes piglet weight gain and health with effects similar to ZnO (2,500 mg/kg).

Prebiotics positively affect animal health and selection of beneficial intestinal microorganisms. Yeast derivatives and polysaccharides can regulate piglet immune systems. Studies show β-glucan has anti-inflammatory properties, promoting production of anti-inflammatory factors in pigs. Yeast derivatives also remove anti-nutritional factors from feed while promoting growth.

In recent years, plant extracts such as polysaccharides, saponins, and essential oils have been widely used as pig feed additives. Research demonstrates that natural plant extracts promote pig growth, benefit pig health, and do not pollute the environment. Some plant extracts also enhance immunity, digestive enzyme activity, and stress resistance. International research on plant extracts for pig health and growth has focused on seaweed extracts due to their high yield, easy availability, and economic benefits. Domestic research has also explored aquatic plants and traditional Chinese herbal additives.

Acidifiers inhibit pathogen activity by reducing digestive tract pH. Organic acids such as lactic and citric acid decrease pH to reduce bacterial populations. Reports indicate that formic, acetic, propionic, and sorbic acids effectively lower digestive tract pH and inhibit Gram-negative bacterial proliferation. Dietary supplementation with compound organic acids reduces populations of *E. coli*, *Salmonella*, and *Enterococcus* in pig intestines, improving growth performance. However, some scholars note that acidifiers cannot completely eliminate threats from harmful microorganisms.

3.2 New Usage Patterns

Traditional copper and zinc additives are primarily inorganic compounds such as copper sulfate and ZnO. Inorganic copper and zinc in diets are easily oxidized, have low absorption and utilization rates, and cause environmental pollution. Therefore, improving copper and zinc efficacy while reducing dietary levels has become a notable research area.

Studies indicate that copper and zinc in chyme bind to digestive tract mucosa, activating pathways that regulate secretion of various growth factors to promote protein deposition and tissue development. Therefore, the biological efficacy of copper and zinc correlates with their contact surface area with the digestive tract. Reducing particle size effectively increases surface area. Micron- and nano-sized particles can increase surface area several-fold for the same mass. However, research on nano- and microparticles shows that while they increase biological efficacy, they also enhance toxicity. Nanoparticles can penetrate biological membranes, alter membrane potential and permeability, cause oxidative stress, and damage genetic material in cell nuclei, causing irreversible DNA damage. Comparative toxicity studies found that oral administration of micron copper (200 mg/kg BW) for 28 days showed no toxicity, suggesting micron-sized copper and zinc premixes may have positive impacts on future swine production.

Additionally, attapulgite clay can be used as a carrier for copper and zinc premixes in pig diets. Attapulgite clay possesses ion exchange, physical adsorption, trace element carrying, and mucosal protection properties. Copper- and zinc-loaded attapulgite clay protects intestinal mucosal structure while delivering growth-promoting and antibacterial effects, playing important roles in increasing intestinal immunoglobulins, improving digestive enzyme activity, and repairing and protecting digestive tract mucosa.

4 Summary

High-copper and high-zinc diets promote pig growth, particularly in weaned piglets. However, excessive use causes heavy metal accumulation in feces and soil, severely contaminating soil and water sources. While copper and zinc are important for animal growth, organ development, immune response, and reproductive regulation, improper use of high-dose diets causes serious health problems including reduced immunity, impaired digestive function, growth retardation, and increased susceptibility. Therefore, research on rational use of high-copper and high-zinc diets, improving their efficacy, and exploring synergistic effects with other substances will be key to advancing their application.

Meanwhile, the growth-promoting mechanisms of high-copper and high-zinc diets and their mediated signaling pathways require further investigation. On one hand, improving utilization efficiency of copper and zinc in pig diets can reduce excessive addition of antibiotics and these minerals, alleviating resistance and food safety issues. On the other hand, seeking new alternative strategies and usage patterns for high-copper and high-zinc diets will provide references for efficient, green, and sustainable development of China' s swine industry.

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Note: Figure translations are in progress. See original paper for figures.