Rare earth elements as alternative growth promoters in pig production

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Abstract

Growth promoters or performance enhancers are used worldwide in pig production. For over 50 years, antibiotics as feed additives proved to be effective in a better utilization of nutrients with an improved feed conversion ratio and better growth rate in most cases. In the EU, most of these feed antibiotics are forbidden now, and the last three ones still allowed will be banned at the end of 2005. In China for more than 40 years, special mineral salts called Rare Earth Elements (REE) or lanthanides with the elements lanthanum, cerium and others are used as feed additives in animal production. Numerous reports in the Chinese literature describe that a small amount of these REE mixtures in the diet can increase the body weight gain of pigs, cattle, sheep and chicken and it is reported that they increase milk and egg production. This finding was totally unnoticed in the western world. In the past five years about a dozen of studies -mainly in pigs- were performed under western animal production conditions. Most of these studies in piglets and in fattening pigs provided significant data, indicating that REE imported from China can improve weight gain and feed conversion. Recently, in Switzerland, REE supplemented pig feed was admitted to the market. The safety of REE, which are ubiquitous at low concentration in all soils and plants, has been proven. Long term studies – even in man for medical purposes - showed that REE toxicity is similar to the one of table salt (NaCl). The mechanism of the action of REE is still debated. It is possible that they develop their activity in the digestive tract since very little is absorbed. However, it is also discussed that these lanthanides - or one of them - have the characteristics of essential trace elements for animals. In summary, REE might be of interest in animal and especially in pig production as a new, safe and inexpensive alternative growth promoter.

Introduction

Antibiotics as feed additives have been banned already for some years in Sweden and in Switzerland. In the European Union, the three last antibiotics, still allowed as growth promoters, will be phased out at the end of 2005, too. Worldwide there is an increasing demand for food which can only be achieved by an increased meat production. The full ban of antibacterial growth promoters might seriously affect post-weaning health and performance (Lynch, 1999). This will almost certainly necessitate the development of new feeding and health care strategies. Therefore, there is a strong need for alternative growth promoters such as pro- and prebiotics, enzymes, organic acids as well as herb extracts (Wenk, 2003). These feed additives have to be efficient, safe and they should not harm the environment (Khan, 2004).

A very new approach in this respect is the supplementation of feed with “Rare Earth Elements” (REE). REE, are the elements scandium, yttrium and the lanthanides from lanthanum to lutetium. Although the rare earth elements are not particularly rare in the earth crust, the term persists. In this article, REE refers mainly to the lanthanides and among them to the elements lanthanum (La, atomic number 57), cerium (Ce, atomic number 58) and praseodymium (Pr, atomic number 59). Lanthanum and cerium occur geologically in the earth at a concentration similar to the essential trace element cobalt and thus are not rare at all (Süss, 2004). Since 80% of the world reserves on REE are located in China, this country became the main producer and supplier of REE in form of mineral concentrates, alloys and oxides. The main application of REE is in metallurgy, chemical industry, electronics and in agriculture (Richter, 1996).

<u>Industrial uses of REE</u>

About 25% of the lanthanides produced are used in carbon-arc lighting applications. Another 25% of the production of lanthanides is used in the form of mixed lanthanide metals and cerium metal. These metals are used in cigarette lighter flints, magnesium alloys, and some of the ferrous alloys. The third 25% of lanthanum production is used in the glass industry. Didymium (a mixture of praseodymium and neodymium), cerium salts, and some separated lanthanides have important uses in both the coloring and the decoloring of glass. The remaining 25% of the lanthanide usage is divided among many miscellaneous applications, including television tubes, catalysts, lasers and for agricultural uses (Evans, 1990).

Agricultural uses of REE in China

In China, REE -usually a mixture of mainly cerium, lanthanum and praseodymium- have been used already for 40 years as performance enhancers in agricultural plant production, and quite remarkable results were reported from Chinese agricultural operations (Wan et al., 1998). Although the reason for these growth promoting and yield increasing effects is still unknown, it is speculated that a physiological interaction of REE and calcium might influence the structure and function of cytoplasma membrane, of photosynthesis or enzyme activity (Hu et al., 2004).

The Chinese data were confirmed in different other countries, e.g. in Australia (Diatloff et al., 1995) and the United Kingdom (Andrew et al., 1983). REE supplemented fertilizer may increase productivity by up to 15% (Wen et al., 2000), but it does not increase the REE content in the products (Xu et al., 2002). In hydroponic studies Tucher et al (2001) showed that there is a strong effect of lanthanum in the culture medium on the composition of the minerals in the plant.

