

## The Key Role of Nucleotides in Pig Nutrition

Klaus Hoffmann, PhD, Chemoforma Ltd, Switzerland

One goal in all types of livestock industry is to maximise the efficiency of production to optimize profitability. But the intensification of production often leads to increased susceptibility of the animals and the resulting reduction of general performance and profit. Bacterial, viral or parasite infections often affect the pigs whose immunity may be compromised by the stressful conditions on farms. The alterations in drug-use policies and consumer attitudes have already impacted feed producers and farmers and thus have prompted interests in developing alternative strategies for growth and health management. The concept of functional feeds represents an emerging new paradigm to develop diets for pigs. Functional feeds extend beyond the satisfying basic nutritional requirements to improve growth and feed utilisation also the general health and stress resistance of the animals. Functional feeds would help to reduce the cost of medication and production and simultaneously improve consumers' perception.

The successes of probiotics and prebiotics in livestock industry are obvious. Nevertheless, the basic requirements of diets to supply adequate quantities of essential and non-essential nutrients for the various organisms must not be neglected. The stimulation of growth of intestinal bacteria by pro- or prebiotics implies the supply of sufficient amounts of other nutrients to enable the multiplication of these microbes. If the supply of basic nutrients can not be guaranteed the beneficial effects of pro- and/or prebiotics will be reduced or even unverifiable. It still needs to be clarified if there are not other possibilities to increase performance and general health of pigs without the risk of extensive biological and environmental consequences.

### Nucleotides

Nucleotides are chemical compounds that consist of three components: a heterocyclic base, a sugar, and one or more phosphate groups (Fig. 1). In the most common nucleotides the base is a derivative of purine or pyrimidine, and the sugar is a five-carbon sugar (pentose).

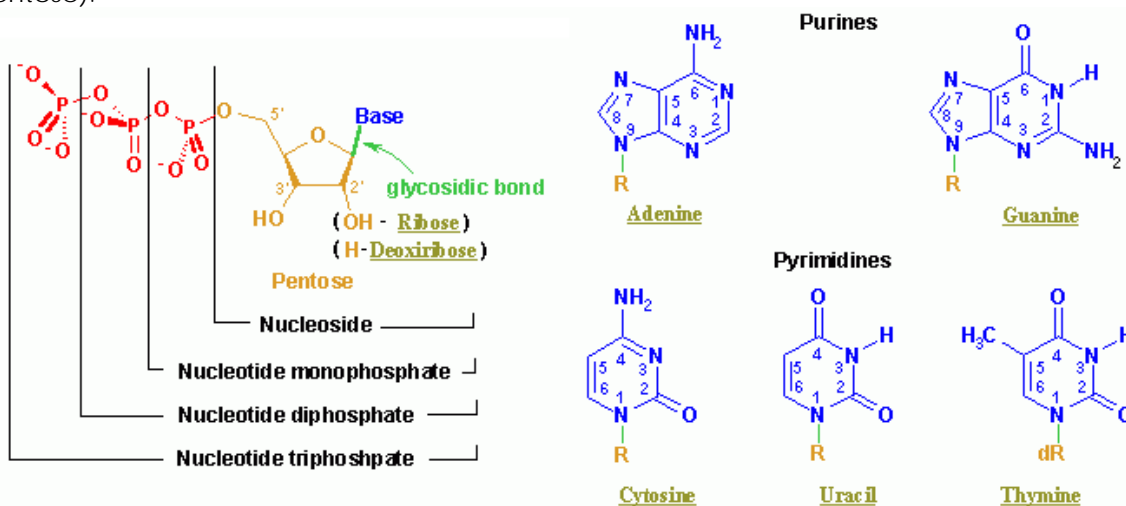


Fig. 1: Chemical Structures and Composition of Nucleotides

Nucleotides have universally valid essential physiological and biochemical functions including encoding and deciphering genetic information, mediating energy metabolism and cell signalling as well as serving as essential components of coenzymes, allosteric effectors and cellular agonists. RNA and nucleotides thus provide basic building blocks for cell proliferation in fauna and flora. Unhindered cell proliferation is a prerequisite for growth, repair, development and functionality of organs and regulatory systems (e.g. the immune system). For years, nucleic acids and nucleotides were not considered essential nutrients for use in any dietary programmes. It was thought that all organisms can supply sufficient amounts of nucleotides to meet their physiological demands (Fig. 2). However, under certain conditions, including rapid growth, limited food supply, stress, immunological challenges and some

