

Active Food Scientific Monitor

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The role of prebiotics in the ancient human diet and implications for modern diets

The term 'prebiotic' was introduced 11 years ago and from then on a lot of research has been conducted, especially on inulin and oligofructose, acknowledging the value of these functional ingredients for improving health. Although prebiotics might be seen as a relative new concept in human nutrition, their importance for health and well-being goes back into ancient history.

At a time people were living as hunter-gatherers, underground storage plant organs containing prebiotic-like compounds were quite abundant and formed an important part of the diet. Study of the detritus from well-preserved ancient cave sites indicates that the human diet, at that time, indeed contained high amounts of prebiotics, delivering an important part of the daily energy intakes. This was a time when human diets were primarily plant-based and high in fibre.

This is in strong contradiction with our modern, Western, diets low in fibre and rich in fat and refined carbohydrates. Although our diet and lifestyle have changed dramatically, our genome has changed very little. Much scientific research is now focussed on determining whether the miss-match between genome and modern

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Interview



In this issue, we present an interview with Jeff Leach, Director and Founder of the Paleobiotics Laboratory in New Orleans (US). Mr. Leach started his professional career as an archaeologist and his interest in the use of cookstones by ancient peoples led him to the field of prebiotics.

Pursuing the answers to questions about what our ancestors ate and how this affected their health has led Mr. Leach to visit archaeological sites all over the American South West and beyond. Mr Leach served as a consultant and published many papers and books describing the early human diet, the importance of fibre and prebiotics, the diversity of prehistoric plants, ancient microflora and the relationships between genotype and diet.



Preface

by Dr. Anne Franck

Inulin and oligofructose have moved into the mainstream of functional ingredients and now consumer education must intensify. That was the message of the opening presentation at the 5th ORAFI Research Conference held on September 28-29 in the Harvard Medical School (Boston, US). The meeting was organised to provide a forum for scientists to discuss the latest evidence on the nutritional and health benefits of inulin and oligofructose.

Joint-Chairman of the conference, Professor Glenn Gibson of the University of Reading (UK), said: "Since prebiotics were first defined 11 years ago, a huge amount of high quality research has been done. I am convinced that the scientific community has now demonstrated the clear, incontestable effects of inulin and oligofructose, and how they fit into the functional foods sector."

And Professor Allan Walker of Harvard Medical School (US), co-chairing the conference, added: "Today consumers are looking for foods and ingredients that offer proven health benefits. The best ways to deliver this is through scientific collaboration and communicating evidence-based health claims. This is why the 5th ORAFI Research Conference is so important. Here we have a forum for the leading scientists involved in inulin and oligofructose, and the chance to communicate the evidence on health benefits to a wider audience".

Since our last conference in 2004, a great deal of progress has been made in the research into inulin and oligofructose. The health benefits for a number of conditions, relating e.g. to gut function and flora, calcium absorption and bone health, are now clear while, in other areas such as immune regulation and cancer risk, we are embarking upon an exciting phase that builds upon the promise of early research. There will be challenges in developing appropriate claims that are understood by the consumer but these will be met by the combination of scientific endeavour, seen at the conference, and the commitment of ORAFI to the exciting field of research into inulin and oligofructose.

You will find more about the scientific data presented at the conference in the State of the Art section of this newsletter and I wish you a very fruitful reading.

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diet could be at the root of modern pandemics in the developed world, such as obesity, heart disease, cancer and auto-immune conditions. The interplay between beneficial bacteria, such as bifidobacteria and lactobacilli, affects various functions in the human body, and this can be beneficially affected by the addition of prebiotics to the diet. Evidence on the health benefits of inulin and oligofructose was recently presented by renowned scientists at the 5th ORAFI Research Conference held at the Harvard Medical School (Boston, US). The archaeologist Jeff Leach gave a keynote lecture on the role of prebiotics in the ancient diet and its relevance for modern nutrition and health.

You introduced the term **Paleo-biotics**? Could you explain this term?

