COPPER IN PIG FEEDS:

a new choice with CoRouge® Part I

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When selecting the source of trace minerals, all premix and feed formulators are familiar with mineral oxides. They use or may use zinc oxide, manganese oxide, but why is copper oxide not a popular source of copper in pig nutrition? This review in two parts will give some reasons and will explain why the situation recently changed with the authorization of the monovalent form of copper oxide.

More restrictive usage of copper in animal feeds

The EU authorities have for decades had a policy of reducing copper levels in animal diets, and especially in pig feeds. Back in 1982, the Scientific Committee for Animal Nutrition (SCAN) concluded that maximal level in total dietary copper should not exceed 125 mg/kg in complete feeds for piglets and pigs. In another Opinion from 1983, SCAN already expressed the concern of higher selection of *E.coli* strains resistant to one antibiotic (chloramphenicol) with higher dietary copper in pig feeds. However, they acknowledged that specific measures could be authorized in some regions where environmental concerns are lower.

Until the early 2000's, maximum authorized levels took into account animal production densities to assess the risk of copper load due to pig manure spraying. At that time, maximum Cu dietary concentration was 175 mg/kg up to 16 weeks of age of piglets. But regulation differed among European countries for pigs after the 17th week of age: in Member States where the mean density of the porcine population was equal to or higher than 175 pigs per 100 ha of utilizable agricultural land, maximum Cu level in the complete feed was 35 mg/kg instead of 100 mg/kg.

The SCAN Opinion from 2003 proposed a compromise to reduce copper burden without affecting performance of farm animals, especially when its usage as a growth promotor is well documented. They suggested reducing the authorized level of 175 mg/kg to 10 weeks of life instead of 4 months. Figure 1 summarizes the literature reviewed at that time, showing that the younger the pig is, the more significant is the growth promoting effect of copper at high supplementation levels.

On the risk of microbial resistance, SCAN communicated that a plasmid from a gut bacteria could contain both a gene encoding resistance to copper and antibiotic resistance genes. Following SCAN Opinion, Regulation 1334/2003 of 25 July 2003 defined new maximum copper levels in pig feeds:

— piglets up to 12 weeks: 170 (total) mg/kg

— other pigs: 25 (total) mg/kg

In 2016, at the request of the European Food Safety Agency (EFSA), two high quality literature reviews were published. Initiated in 2012, an updated report on the influence of copper on antibiotic resistance of gut microbiota in pigs, including piglets, was supervised by Ghent University. Of a total of 901 references, only 33 were found eligible. Authors concluded that they could not exclude the possibility of a positive correlation between copper supplementation above requirements and development of antibiotic resistance. Another