REE as feed additives

In animal production, as with plants, amazing results have been reported in the Chinese literature, while in the western world there was no knowledge at all of these growth promoters. According to these numerous publications, a small amount of REE in the feed can increase the body weight gain of cattle, pigs, chicken, fish and rabbits, and might increase milk production of dairy cows and egg production of laying hens (Shen at al., 1991). Feed conversion ratios were also improved in nearly all animal categories (see table 1).

For pigs and piglets, multiple Chinese articles concerning performance enhancing effects of REE exist. For example in weaned piglets with a body weight of about 7 kg, the body weight gain was increased by 5% to 23% and the feed conversion was improved between 4% and 19% under the influence of REE (He and Xia, 1998). In piglets with a body weight between 13 and 17 kg, improvements in weight gains of 11% to 20% and of feed conversion ratios of 5% to 9% were reported (Li et al., 1992; He and Xia 1998). In growing pigs in a body weight range of 30 to 50 kg, REE caused an increased body weight gain of 9% to 13% and the feed conversion ratios were improved by 6% to 8% (Cheng et al., 1994) and in a recent paper by Wang and Xu (2003) a weight gain of 13% and an improved feed conversion ratio of 7% were found.

In general, no particular REE elements were added to the feed, but varying mixtures of mainly cerium, lanthanum and praseodymium with traces of the other lanthanides. Furthermore, the anions of the REE salts are differing. Nitrates and chlorides were mostly used at the beginning, while organic compounds are used in recent studies. These include REE citrate, gluconate, or the aminoacids methionine, lysine and glutamine may be bound. The concentration applied also varies. In pigs, for example between 100 mg and 600 mg of the REE salts with varying purity were added per kg of feed, and therefore the data are hardly comparable. Since the literature on the effects of REE is predominantly written in Chinese, detailed results are scarcely available to occidental scientists, and the sources are difficult to assess, because quite often details concerning experimental methods are not given and statistical treatment of the data was not performed. Thus, important research questions in the

Chinese reports are still open, making a comprehensive understanding of the action of REE as feed additives rather difficult.

Feeding studies under "western condition"

Since Chinese animal husbandry conditions can hardly be compared with those in Europe or the United States, and since western conditions with high performance animal breed and optimised feed may be less suspectable to growth promoters and performance enhancers, it seemed urgently needed to redo the REE feeding studies under "western conditions".

The first in a row of feeding studies (see table 2) in pigs was performed in 1999 (Rambeck et al., 1999). A total of 72 crossbred piglets (Deutsche Landrasse x Pietrain) with an average body weight of about 7 kg were given different REE salts, either rather pure lanthanum chloride (99.7% $LaCl_3 x 6H_20$) or a REE mixture of 38.0% $LaCl_3 x 6H_20$, 52.1% $CeCl_3 x 6H_20$ and 3% $PrCl_3 x 6H_20$. The REE were supplemented at 75 mg/kg and at 150 mg/kg to a complete diet (52.7% barley, 20% wheat, 18.8% soybean, metabolic energy 13 MJ/kg, digestible crude protein 184 g/kg) which was given for 5 weeks. The best results were obtained in the REE-mixture. Body weight gain improved by up to 5%, feed conversion ratio by up to 7% ($p<0.05$).

In a second study (He et al., 2001) crossbred piglets with 17.5 kg body weight were given a diet, supplemented with 300 mg REE-mixture per kg. After 1 month the REE group had a significantly higher body weight gain of 19% and the feed conversion ratio improved significantly by 11%. After another month of REE supplementing, body weight gain was still 12% better and feed conversion ratio still 3% better than the control group (not significant). The health of the animals, the meat quality and the safety of the animal products were not influenced by REE. The results from slaughtering and meat quality control showed that according to the quality class "EUROP" all animals were graded E or U (the two best classes). Also other meat quality parameters were not affected by REE either pH_1 and pH_{24} as well as the brightness of the meat and the ratio meat to fat did not differ significantly (Rambeck et al., 2004). The REE contents in the samples of muscle, liver and kidneys from pigs in both experimental groups were very low. Although the content of La in the REE group was higher than that in the control group, generally the accumulation rates in all the experimental pigs were very low and close to the limit of detection.

In a field study in Switzerland, two trials were performed, one with 97 piglets (11.2 kg at the beginning), the other with 176 piglets (8.3 kg at the beginning) (Schweizer Edelschwein). After 16 days, and 30 days of feeding respectively, a 200 mg REE-mixture per kg body weight gain was higher by 3 to 10% and feed conversion ratio improved by 2 to 9% as compared to the controls. This was the first time that REE were shown to be effective under field conditions (Eisele, 2003).

