25+ YEARS OF FEED ENZYME INNOVATION FROM DANISCO ANIMAL NUTRITION.

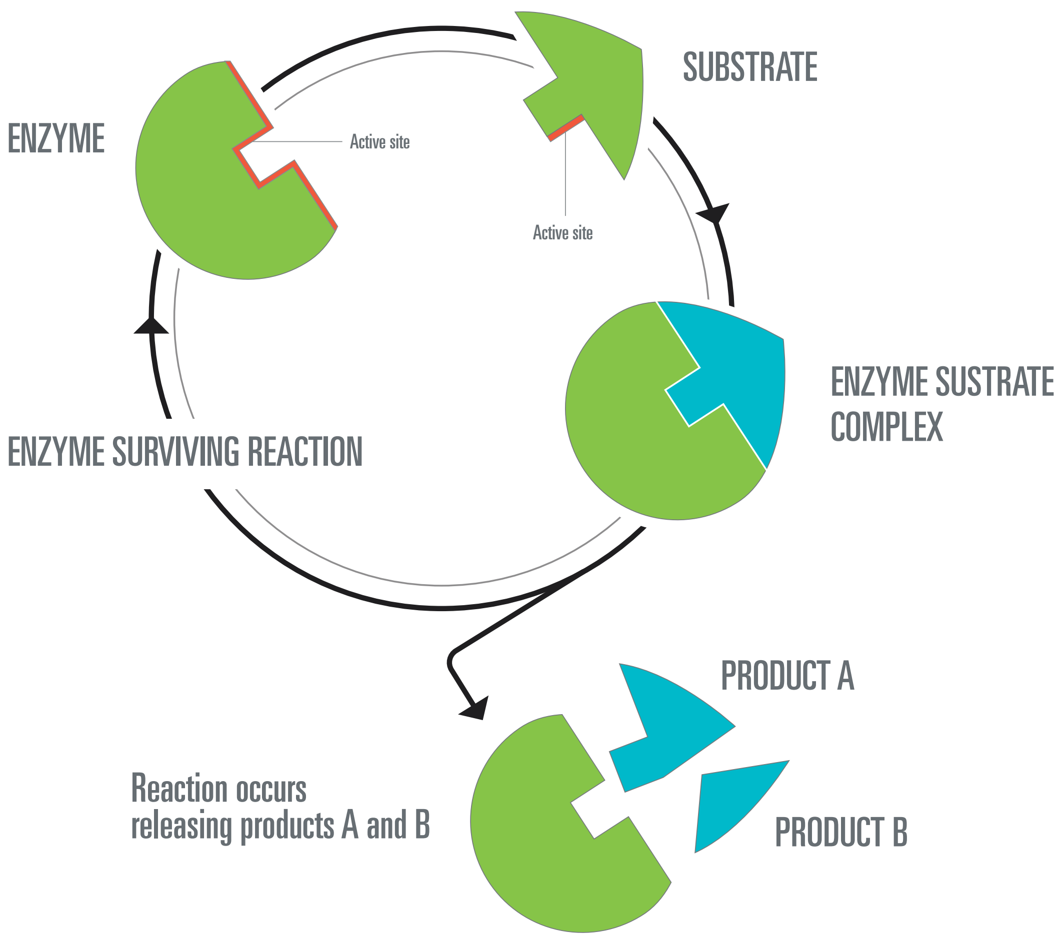
SOWINGTHESEEDSFORWIDESPREADFEED ENZYMEADOPTIONINTHE1980sAND1990s

The catalytic properties of enzymes - proteins produced through fermentation that compliment an animal's own digestive enzymes - were first truly recognized as a means of optimizing nutrition when the first US patent was granted in 1894[(1)].

Phytase[(2)], the most popular feed enzyme today - and phytate[(3)], the anti-nutrient it destroys - were discovered not long afterwards in the early 1900s.

However, the use of feed enzymes to achieve cost efficiencies in animal production only really became mainstream in the late 1980s. By this time, it was clear that there was a need to produce more high quality protein more quickly in order to meet the needs of a growing population. It was also obvious that converting feed to protein was not a very efficient process.

Although their digestive systems are one of the most efficient in the animal kingdom, poultry don't digest upwards of a quarter of what they eat even if the diet is quite simple. For pigs, the figure is more like 70%. Young birds and pigs are particularly lacking in the relevant enzymes to digest more fibrous diets.



Mode of action of enzymes and the particular substrates they tackle

ENZYME	SUBSTRATE
Xylanase	arabinoxylans
Amylase	starch in feed
Protease	proteins in feed
Beta-glucanase	mixed linked beta-glucans in plant fibre
Phytase	phytate in plant material

This digestibility challenge was an issue in terms of pollution too. When it comes to 'bound' minerals such as phosphorus, livestock excrete up to 70% of this expensive mineral in manure.

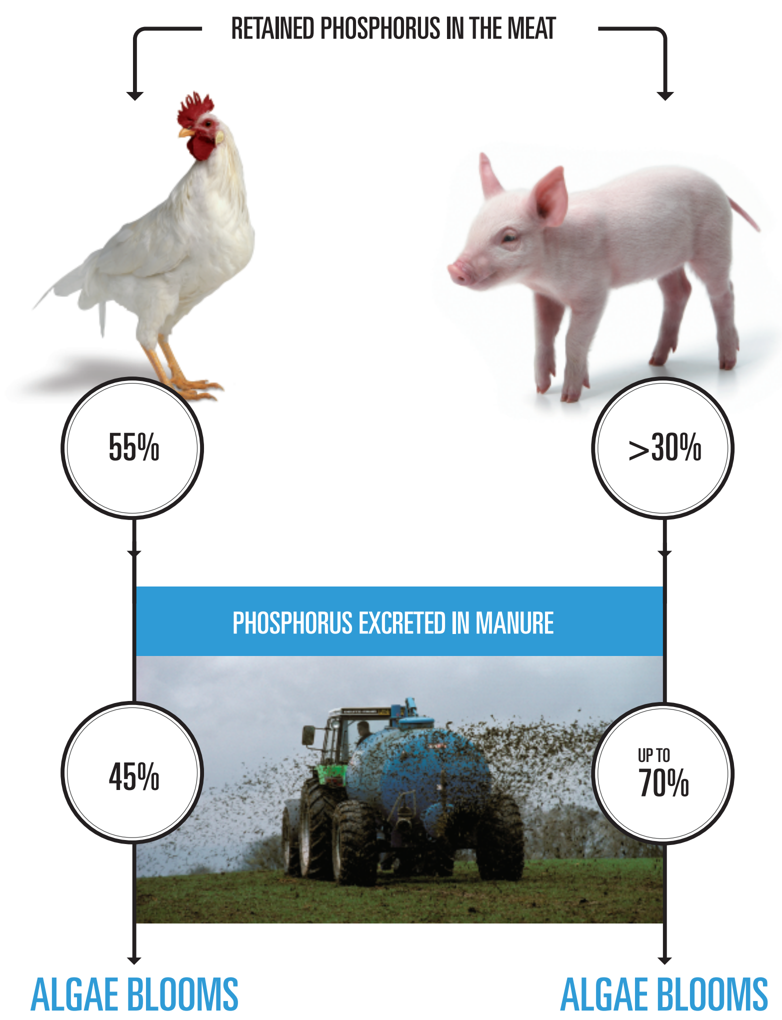
The manure, which is spread onto the land and can cause a threat to already scarce fresh water supplies, causing eutrophication as a result of algae blooms.