others, dietary nucleotides turn to conditionally essential nutrients (Fig. 3). Addition of a balanced formulation of purified dietary nucleotides (Fig. 4) help to cope with challenges by filling the internal nucleotide pool as reported in numerous scientific publications.

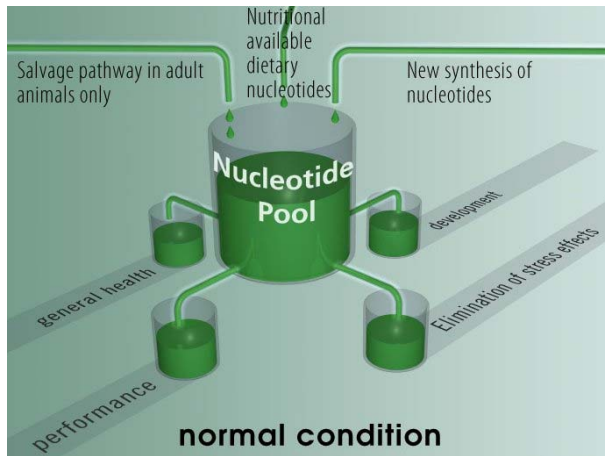


Fig. 2: Under normal conditions the supply of nucleotides is guaranteed through internal metabolic and catabolic processes. The de-novo synthesis of nucleotides, or the reuse of nucleotides from dead cells (so-called "salvage pathway") and the nutritional available dietary nucleotides allows meeting even temporary peaks in the demand for nucleotides without losses in performance.

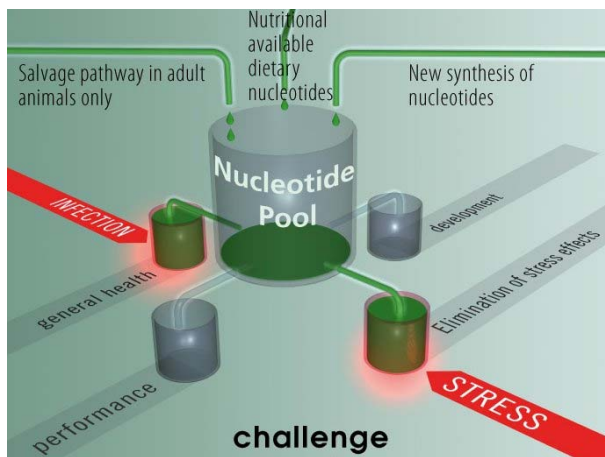


Fig. 3: Under detrimental conditions universal in modern farming, the supply of nucleotides cannot be guaranteed by internal resources. An effective reaction to health challenges or regenerative activities can only be guaranteed at the expense of performance as there are not enough nucleotides available for growth, reproduction or development.

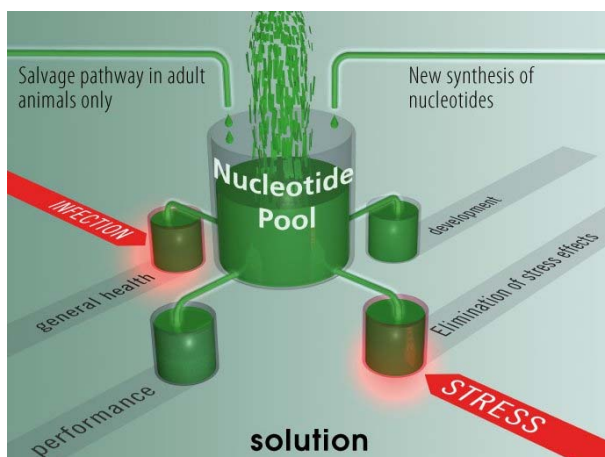


Fig. 4: Supplementing feed with adequate amounts of high-quality nucleotides replenishes the internal pool and thereby supports performance even under adverse conditions. Dietary nucleotides are a management tool to maintain general health, enhance performance and manage the harmful effects of stress.