Since it is known that the bioavailability of REE salts is influenced by its anion (Shan et al., 2002), the effect of REE-citrate was studied. While REE-citrate had shown to increase significantly body weight gain by 7% in chicken (Halle et al., 2003), REE-chloride under similar conditions neither influenced weight gain nor feed conversion (Schuller et al., 2002). Therefore, feeding studies with REE-citrate were initiated in piglets. This REE salt has the advantage that it is much less hygroscopic than REE-chloride and therefore much better to handle as a feed additive.

In a feeding study, lasting 6 weeks, 50, 100 and 200 mg of REE-citrate were given to 28 piglets (n=7 per group) weighing 8.6 kg. A dose dependent response in the form of increased weight gain by up to 22% and feed conversion ratios of up to 19% were observed in this trial (Knebel, 2004).

Significantly better performance in pigs fed REE-citrate for the whole fattening period were obtained by Kessler (2004). When REE-citrate was given at a concentration of 250 mg/kg diet, it took control animals 102 days to reach 104 kg body weight, while

REE-citrate supplemented animals needed only 93 days. The average weight gain per day was 782 g/day vs 851 g/day. Feed conversion ratio improved from 2.5 in the control to 2.4 in the REE-citrate group. All these differences were significant. What was especially astonishing and what had not been described before was that the effect in female animals was roughly twice as high as in male castrated animals (see figure 1 and 2).

It has to be mentioned that feeding studies have also been published where no improvement of growth and feed conversion was found. In a feeding study with fatting pigs for example, diets with different REE anions in a concentration of 100 mg per kg feed showed no growth promoting effects (Halle et al., 2002). But referring to the Chinese literature, only a distinct concentration of REE in the diet can improve body weight gain and feed conversion, a low content of REE may have little or even no effects at all. In another trial, REE chlorides had no effect at all on weight gain and feed conversion, however in this case the piglets had to be treated first with antibiotics for diarrhea (Eisele, 2003).

<u>Possible Mechanisms</u>

What are the possible explanations for this striking effect of REE in pigs? As REE are poorly absorbed from the gastrointestinal tract, it was thought that REE influence the microbial composition in the gut and thus improve digestibility and utilization of nutrients in the diet (Li et al., 1992). High concentrations of lanthanides are usually required for inhibition of bacterial growth, while several authors have reported that low concentrations may stimulate bacterial growth (Muroma, 1958).

Different reasons for the bactericidal action and the bacteriostatic activity of REE are discussed. Biochemical and histological evidence confirms the binding of lanthanum to the surface of bacteria. This reduces the surface charge and retards electrophoretic migration. When the surface charge is completely neutralized, flocculation occurs (Evans, 1990). Additionally bacterial respiration is strongly inhibited by lanthanides.

In general, bacteria seem to be more susceptible to lanthanides than fungi, and the heavier lanthanides tend to be more detrimental than the lighter ones. But lanthanides also inhibit the formation and germination of fungal spores (Talburt and Johnson, 1967).

However, analysis of the gut flora in chicken revealed that the main microbial populations of the alimentary canal were unaffected by REE supplementation (Schuller et al., 2002). In vitro studies in a RUSITEC (Rumen Simulation Technique) system indicated that ruminal fermentation and ruminal microorganisms were not influenced by REE (Knebel, 2004).

Another possibility might be an influence of REE on the activity of certain hormones and enzymes, like growth hormone or T3. Data from Xu et al. (1999) and He et al. (2003) point in this direction. In growing rats, lanthanum as well as a mixture of different REE chlorides had positive effects on body weight gain and improved feed conversion ratio significantly. Furthermore, supplementation of REE had clear effects on blood parameters. Some enzymes like alkaline phosphatase and alanine aminotransferase increased significantly, blood glucose decreased and creatinine in blood increased. This suggests that even when only a very small amount of REE is absorbed, this might affect the physiological metabolism in the animal. Studies with preadipocytes in cell culture indicate that REE stimulate the proliferation of these cells and influence the concentration of fatty acids, suggesting an effect on adipogenesis and lipogenesis rates in adipose tissue (He et al., 2004). Because there is a special relationship between REE and calcium, it was also suggested that REE may affect activities of hormones or enzymes by replacing or inhibiting calcium (Hanioka et al., 1994). It might also well be that the lanthanides are essential trace elements for man and animals, a fact that might be overlooked since they are ubiquitous, occurring at low concentrations in all kinds of soil and in all plants (Wyttenbach et al., 1998; Krafka, 1999). Though REE have attributes of essential trace elements, there is no proof at all yet.