In the 1970s, a series of environmental legislation was introduced in the US to reduce the excretion of harmful indigestible substances into fresh water supplies.

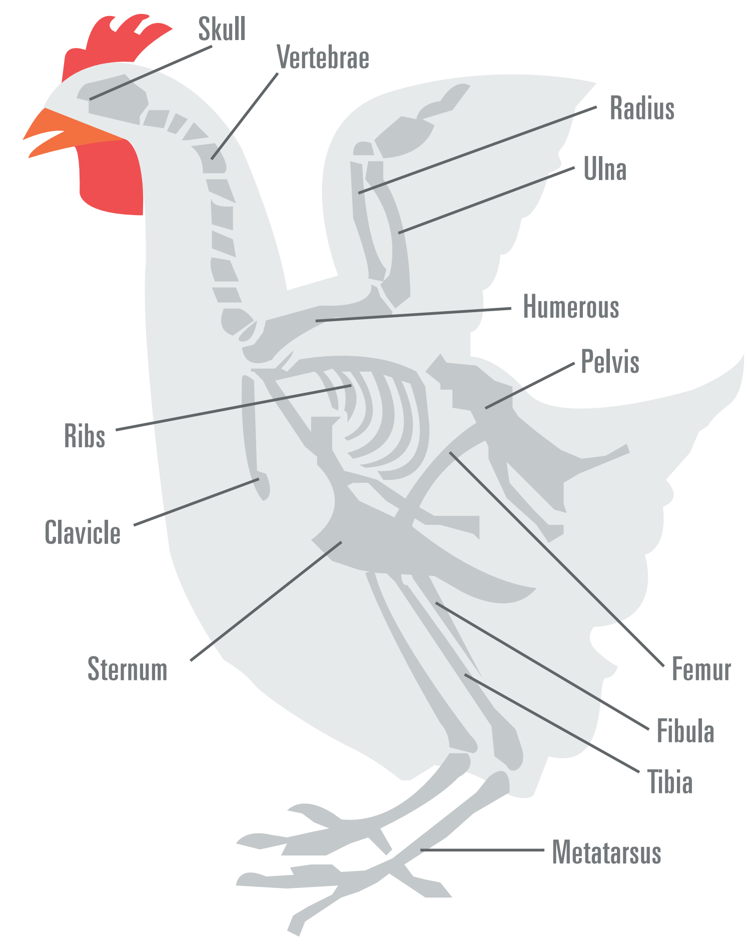
But Holland was the first country in the world to impose fines designed to limit the amount of phosphorus that can be disposed of on land in the late 1980s/early 1990s (followed closely by Germany). Indeed, phytase was first introduced to the market when Dutch producers were faced with paying this phosphorus tax.

The fact that phytase also offered improved absorption of phosphorus, a vital mineral for skeletal growth, and therefore meant less reliance on expensive and finite organic phosphorus sources.

This soon meant that producers were relying on it to get the best value from feed as well as to avoid compliance costs. A subsequent ban on the use of meat and bone meal in the European Union, is another factor that has accelerated the growth of phytase.



Phosphorus excreted in manure can lead to fresh water pollution, which is taxed in many countries. Phytase helps resolve this issue when added to the feed at the correct dose.



Rapid broiler growth results in ~6% of flock being lost due to skeletal issues such as black bone syndrome and tibial dys-chondroplasia. Similarly lameness in sows causes major herd productivity losses. Phytase application can help address these issues through release of bound phosphorus. View webinar

