COPPER IN ANIMAL NUTRITION:

a new choice with CoRouge® Part II

By Valérie Kromm and Stéphane Durosoy

CoRouge®, the red source of cuprous oxide, newly authorized in the EU, was introduced in the previous issue (*Feed Compounder* November/December 2017, p. 24). This monovalent source of copper is characterised by superior technological properties but also by some specific chemical properties differentiating it from other feed grade source of copper. High bioavailability and improved animal performance have been shown in University studies.

Highest copper concentration

As the copper content is the highest in CoRouge® (75%), it offers many advantages for the feed industry:

-less space in premixes

-less warehousing

-less transportation

Like other metallic compounds, copper compounds are highly regulated feed additives. They are classified as hazardous chemicals according to the Regulations on Classification, Labelling and Packaging (CLP). The new CLP classification of copper based products will apply from 1 March 2018.

Figure 1: CLP pictograms of copper compounds

Chemical form	CAS Number	Corresponding CLP pictograms
Copper(I) oxide (CoRouge®)	1317-39-1	
Copper sulphate pentahydrate	7758-99-8	
Dicopper chloride trihydroxide (TBCC)	1332-65-6	
Copper carbonate	1184-64-1	
Copper chelate of amino acids	No chemical formula	To be determined
Copper chelate of glycine		
Copper chelate of hydroxy analogue of methionine		

The highest Cu concentration in CoRouge® is of special interest for premix manufacturers who are concerned by Seveso III Directive. Replacing other Cu sources by CoRouge® gives an opportunity to decrease the quantity of stored products which are classified as dangerous for the environment. This is even more critical with the current replacement of ethoxyquin, recently banned, by classified synthetic antioxidants.

Lower contamination levels in heavy metals

All copper feed grade sources must comply with stringent regulation on undesirable substances. Heavy metals and dioxins are the most critical risks for the feed and food chain. The higher the copper concentration, the lower is the contribution to contamination in the feed. Figure 2 illustrates this advantage with the example of lead.

Figure 2. Relative contribution of copper sources to Pb content in the complete feed

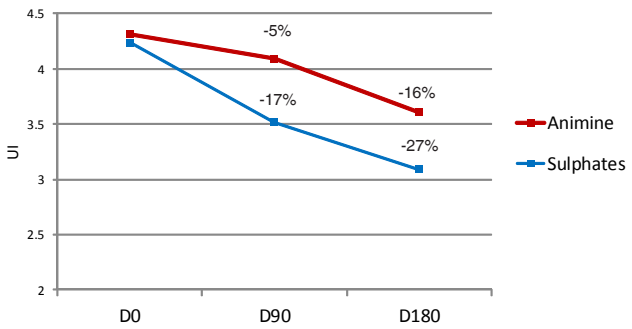
	Copper concentration (%)	Maximum authorised Pb concentration (ppm)	Relative contribution to lead content in the feed
Copper sulphate, pentahydrate*	25 %	100	100 %
Copper chelate of amino acids	15 %	100	170 %
Copper bilysinate	15 %	100	170 %
Copper chelate of hydroxy analogue of methionine	18%	100	139 %
Copper chelate of glycine	25%	100	100 %
Dicopper chloride trihydroxide	55 %	100	45 %
Copper carbonate	55 %	200	90 %
Copper(I) oxide (CoRouge®)	75 %	200	66 %

* Benchmark at 100 %

Non water soluble copper source

There are many advantages in favour of non-water soluble compounds, under the condition that they are enough solubilized in the proximal part of the digestive tract for intestinal uptake. Copper sulphate is well known for its hygroscopicity. Metal sulphates are water soluble compounds and as such they can create negative interactions in the premix and in the gut. Already in the early 2000's, it had been shown that metal oxides were less aggressive on vitamin stability when mixed in vitamin/mineral premixes. Since, vitamin manufacturers have improved their stability so that they are less sensitive to negative effects from other

Figure 3: Vitamin A stability in a piglet premix



compounds and from storage conditions. However, a recent study showed that vitamin A is 12% less degraded in a typical premix for piglet feeds when mixed with Animine products (potentiated zinc oxide HiZox® and CoRouge®) than with zinc and copper sulphate, even at a mild temperature of 25°C (Figure 3).