Figure 1: Effect of copper level on body weight gain

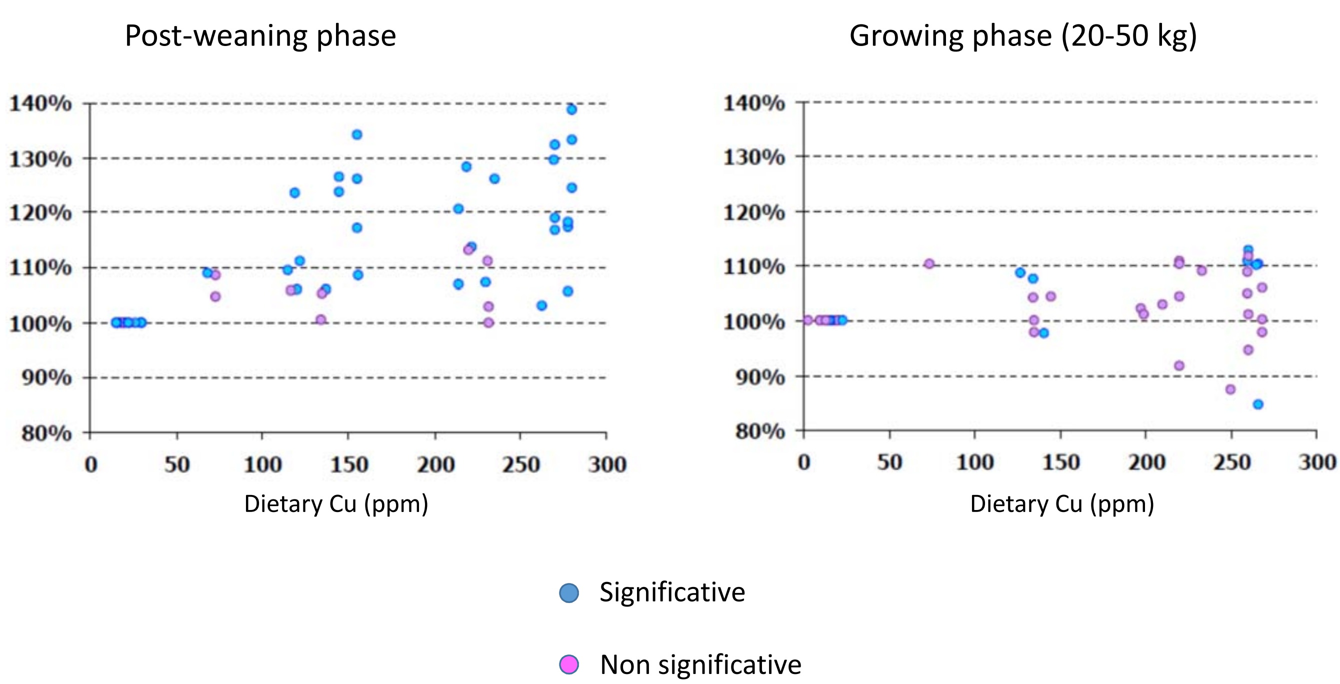


Table 1: Copper concentration in feeds

Animal species	*Animal category*	*n*	*Cu (mg/kg complete feed)*		
			Median	*10% Percentile*	*90% Percentile*
Poultry	Broiler starter	63	14	10	25
	Broiler fattener	360	19	12	24
	Laying hens	440	15	9	23
	Ducks/geese for fattening	91	17	12	23
	Turkeys for fattening	203	14	18	24
Pigs	Piglets	1420	136	23	168
	Fattening pigs	2034	18	12	26
	Sows	546	20	13	29
Control data submitted by 14 European countries					

systematic literature review focused on the effects of copper intake levels in the gut microbiota profile of target animals. Authors concluded that copper, even at low concentrations (<50 mg/kg in complete feed) may affect the microbiota in the gastrointestinal tract. From these reports, EFSA published a 100 pages Opinion in 2016 for the revision of maximum contents of dietary copper. The suggestion with the highest impact on animal performance was to reduce the Cu concentration from 170 to 25 mg/kg in piglet feeds, thus suppressing its growth promoting effect. It created a strong reaction from the pig industry in the EU. Table 1 shows that all piglet feeds which were collected and analysed, reached the highest permitted level, as the effect on weight gain and fecal score is well known.

Regulatory authorities want to restrict safety margins in copper supplementation. They have to choose solutions which maximize animal performance while minimizing the impact on the environment. A new tool is now available to simulate the impact of copper in the feeding program of the pig, from weaning until slaughter. It takes into account the growth performance of the animals and Cu dietary concentration in each feeds. The software calculates the copper balance, which means that pig farmers can visualize the quantity of excreted copper and how to decrease it. siMMin™ is a user friendly tool, available on line in English at http://animine.eu/mineral-simulator-software/

Figure 2

In combination with copper level, nutritionists need to select mineral sources which offer the best proofs of bioavailability and of animal performance.

Back to the 80's in the USA

Premix and feed manufacturers prefer feed ingredients which offer the best physico-chemical properties. In the 80's in the USA, the most popular source of copper used at that time was copper oxide. Copper concentration was close to 80% and this compound was not hygroscopic, in contrast to copper sulfate. There were no severe problems of mineral deficiency as supplementation levels were far above animal requirements. However, the situation changed when studies supervised by Dr David Baker at Illinois University revealed that the bioavailability of copper oxide was very poor. Then this compound disappeared from formulas, and for decades animal nutritionists have believed that the oxide form of copper cannot be used as a feed additive. However, when looking in more detail, it appeared that the compound used by the US industry was a black powder. This is the divalent form of copper oxide: more exactly cupric oxide. All chemists know that copper can have two oxidation states, and that these chemical forms have totally different properties. Figure 3 shows that the cupric and cuprous oxide can easily be recognized based on their respective colour.