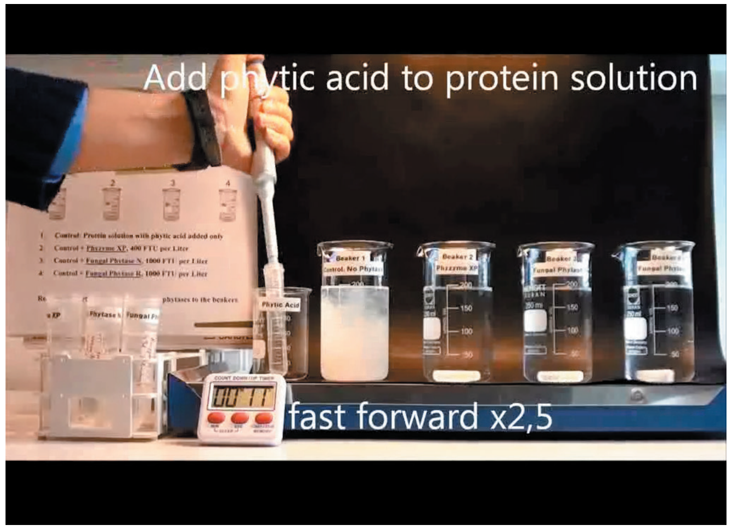
THE TURN OF THE CENTURY; A TURNING POINT FOR FEED ENZYME USE

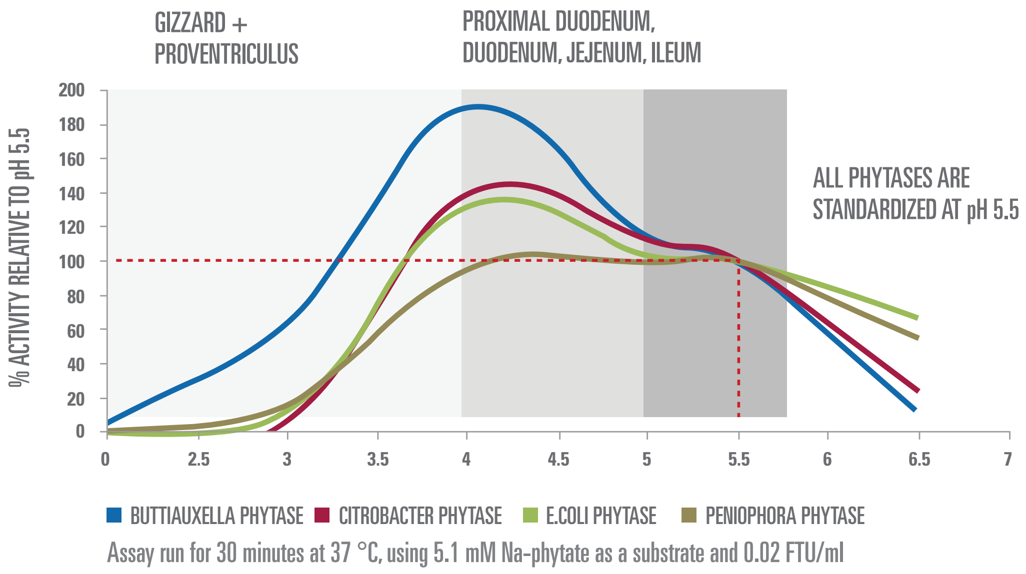
Our understanding of the role of phytate in animal nutrition has advanced substantially in recent years, leading to the realization that novel phytases can offer benefits beyond phosphorus release.

New, highly bio-efficacious phytases have been shown to quickly reduce the anti-nutrient effects of phytate in animal diets by degrading it, thereby increasing the availability of energy and amino acids to the animal. This offers producers the potential to further reduce the cost of feed, particularly when the price of energy and protein/amino acids in diets is high.

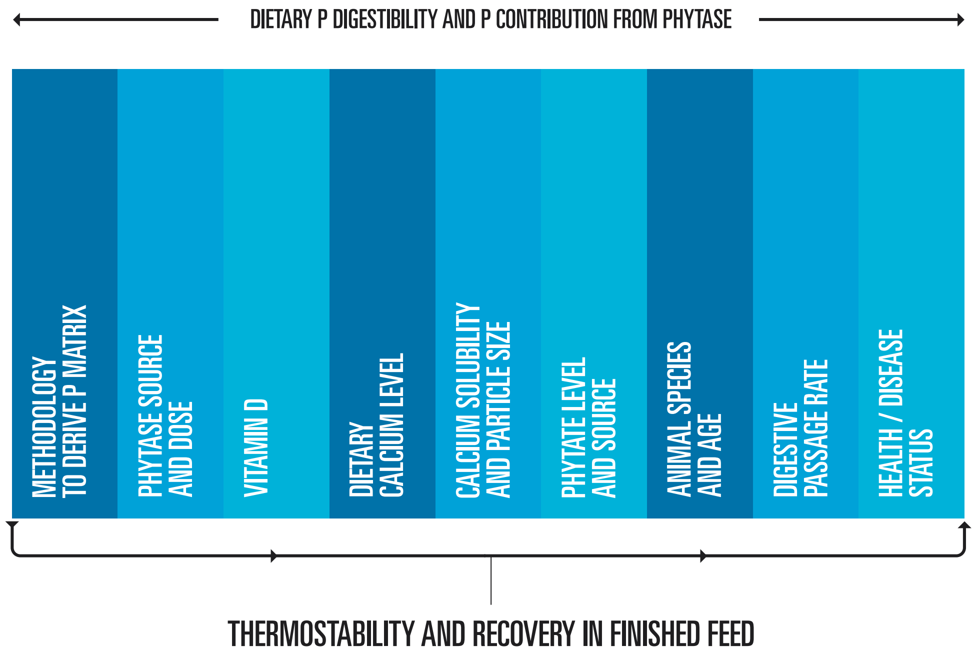
Danisco Animal Nutrition has been at the forefront of developments of new generation phytases. We launched the first E.coli phytase on the market - Phyzyme ®XP - in 2003, offering a 20% improvement in bio-efficacy and associated feed cost savings compared to the traditional fungal phytases available at that time.

We followed this in 2007 with the first lau nch of the unique Thermo Protection Technology (TPT) granule product form coating. This not only ensures that enzymes can survive the harsh steam pelleting conditions up to a temperature of 95° C (203°F); but it also allows rapid release of phytase in the upper part of the gut to achieve optimum bio-efficacy.