From a physiological point of view, the immune system is one of many systems that must be in balance with other systemic functions. Health impediments tax the organism, and the animal's natural drive to survive reduces performance and productivity and thus the financial return to the producer.

Sows for instance, suffering from latent or apparent health challenges will not achieve litter sizes and farrowing rates that might be accomplishable from their biological potential. Likewise the same is true for piglets. Their performance will suffer from challenges of the immune system or stress due to handling as well as vaccination just to mention two.

According to the definition, nutraceuticals need to support the function of the immune system to improve general animal health. RNA/nucleotides are the building blocks for life and involved in diverse cellular processes. They facilitate immune response by supporting the crucial proliferation of cells involved in cellular and humoral defence mechanisms (Tab. 1). RNA/nucleotides are natural substances, which, when purified and balanced accordingly, will not stimulate innate or acquired immunity but support natural processes without creating undesirable side effects like resistance or adaptation. Animals fed nucleotide-supplemented diets generally have shown enhanced resistance to viral, bacterial and parasitic infections. The reasons for the immunofacilitating properties of RNA/nucleotides include dietary provision of physiologically required levels of nucleotides due to limited synthetic capacity of certain tissues, inadequate energetic expenditure for *de novo* synthesis or salvage, immunoendocrine interactions and modulation of gene expression patterns.

Immunoglobulin G (IgG; mg/ml)			
	Control	ASCOGEN® 500 g/tonne of feed	ASCOGEN® 1000 g/tonne of feed
Pre-LPS	27.3	32.5	30
1 h post LPS	27.9	29.5	34.1
2 h post LPS	29.8	40.4	47.9
8 h post LPS	41.9	58.0	67.4
	<b>+ 14.6</b>	<b>+ 26.7</b>	<b>+ 37.4</b>
FMD neutralizing antibody titres			
Pre-vaccine (12 weeks)	3.7	3.9	3.5
Post-vaccine (3 weeks)	29	<b>49</b>	<b>111</b>

Tab. 1: Facilitated immune response upon artificial stimulation of the immune system with LPS. The application of balanced formulations of RNA/nucleotides significantly reduces the time needed to react on an immunological challenge.

Upon balance formulations of RNA/nucleotides more specific antibodies are produced in a shorter period of time. This leads to a faster and better protection after any kind of vaccination.

The fortification of feed with extra RNA/nucleotides has various effects in sows. When RNA/nucleotides are added to sow feeds an increase in the number of litters per year, the litter size and the number of piglets weaned became obvious. The farrowing rate was increased and the number of sows returning to service was reduced. Moreover the uniformity of the litter was improved. Similar effects have been obtained upon toxin contamination of the feed. After addition of RNA/nucleotides, performance returned to a normal level. This clearly indicates that RNA/nucleotides besides facilitating general health and performance in addition support self-healing processes under challenging situations.

The early development of the piglets is facilitated and improved significantly. The design of a representative trial is illustrated in Fig. 6. The results of the trial are summarized in Tab. 2. Although suffering from severe enteric problems the performance of the piglets was improved in all trial groups compared to the control.



Fig. 6: Trial setup for a piglet trial with animals suffering from enteric problems.

	Feed Intake (kg)	FCR	DLWG (g)
Feed 1: Control feed	8.80	1.42	325
Feed 2: 7 days before weaning	9.75	<b>1.12</b>	<b>395</b>
Feed 3: 25 days after weaning	9.63	1.36	355
Feed 4: 7 days before + 25 days after	10.0	<b>0.90</b>	<b>430</b>

Tab. 2: Comparison of Feed intake, Feed Conversion Ratios (FCR) and Daily Weight Gains (DLWG) of piglets suffering from enteric problems upon nucleotides.