Safety

Only very small amounts of REE are absorbed when given orally. Determination of REE in muscle and in liver and kidney after 3 months of REE feeding to pigs was performed by neutron activation analyses and by ICP-MS (He et al., 2001). REE concentration was partially below the limit of detection, and lower than the content of REE in plants, fruit and vegetables (Krafka, 1999).

Studies on the eventual toxicity of orally given REE are numerous. One of the very recent ones (Richter, 2003) states that the oral, acute toxicity in animal experiments is very low with an LD_{50} of up to 10 g / kg body weight. This toxicity is even lower in the presence of complexing agents like citrate. Longterm studies from China where REE are applied to a large extent in fertilizer show that there are no negative effects. The low oral toxicity of the REE can also be deduced from the fact that its LD_{50} is the same as the one of table salt (Wald 1990).

Since the chemical and biochemical behaviour of the different REE are very similar, the new numerous studies on lanthanum alone for human medicine purposes are most interesting in this respect. Lanthanum carbonate is a novel treatment for hyperphosphatemia in dialysis patients. In the course of obtaining the registration for this new alternative phosphate binder, comprehensive toxicological, pharmacological and clinical long term studies treatments were performed in man. Up to 3 g of elemental lanthanum per day and person for up to 4 years were well tolerated, no adverse and toxic effects occurred and there was no evidence of significant systemic accumulation (Harrison and Scott, 2004; Hutchison et al., 2004; Locatelli et al., 2004; Ritz, 2004).

<u>Conclusions</u>

From October 2004 on, only that feed additives that passed a renewed European Food Safety Authority (EFSA) procedure can be put on the market in the EU. Under these new rules feed additives will be categorised as technological additives, zootechnical additives and coccidiostats and histomostats (Khan, 2004). The terms growth promoters or performance enhancers do not occur anymore. If it can be proven that REE have the character of trace elements, they belong to the nutritional additives, if they enhance the digestibility or stabilize the gut flora, they are zootechnical additives.

How costly the procedure of registering feed additives will be, has been described recently (Pape, 2004), but the market for feed additives is big (in Germany total turnover of feed additives in 2003 was about 256 million Euro), and especially after the ban on in-feed antibiotics, it started to move quickly.

In Switzerland, REE obtained a temporary registration under the trade name "Lancer®". It can be supplemented like other essential trace elements to the feed of piglets and pigs at a concentration between 150 and 300 mg REE per kg feed. Farmers unanimously report a better faeces quality and an increased health status, however, these are mostly subjective observations (Zehentmayer, 2004).

In conclusion, rare earth elements may well be of interest in animal - and especially in pig production as a new, safe and inexpensive alternative feed additive.

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Table 2: Chinese feeding studies with Rare Earth Elements

Species	REE dosage	Effects	References
laying hen	200 - 800 mg / kg	+ 3.9 -8.85 % EY + 0.5 - 1.33 g EW	Wu et al. (1994)
broiler	300 mg / kg	+ 20.3 % WG	Zhang and Shao (1995)
	400 mg / kg	+18.6 % WG	
	500 mg / kg	+ 6.6 % WG	
broiler	65 mg / kg	+ 6.3 % WG	Xie and Wang(1998)
	130 mg / kg	+ 10.71 % WG	
	195 mg / kg	- 0.09% WG	
pig	100 mg / kg	+ 8 % WG - 8 % FC	Chen (1997)
	130 mg / kg	+ 25 % WG - 19 % FC	
pig	200 mg / kg	+ 3.97 % WG - 1.66 % FC	Hu et al. (1999)
	400 mg / kg	+ 8.93 % WG - 4.65 % FC	
	600 mg / kg	+ 32.34 % WG - 11.29 FC	
pig	50 mg / kg	+ 6-12% WG -4 – 10% FC	Xia and He (1997)
	100 mg / kg	+ 13% WG -6 – 7% FC	
	150 mg / kg	+ 6-12% WG -4 – 10% FC	
piglets	300 mg / kg	+ 12% WG -11% FC	Shen et al. (1991)
	600 mg / kg	+ 14% WG -14% FC	
	900 mg / kg	+ 7% WG -6% FC	

piglets	48 mg / kg	+ 11-19% WG -9 – 19% FC	Yuan (1994)
piglets	75 mg / kg	+ 13-20% WG -5 – 8% FC	He and Xia (1998)
pig	100 mg / kg	+ 13.26 % WG - 8.50 % FC	Xu et al. (1999)
pig	100 mg / kg	+13.06 % WG - 6.53 % FC	Wang and Xu (2003)