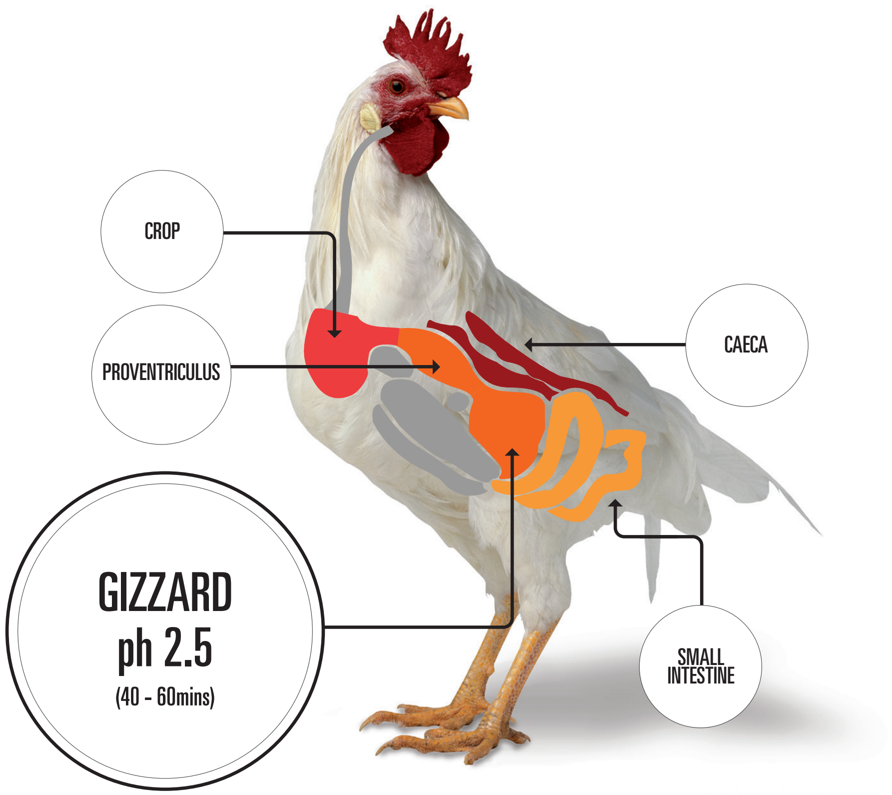


Different phytases have different pH optima and different relative activity at low pH, versus ph5.5 (at which FTU is defined)



Many different factors impact phosphorus contribution from phytase

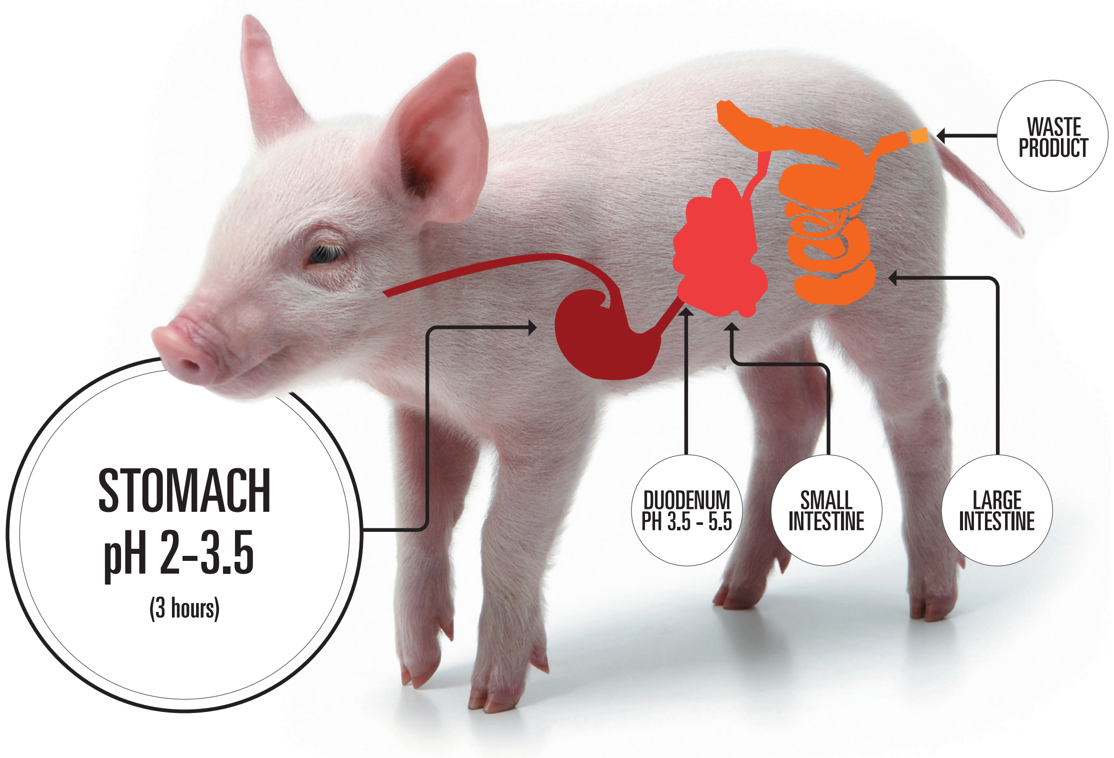
Commercial trials have shown that Axtra® PHY, our new generation Buttiauxella phytase introduced in 2013, offers unprecedented digestibility and phytate destruction benefits over bacterial equivalents due to its exceptionally high and rapid activity in an animal's upper digestive tract.



One of the benefits of high phytase doses/phytases that are optimized to work rapidly to degrade phytate in the acid stomach is more consistent phytate hydrolysis and less possibility of calcium/phosphorus imbalance.

In terms of benefits, compared to the average performance levels of incumbent leading E.coli phytases, this higher bio-efficacy equates to:

- Additional cost savings of ~$1.08 per tonne of pig feed through availability of ~20% more phosphorus and calcium earlier in the digestive process. For poultry, the potential savings are even higher; an additional ~$1.50 per tonne of feed at 500 FTU and potentially greater savings from improved nutrient release at higher doses.
- Availability of ~10% additional digestible energy (and costly amino acids) to the pig through superior phytate degradation in the upper gut. For poultry, the percentage is even higher at ~30%, equating to an additional $1.36 per tonne of feed.

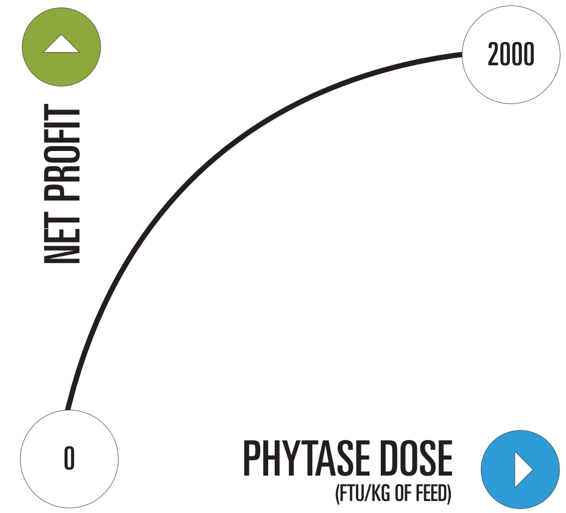


Having been the first company to understand that getting the right dose of the right type of phytase was the key to maximizing profitability, we launched the Phycheck® software service in 2006 to support optimized dosing.