The effect of RNA/nucleotides was most pronounced when piglets received the RNA/nucleotides pre-weaning. Therefore the feeding should start as early as possible after

birth, despite the low pre-weaning feed intake. RNA/nucleotides fed in early stage of life enhance the development of intestinal structures and micro flora leading to an increase in the active surface of the intestinal tract, facilitates the digestion of feed and the uptake of nutrients. The feed conversion ratio (FCR) is thus improved. Moreover at this stage the development of the immune system is actively supported. Piglets are born without a functional immune system. After farrowing the defence is enabled by maternal antibodies present in colostrum and milk. The concentration of antibodies in the milk is progressively reduced. Simultaneously the internal immune system of the piglets needs to be developed. This development is not finished at weaning dropping the piglets into an immunological gap, as the supply with maternal antibodies is suddenly stopped but the internal immunity is not yet fully established. At this stage most farmers are faced with health problems and diarrhoea of post-weaned piglets. This can be remarkably reduced as the development of regulatory systems and organs is facilitated upon RNA/nucleotides.

The effects of RNA/nucleotides are dose-dependent as shown in a dose response trial (Fig. 7). The final weight, the daily weight gain (DLWG) and the improvement of the feed conversion ratio (FCR) are dependent on the dosage of the RNA/nucleotides in the feed.

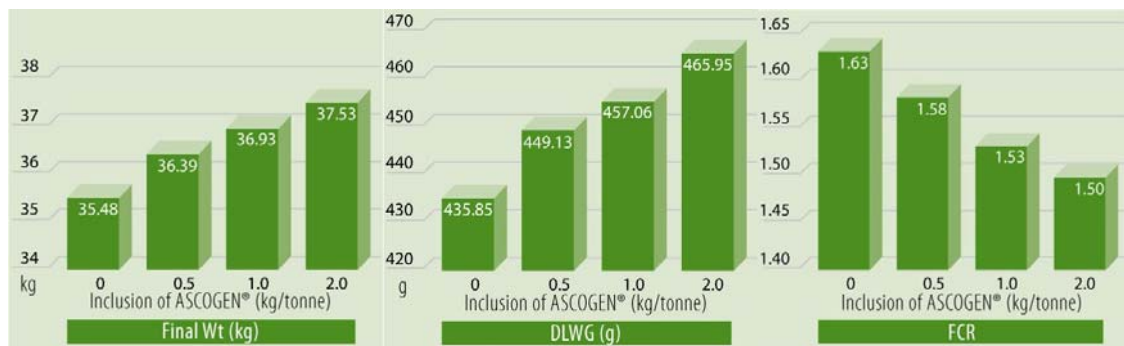


Fig. 7: Dose dependent effects of RNA/nucleotides on performance of piglets

Although not fitting into the classic definition of essential or semi-essential nutrients the fortification of feed with RNA/nucleotides boosts the performance of sows and piglets. The negative effects of stress are quenched and health challenges or routine farm management not necessarily lead to reduction in performance and financial losses for the producers. RNA/nucleotides must be regarded as a management tool to maintain general health, enhance development and performance and manage the deleterious effects of stress. However, the requirements of RNA/nucleotide products for the development of functional feeds on part of feed producers and farmers need urgently to be defined. The ideal nucleotide supplement would be composed of purified Guanosine, Adenosine, Cytidine, Thymidine and Uridine. The degree of purity of the active ingredients will ensure the rapid uptake of the nutrients in the intestinal tract and their unhindered supply to cells, tissues and regulatory systems with high demand for nucleotides. Purified RNA (containing the nucleotides Guanosine, Adenosine, Cytidine and Uridine) may also be used as an active ingredient to spare some costs in purification of single nucleotides. The composition of the additive in terms of the different nucleotides needs to be adapted to the need of the animals as well as it has to take into account the nucleotides already present in a given feed. This would ensure a nutritionally balanced additive without generating an artificial limitation of one or several nucleotides in the finished feed. Pigs could grow like mushrooms if the recommendations of nutritionists and vets in the development of functional feeds are followed.