Attention given to vitamins' stability in premixes and feeds is even more critical after the ban of ethoxyquin, and especially when vitamins levels are reduced due to extremely high prices or product shortage.

Less antagonism with phytase

Minerals like calcium, zinc, copper and iron may bind to phytic acid, thus lowering its solubility in the digestive tract. If such antagonists rapidly chelate phytate after ingestion, then its hydrolysis by endogenous or supplemented phytase will be impaired. This negative interaction will be severe in such conditions:

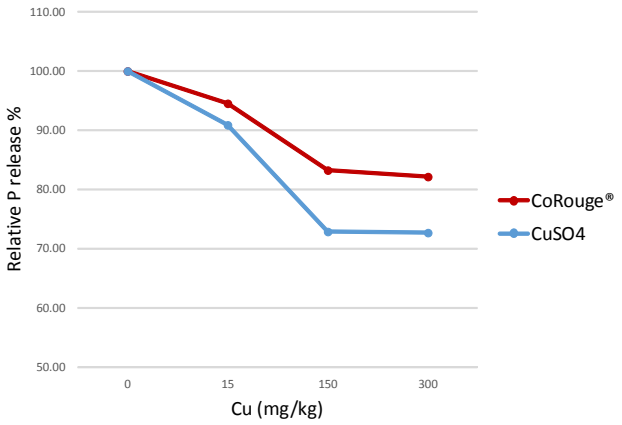
-by the supplementation of high dosages of trace minerals,

-by the supplementation of readily soluble sources like sulphates,

-when supplemented phytase is slow acting.

Phytic acid has a strong affinity to bind with di and trivalent forms of minerals. In contrast to other copper compounds, dicopper oxide is a monovalent form of metal. With a non-water soluble and monovalent source of copper, CoRouge® is less likely to negatively interact with the release of phytic phosphorous. This has been shown in an in vitro study performed by the University of Barcelona (Spain).

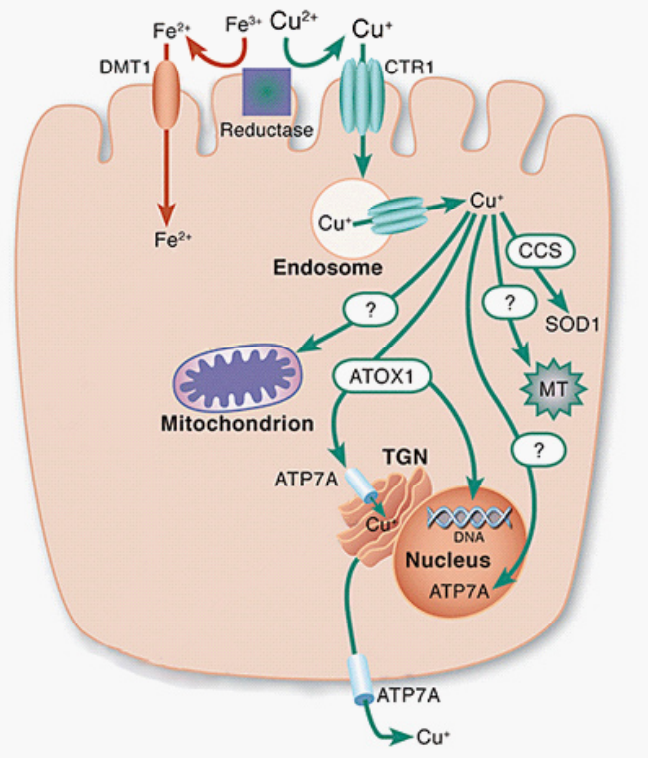
Figure 4: Effect of copper on P release



Direct intestinal absorption

Active absorption of copper involves various intestinal transporters, the most important one being CTR1. Copper absorption depends on its oxidation state. Uptake of copper by CTR1 is possible only with the monovalent form of the copper ion, i.e. the cuprous form Cu^{+}. However, other copper sources authorised in animal nutrition include copper ions in the divalent form, i.e. the cupric form Cu^{2+}. Consequently, some membrane proteins are needed to reduce Cu^{2+} into Cu^{+}; currently, these proteins are not fully identified, but the main hypothesis refers to Steap proteins, like Steap2, also identified as Fe^{3+} reductase. A monovalent form of copper supplied from CoRouge® will be directly absorbable, thus less prone to interferences.