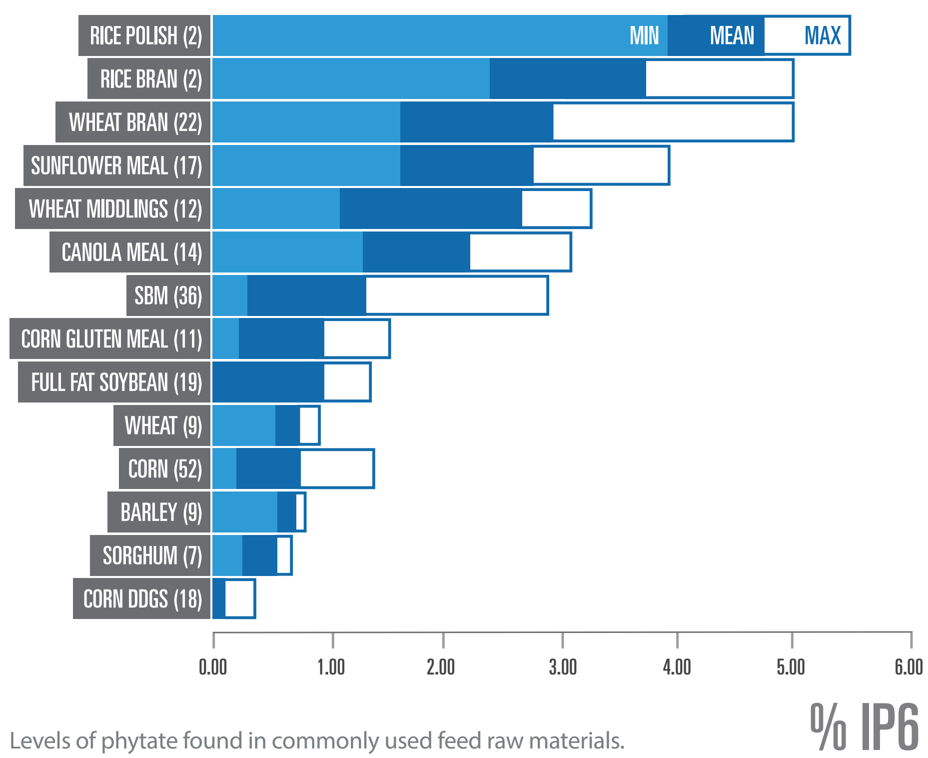
In 2014, we have 'upgraded' Phycheck®, by making it available in a more easy to use, online platform - the Optimize Feed® Service. This uses accurate and well-researched matrix values based on animal species, diet variation, substrate levels and the age of the animal to help customers determine the right dose of phytase to:

- Maximize uptake of phosphorous, reducing the need for costly inorganic phosphorous supplementation, and balancing calcium levels.
- Minimize the impact of phytate and other anti-nutrients in the diet using extensive up to date worldwide global data on raw material substrates.

2014 also saw the launch of the company's new semi-quantitative Axtra® PHY FASTkit™ assay. Unlike other feed assays, this detects the presence of only the active Axtra® PHY phytase in the feed. It does this in only one hour, giving customers rapid confirmation that the appropriate level of enzyme activity is present in the final feed.



Depending on many factors - species type, age and health status of the animal, diet and substrate levels, and production challenges - a phytase dose above the industry standard FTU can deliver stronger results.



Levels of phytate found in commonly used feed raw materials. Number of samples used are provided in parentheses (Harvest data, Danisco Animal Nutrition, 2013)

DEALING WITH VARIABILITY; A RECURRING ISSUE SINCE THE 1980s

For many years, however, glycanases - fibre degrading carbohydrase enzymes that cleave the non-starch polysaccharides (NSP) in 'viscous' cereals - were the primary feed enzyme type worldwide.

GRAIN	ARABINOXYLAN CONTENT %	ARABINOXYLAN SOLUBILITY %	ß-GLUCAN CONTENT %
Wheat	6.0	25	0.7
Barley	7.4	12	3.8
Rye	8.5	33	1.8
Triticale	5.7	24	1.5
Oats	8.6	5	2.5
Corn	3.9	8	0.1

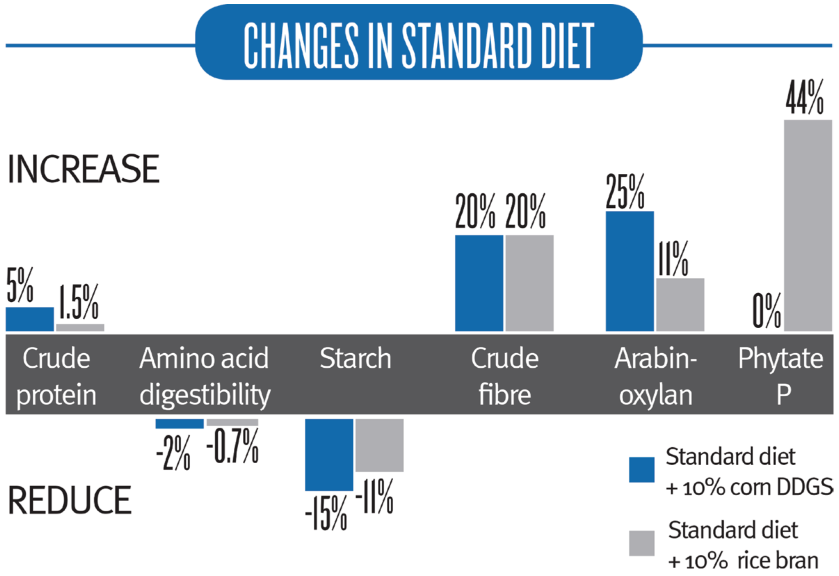
The non-starch polysaccharide content of commonly used raw materials (Choct 2006)

Their introduction in the late 1980s was a genuine breakthrough in parts of the world where wheat and barley are poultry and piglet diet staples, such as notably Europe, Canada, Australia and New Zealand.

Even in pigs, who have less digestibility issues than poultry, fibre can cause a potential increase in maintenance energy and protein costs. Fibre also causes an increase in faecal volume which, in turn, has implications on manure management and other environmental compliance costs.