WG = weight gain

FC = feed conversion

EY = egg yield

EW = egg weight

Table 2: Feeding studies with Rare Earth Elements under „western conditions“

Species	REE	REE dosage	Effects	References
piglets	REE-chloride	75 mg / kg	+ 2 % WG - 4-5 % FC	Rambeck et al. (1999)
		150 mg / kg	+ 0-5 % WG -3-7 % FC	
broiler	REE-chloride	150 mg / kg	no effects on WG, FC, EY or EW	Schuller et al. (2002)
		300 mg / kg		
Japanese Quails		75 mg / kg		
		150 mg / kg		
		300 mg / kg		
broiler	REE-chloride	100 mg / kg	+ 5 % WG	Halle et al. (2002)
	REE-nitrate		+2 % WG	
	REE-ascorbate		+7 % WG	
	REE-citrate		+ 6.5 % WG	
fattening pigs	REE-chloride	100 mg / kg	- 3.6 % WG	Böhme et al. (2002)
	REE-nitrate		- 3.6 % WG	
	REE-ascorbate		- 3.4 % WG	
	REE-citrate		- 1.1 % WG	
piglets	REE-chloride	150 mg / kg	+ 19 % WG - 11 % FC	Borger (2003)
fattening pigs		150 mg / kg	+ 12 % WG - 3 % FC	
piglets	REE-chloride	300 mg / kg	+ 4-5 % WG	Eisele (2003)
fattening pigs		200 mg / kg	+ 3-10 % WG - 2-9 % FC	
fattening pigs	REE-chloride	200 mg / kg	+ 8.8 % WG - 3.6 % FC	Kessler (2004)

WG = weight gain

FC = feed conversion

Figure 1: Feed conversion ratio of female and male pigs during the feeding study of Kessler (2004) (* p<0.05)

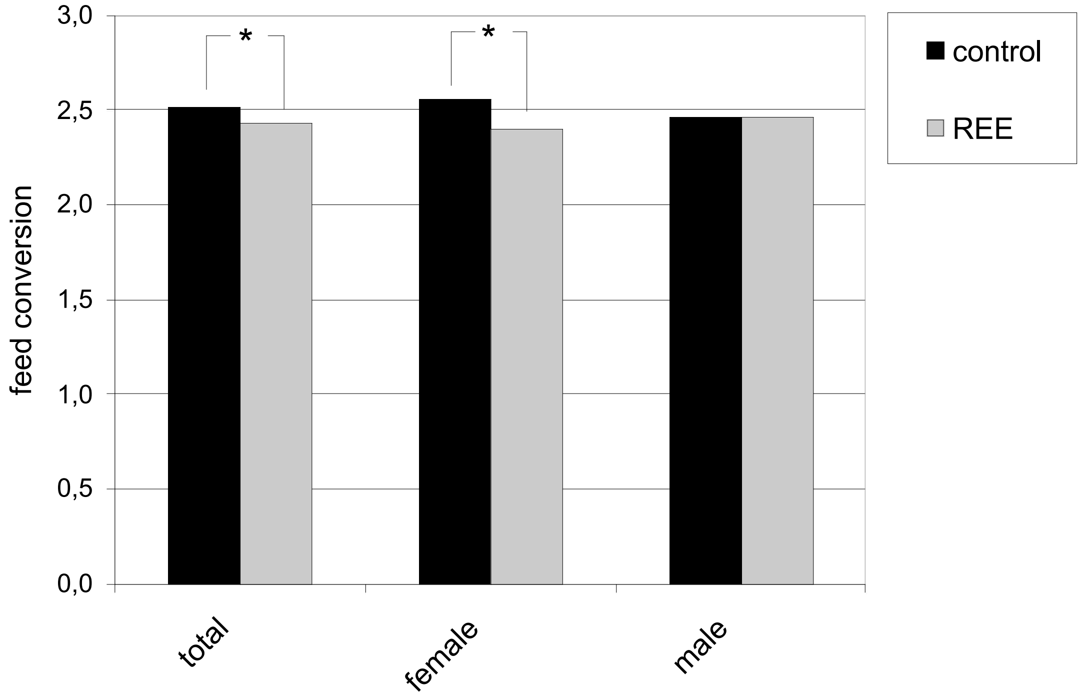

Figure 2: Daily body weight gain of female and male pigs during the feeding study of Kessler (2004) (* p<0.05)