Figure 5: Copper uptake in the enterocyte

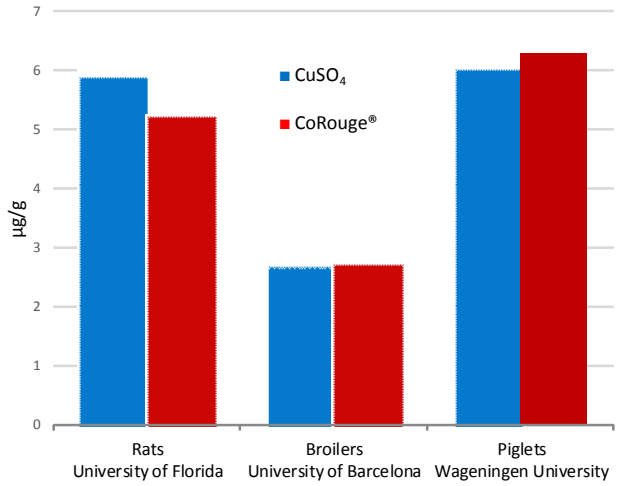


High bioavailability

EFSA Journal in recent years has published several Opinions on the bioavailability of copper compounds. In 2008, it was concluded that copper chelate of hydroxy analogue of methionine had a bioavailability comparable to copper sulphate in broilers. In 2013, no evidence was confirmed that the bioavailability of copper chelate of amino acids would be higher than copper sulphate. In 2014, an equivalent bioavailability was shown between copper bilysinate and copper sulphate.

The high bioavailability of dicopper oxide in CoRouge® has been verified in laboratory animals and in farm animals. In comparison to livestock, it is much easier to deplete rats in copper, and to measure how dietary sources can replenish animals. Such experimental protocol is necessary when we lack sensitive biomarkers of mineral status. This has been realized at the University of Florida under the supervision of Dr Jamie Collins. Measured with liver concentration and serum ceruloplasmin activity, copper status of rats was equivalent between copper sulphate and CoRouge®. The high bioavailability of dicopper oxide has been demonstrated also on piglets and broilers, when supplied at low dosages. An experiment performed at Wageningen University (Netherlands) showed that copper concentrations in plasma, liver and bile were equal when piglets were fed either copper sulphate or CoRouge®. A similar study was carried out on broilers in Barcelona University. Results obtained with copper sulphate were not different from those obtained with CoRouge® (Figure 6).

Figure 6: Copper concentration in liver



At nutritional levels, it is confirmed that the monovalent form of copper oxide shows high bioavailability for the animals, comparable to copper sulphate or chelated compounds.

Growth performance of piglets

The growth promoting effect of copper supplementation on weaned piglets is well documented, but its mode of action is not yet fully elucidated. Copper is known for its antibacterial action and this remains the most assumed effect on intestinal health. Ionic form may play a role, as antibacterial activity of Cu^{+} ions has been shown stronger compared to Cu^{2+} ions.

It is generally perceived that the growth promoting effect of some additives such as copper is limited under good nutritional and management practices. However, this has not been confirmed in two recent experiments supervised by Dr Paul Bikker (Wageningen University). The first experiment tested different copper doses, from 15 to 160 mg/kg supplied as copper sulphate. A dose-response effect was confirmed for growth performance: average daily gain (ADG) increased as Cu dose increased ($p < 0.01$), while feed conversion ratio decreased ($p < 0.01$). Piglet's weights were improved by 2.8 kg after 40 days of supplementation: it is very unlikely that most feed additives can achieve such performance

The most recent study was also performed on a high number of animals. 600 piglets, weaned at 26 days, received two wheat/barley/maize based diets, a prestarter (17% CP) for two weeks followed by a starter diet (15%) for three weeks. There were no medicated zinc oxide or antibiotics in the feeds. The experiment compared different doses of copper, supplied either with copper sulphate or with CoRouge®. At 14 days of supplementation, a clear dose response was already observed, with CoRouge® fed piglets growing faster. After 35 days of supplementation, piglets gained 3.3kg weight when fed 160 mg/kg of copper in comparison to 15 mg/kg. Piglets which received 160 mg/kg Cu from CoRouge® achieved even higher final BW at 21.4 kg, resulting from improved feed intake and feed conversion ratio. To conclude, the beneficial effect of high Cu dose on piglet weight gain is still exceptional, and this effect is maximized with CoRouge® (Figure 7).