Benefits of the key glycanase enzymes, xylanase and beta-glucanease include improved digestion, nutrient release and absorption. Visible benefits included improved uniformity due to improved nutrient uptake and litter/ manure quality.

Again, we led the way in carbohydrase innovation with the first products and services tailored to specific species and diet types, including Porzyme® products for barley starter pigs and Porcheck, a unique software - based service to determine optimum dosing for swine.



Changes in the level of crude protein and fibre, substrates and subsequent starch and amino acid digestibility when DDGS and rice bran are added to standard corn-soy diets.

Optimized multi-enzyme combinations of xylanase, amylase and protease were also launched in the early 1990s for poultry diets - under the Avizyme® brand.

Amylase maximizes starch digestion, while xylanase targets soluble and insoluble arabinoxylan to release captured nutrients. Protease improves amino acid digestibility and helps offset anti-nutritional factors such as trypsin inhibitors and lectins.

While the same basic issues of 'profit, performance and planet' are being faced by animal producers today as were faced in the 1980s and 1990s, the last decade has also seen demand for protein soar in line with population and income growth. Poultry consumption has risen by 32% and pork by 15%. This increasing demand is set against a backdrop of unpredictable challenges for animal producers such as soaring raw ingredient prices, extreme weather conditions and pandemics

After energy, protein is the greatest cost in feed so there has been a move in recent years to use less expensive, protein rich ingredients to improve profitability. Due to government led initiatives to produce more sustainable fuels, corn Dried Distillers Grains with Solubles (DDGS), a by-product from bio-ethanol production, has become readily available.

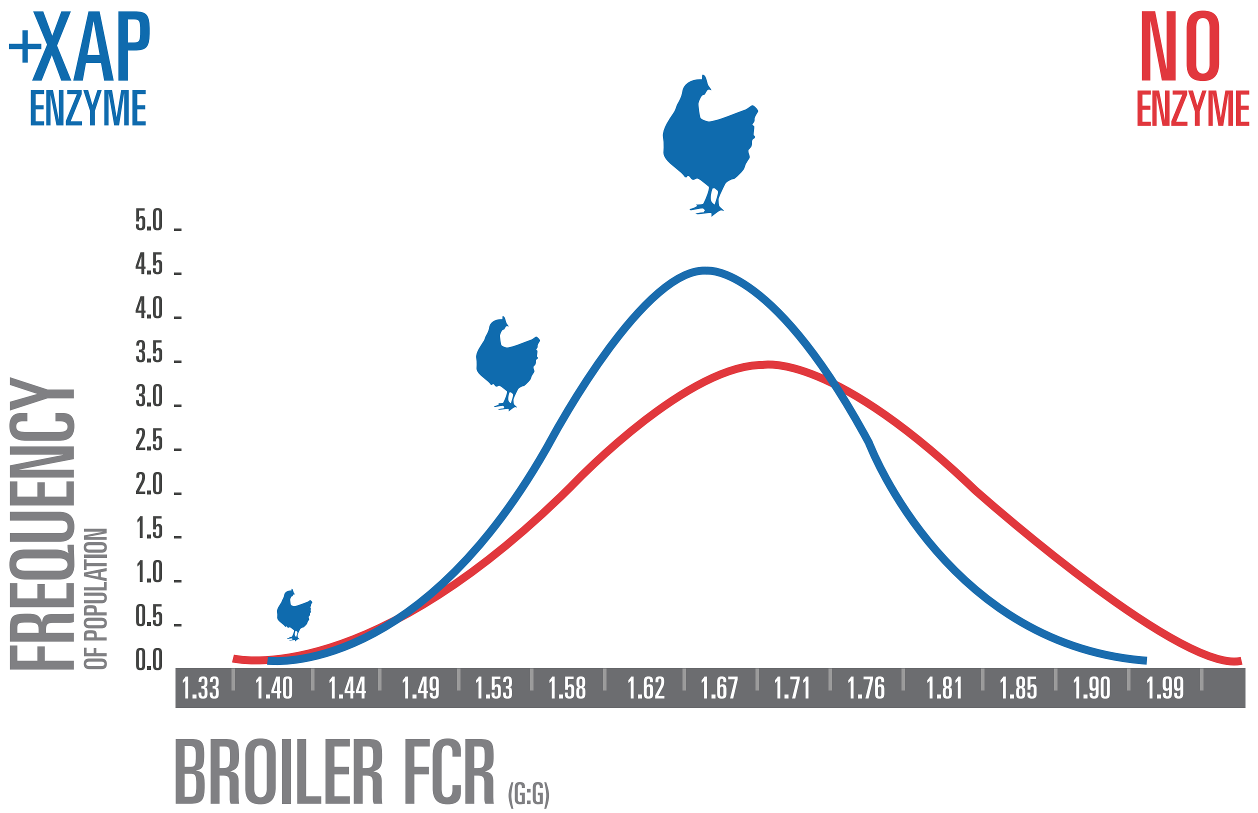
This and other inexpensive, protein rich by-products - such as rice bran - are also much more fibrous and less easily digestible.
The move from simple diets to these more complex ones has a significant effect on the dietary substrates available for digestion by the animal and decreases the starch levels and digestible amino acids in the diet.

Cultivation methods and harvest conditions can produce varying feed substrate levels, which in turn lead to similar digestibility and performance issues.

Corn, for example, is the most common feed grain used globally, but its feed value is universally recognized as being variable - sometimes just as variable as viscous grains such as wheat. Broiler trials with our Axtra® XAP, launched in 2011 to deal with effective feed formulation in modern diets, have shown that variability in feed conversion ratio caused by variability in corn and its digestibility can be improved by a combination of xylanase, amylase and protease enzymes, each targeting a different problematic substrate in the diet and optimizing nutrient digestibility.

Producers using mainly "viscous" grains such as barley and wheat still face the same challenges as they faced in the 1980s but more research had been undertaken into the variation of Non-Starch Polysaccharide (NSP) content and the ability of xylanase and beta- glucanase enzymes to reduce feed costs. Axtra® XB, our solution for mixed grain diets that was also launched in 2011, can be used with or without phytase in diet specific doses to improve fibrous diet digestibility performance.