Dr Baker had also pointed out that, as opposed to cupric oxide, the monovalent form of copper oxide showed a high bioavailability

Figure 3: Two forms of copper oxide

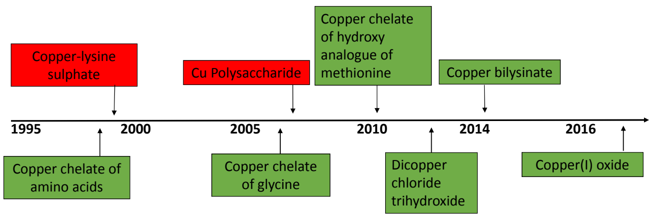
Cupric oxide CuO Copper(II) oxide	Cuprous oxide Cu2O Copper(I) oxide

in animal studies. Against this background, Animine decided to invest in the authorization of cuprous oxide as a feed additive in the European Union.

Authorization of feed grade sources of copper in the EU

The creation of the EFSA and the strengthening of feed legislation has favoured a clearer regulatory situation for the authorization of feed additives. From the old Regulation 70/524/EEC consolidated for 30 years, procedures concerning feed additives have gained in scientific expertise with the implementation of Regulation 1831/2003. Up to 2010, only two new sources of copper had been authorized: chelated copper of amino acids obtained from hydrolyzed soya protein, later followed by a more restricted definition of the ligand (synthetic glycine). In the last seven years, four new sources of copper have been registered as shown in Figure 4.

Figure 4: Authorisation of copper sources in the EU



Animine has submitted, in 2014, a dossier to grant the authorization of cuprous oxide in animal nutrition. EFSA published a Positive Opinion in June 2016, later followed by Regulation 2016/2261 in December 2016.

Authorization and definition of CoRouge

Nutritional feed additives (trace minerals, vitamins, amino acids) are authorized as generic approvals, which means that product registration is not exclusively linked to the petitioner. However, an evolution has been noticed with a more restrictive definition in the Annex entry of the Community Register of feed additives. It implies that the active substance is approved under the condition that some physico-chemical criteria are respected. Such policy has been initiated to secure the level of purity and safety of authorized feed additives. This is exactly what happened for the approval of cuprous oxide, based on the full dossier submitted by Animine. A formulated compound has been authorized with the following criteria:
Preparation of copper(I) oxide with :

-a minimum copper content of 73 %
-sodium lignosulfonates between 12 % and 17 %
-1% bentonite.
Granulated form with particles < 50 µm: below 10 %

This is the definition of CoRouge, exclusively supplied by Animine.

Particle size distribution is an essential feature for a trace mineral compound. It defines solubilisation kinetics in the gastro-intestinal tract, thus predicting bioaccessibility of the mineral. Dust content is also an essential product specification to secure workers' safety. EU scientific and political authorities have expressed their wish to authorize non dusty powders in order to reduce the proportion of respirable and inhalable particles in premix and feed factories. Animine will specify on the Certificate of Analysis of each batch that the proportion of particles below 50 microns is well below 10%.

Figure 5: picture of CoRouge®

The official term for this new authorization is copper(I) oxide, instead of cuprous oxide or dicopper oxide. It emphasizes the monovalent state of this chemical form, differentiating it from other feed grade sources. In the EU and outside the EU, we should expect, from now on, that the generic term "copper oxide" will not be utilized any more by animal nutritionists, and that the oxidation state will be always specified.

Copper concentration in feed grade copper sources in the EU

	Copper concentration
Copper chelate of amino acids	10-15 %
Copper bilysinate	15 %
Copper chelate of glycine	15-25%
Copper chelate of hydroxy analogue of methionine	18%
Copper sulphate, pentahydrate	25 %
Dicopper chloride trihydroxide	53 %
Copper carbonate	55 %
Copper(I) oxide (CoRouge®)	**75 %**

As the copper content is highest in CoRouge®, it offers many advantages for the feed industry The second part of this article, to be published in the Jan/Feb 2018 issue, will develop the different consequences of this high copper concentration and review the other specific properties and effects of CoRouge®.