If in the future European authorities decide for a drastic decrease in Cu supplementation in piglet diets, growth performance would be significantly impaired. However, at 15 mg/kg Cu, piglets fed CoRouge® would gain 800g more BW in comparison to copper sulphate after 5 weeks of supplementation.

Figure 7: Effect of copper on piglet weight gain (Wageningen University)

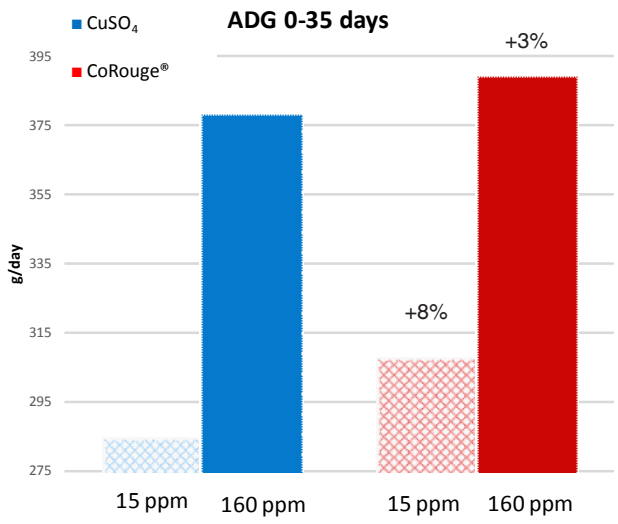
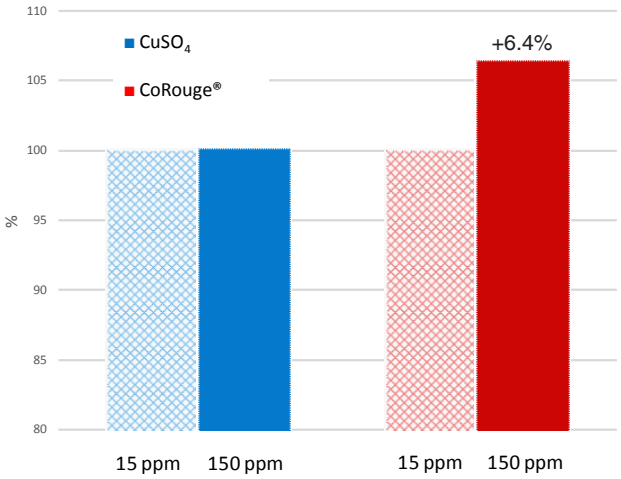


Figure 8: Effect of copper on broiler growth (Barcelona University)



Growth performance of poultry

In the European Union, dietary copper is supplied for poultry up to a maximum of 25 mg Cu/kg, which is higher than animal requirements estimated at less than 10 mg/kg according to scientific bodies. In other world areas, inclusion of 125 to 250 ppm copper sulphate as growth promoting agent is quite popular if allowed. However, literature shows variable results from high copper sulphate supplementation levels on broiler performance. These effects can be positive, neutral but also negative. This response has been recently tested in Barcelona University, not only with copper sulphate but also with CoRouge® at 2 levels of supplemented copper : 15 and 150 mg/kg. 384 one day male Ross broilers were raised with 12 chicks/pen and 8 pens/treatment. Body weight and feed intake were recorded weekly. After 35 days of supplementation at 150 mg/kg, only CoRouge® increased growth performance.

Growth of birds fed 15 or 150 mg Cu/kg as copper sulphate was not affected. Only supplementation with 150 mg Cu/kg as CoRouge® improved feed efficiency, resulting in increased final BW. Further studies are planned to better understand how the source of copper can impact broiler performance.

CONCLUSION

Copper is an essential nutrient for livestock animals, but is also under scrutiny by the authorities due to its possible effect on environmental accumulation and development of microbial resistance. The feed industry is forced to improve current practices in order to find a compromise between animal performance and sustainability. Despite widespread usage over decades, the modes of action and dose responses of copper supplementation are still debated. New doses and sources of phytase raise new questions on interactions with macro and microminerals. With the authorisation of dicopper oxide (CoRouge®), nutritionists have a unique opportunity to utilise this innovative source of copper and to accompany regulatory changes in the European Union.