These solutions also reduce the impact of feed variability which is important given that the biggest single risk to animal gut health has been shown to be the type, amount and availability of undigested nutrient substrate present in various segments in the gastrointestinal tract.(check ref)



The impact of xylanase, amalyse and protease addition to 56 different corn samples included in broiler diets reduced the variation in performance measured as FCR. (Danisco Animal Nutrition, 2011)

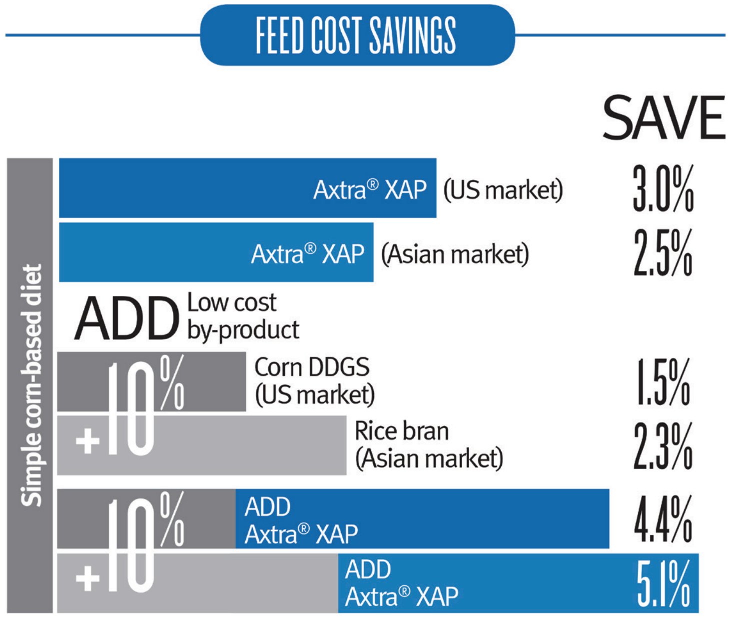
A NEW ERA OF HEALTHY NUTRITION

Research[4] has indicated the role that carbohydrase and protease enzymes have in supporting gut health through changes in the available substrates for the gut microbiota.

The effect of these enzymes is multi-faceted. Xylanases, for example, can reduce digesta viscosity through the hydrolysis of arabinoxylans, which in turn generates xylo-oligosaccharides. These act as prebiotics, promoting the growth of beneficial bacteria and the production of short chain fatty acids (SCFA), which can be utilized as an energy source by the animal[5]. Reducing the viscosity of the digesta also enables other endogenous and exogenous enzymes to access previously unavailable substrates, which results in increased nutrient digestion[6].

By maximizing the digestibility of substrates in the gut, not only are more nutrients available for growth, but there are fewer undigested fractions that could act as substrate for pathogenic bacterial strains. This is particularly the case for undigested protein, which is linked to Clostridium perfringens, the bacteria responsible for necrotic enteritis [7].

As animal producers look to formulate diets to achieve better performance at less cost, it is important to consider feed enzyme interactions and responses - with substrates, other exogenous enzymes being used in the diet with and with other feed additives.



Xylanase

- Targets soluble and insoluble arabinoxylans in dietary fibre - releasing encapsulated nutrients
- Particularly suitable for corn-based complex diets

Amylase

- High bio-efficacy to maximize starch digestibility, providing energy to fuel growth

Protease

- Targets storage proteins improving amino acid digestibility and starch accessibility

To address gut health challenges, we launched an enzyme (xylanase, amylase and protease) and probiotic (multi-strain Bacillus) combination early in 2014 which is designed to fully unlock healthy nutrition benefits from animal feed.

Specific healthy nutrition benefits that this enzyme and probiotic combination, Syncra® AVI, offers include:

- A 14% net improvement in relative cost per pound live-weight gain* for Clostridium perfringens challenged birds
- An approximate three-to-one return on investment even for low challenge birds, resulting from significantly improved digestibility and gut health support

DEALING WITH VARIABILITY; A RECURRING ISSUE SINCE THE 1980S

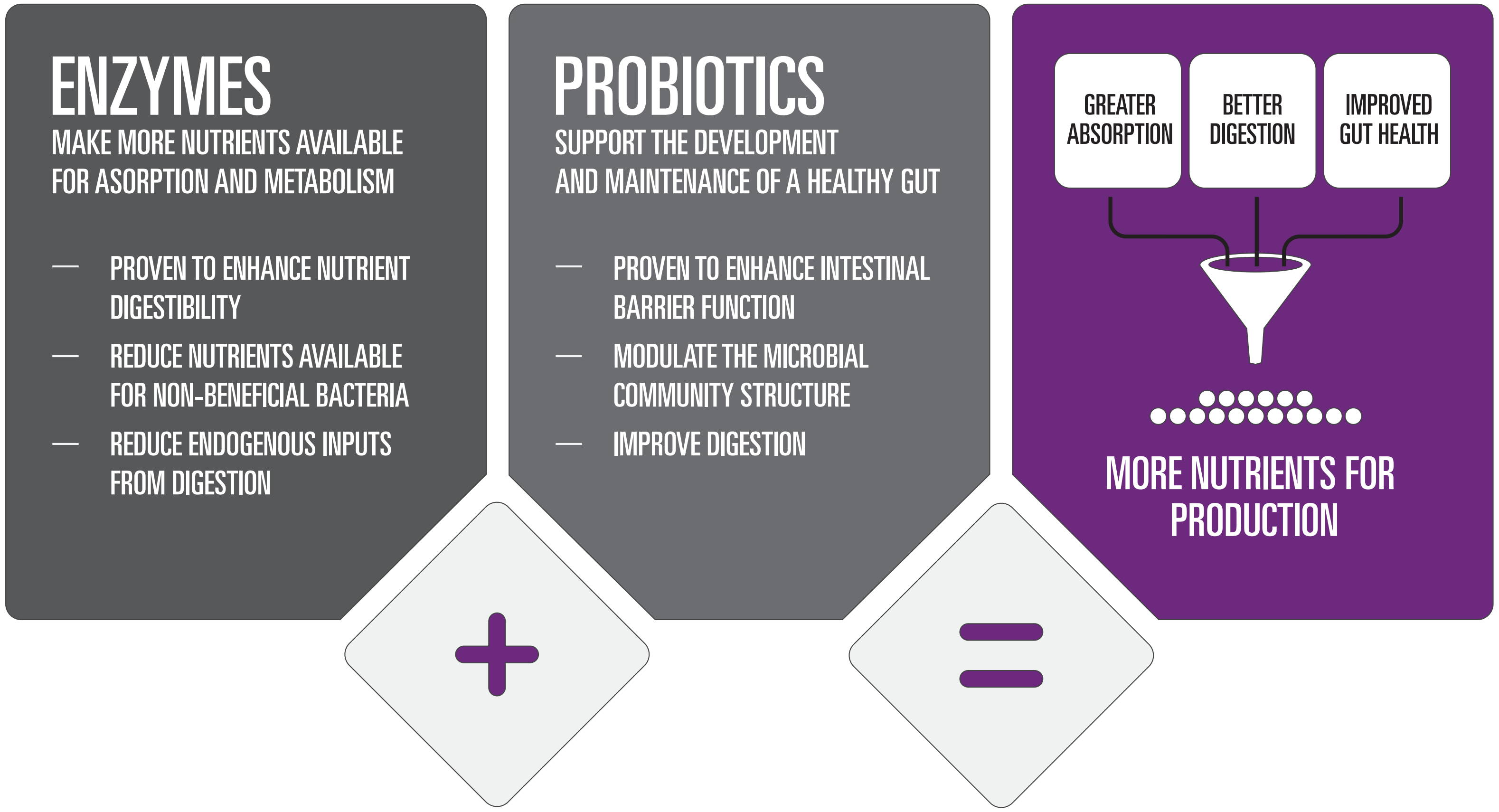
Further advances in developing technology in enzyme thermostability will give the animal feed industry even more confidence in use in steam-conditioned and pelleted feeds.

* Based on early 2013 feed costs

Enzyme technologies will also open up opportunities for future use of new and less expensive non-conventional feed raw materials.

At DuPont, our animal nutrition and bio-refinery businesses are already collaborating to develop ways to make use of 'side streams' from bio-ethanol production as potential lower cost animal feed alternatives.

Advances in this area could help reduce the price volatility that has plagued the animal feed industry in recent years, and radically reduce the cost and sustainability of animal protein production.



Xylanase, amylase, protease enzymes and Bacillus probiotics combined – the benefits of their complementary modes of action

25+ years of enzyme innovation... and this is just the start.

If you want to find out how we can help you maximize profitability and performance from current or future feed enzyme use, contact us on info.animalnutrition@dupont.com or find your nearest sales office/ distributor at http://animalnutrition.dupont.com/contact/

1982 Start of feed enzyme development with Cultor/Finnish Sugar Company

1984 First ß-glucanase enzyme for barley-based poultry feeds commercialized

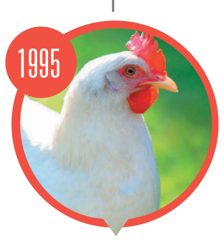
1988 First to market with species-specific multi-enzyme solutions including Porzyme® for barley-based pig starter diets and Avizyme® for poultry diets

Cultor/Hendrix International research co-operation starts

1989 Finnfeeds International Limited (FFI) started operations

1993 Degussa AG takes 40% equity in Finnfeeds

1995



First launch of unique service for maximizing the value of poultry enzymes (Avicheck®)

1997 Cultor acquires 40% stake held in FFI from Degussa AG

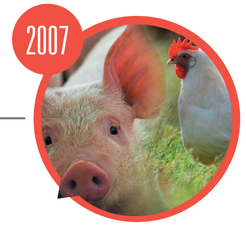
1999 Danisco A/S of Denmark agrees to acquire Cultor Corporation. FFI becomes a strategic business unit within Danisco Cultor Ingredients

2003 First to market with an *E.coli* phytase (Phyzyme® XP) with 20% greater bioefficacy than traditional fungal phytases

2005 Danisco A/S buys out Eastman Chemical's shares of Genencor Inc

2006 Launch of two unique services: Avicheck® Corn, for maximizing the value of poultry enzymes in corn feed and Phycheck® which maximizes the value of phytase in broiler diets

2007



Pioneered Thermo Protection Technology (TPT) launching Phyzyme XP TPT, which guarantees optimum thermostability and phytase activity, (at up to 95°C/203°F) satisfying a pressing industry need that prior phytases failed to meet

2011

DuPont takes over Danisco and becomes a global leader in nutrition and health, and industrial biosciences

The pioneering continues with the launch of the first two products from a new generation of enzyme solutions to tackle variability in simple and complex diets: Axtra® XB and Axtra® XAP

First launch (in US) of Axtra® PHY, a patented, highly bio-efficacious bacterial phytase, offering radical feed cost savings compared to the three leading phytases available at the time

2013

Danisco Animal Nutrition marks 25+ years of innovative product launches with yet another 'industry first' - Syncra® AVI, a combined enzyme and multi-strain probiotic solution designed to completely unlock the potential of poultry feed

Launch of the Optimize Feed™ Service, an easy-to-use online service that helps customers determine the most profitable dose of Danisco Animal Nutrition phytase.

Semi-quantitative FASTKit™ assay developed to quickly detect the presence of active Axtra® PHY phytase in the feed.

References and notes

1. The first US patent was granted in 1894 to Dr. Jokichi Takamine, one of the pioneers of biotechnology.

2. Suzuki, U., Yoshimura, K., and Yamazaki, M 1907. Über ein enzyme "phytase" das anhydro-oxy-methylen-diphosphosaure spaltet. Coll. Agric. Bull. Tokyo Imp. Univ. 7:503-505.

3. Mullaney, Edward J.; Ullah, Abul H.J. "Phytases: attributes, catalytic mechanisms, and applications". United States Department of Agriculture–Agricultural Research Service. Retrieved May 18, 2012

4. Snel et al., 2002, Romero et al, 2011

5. Fernandez et al., 2000

6. Satchithanandam et al., 1990

7. Liu et al , 2012

8. Snel et al., 2002; Romero and Ravindran, 2011