This term represents the interplay between beneficial bacteria (probiotics) and the archaeological evidence of their use. The aim was to appeal to archaeologists and the broader field of anthropology to encourage research in this important area. Genetically we are hunter-gatherers living in a nutritional landscape which provided a high fibre, plant-based diet that was compatible with our genome. While human physiology and microbiology is still essentially in hunter-gatherer mode, modern diets offer a fare of low fibre, high-fat, refined carbohydrate foods. Our modern foods wouldn't be recognized by our ancestors as a proper diet. And the same goes for our microflora.



Was there a role for prebiotics in these ancient diets?

Absolutely, prebiotics may be seen as modern phenomena but they were quite abundant in ancient diets. Evidence from archaeological sites throughout the world suggests that not only were prebiotics consumed by our ancestors more than 40,000 years ago, but in many cases they contributed a considerable proportion of the daily energy intake. Indeed, the genus Homo had ample ecological opportunity to include prebiotic underground storage organs found throughout the African savannah into his diet as early as 2.5 million years ago.

Research from the arid regions of the Chihuahuan and Sonoran Deserts of the American South West shows that potentially prebiotic plants were cultivated, gathered and cooked by hunter-gatherer and agricultural farmers. The evidence for this comes from the presence of cookstones, thermally-altered rocks that were used by generations of hunter-gatherer groups, to cook tubers and fibrous plants in huge underground ovens. Analyses of detritus from well-preserved ancient cave sites in the Chihuahuan Desert

and components in coprolites (5-8000 year old faeces) have led scientists to hypothesise that the ancient human diet contained up to 50g per day of inulin and around 200g per day of total dietary fibre.

How does this relate to our modern diets?

From an evolutionary perspective we are not eating enough prebiotics and fibre. Average intakes contain 2-4g per day of prebiotics, and less than 20g per day of fibre in most developed countries. This is a quarter or less than that eaten by our ancestors. Studies that attempt to link health with dietary fibre or fruit and vegetable intake have often found null results. This might be because even the 'high fibre' intakes in those studies were in the region of 25-30g per day; which is not even close to the amount required for health if early human diet is used as a marker. In my opinion, a daily intake of 50-75g of fibre, including 10 to 25g per day from prebiotics, might be optimal. There is also the issue of fibre diversity. Ancient humans, and modern hunter-gatherer groups, consumed a much greater diver-

sity of plants than do modern humans. For some ancestral groups this meant hundreds of species of plants were consumed annually. In contrast, Western diets contain only a handful of different plant species. This reduction in diversity might have an impact on our microflora.

Optimal health and well-being depends upon diversity of fibre, quantity of fibre and, particularly, daily consumption of prebiotic fibres. This type of diet most closely resembles the nutritional landscape upon which our ancient genomic blueprint was developed.

What is known about the importance of prebiotics in human evolution?

Not enough. The archaeological record residing from cookstone ovens and cave deposits, the proximity of prebiotic-rich tubers and plants to abandoned cookstone sites, and the activities of modern hunter-gatherers, all point towards a heavy reliance on prebiotics before, during and after the shift from the nomadic lifestyle to early agriculture. Our ancestors ate a very high fibre diet, loaded with prebiotics. This in turn would have had an impact on the colonic microflora, favouring beneficial species and consequently health.

The importance of the intestinal microbiota and its requirement for prebiotics are nowadays being ignored at our peril. Our evolutionary-determined diet provided around 60% of daily energy intake from plants that contained prebiotic fibres, with the rest made up from meat and

starch-containing leafy vegetables. Refined carbohydrates, wheat, cows' milk, sugar and alcohol were all but absent. Compare this with the modern diet, which is the complete opposite, and you can see the consequences are already here in the guise of colo-rectal cancer, auto-immune conditions, obesity and metabolic syndrome. Although humans are living longer we should aim to improve health and well-being during those extra years.

With this in mind, how can modern diets be adapted to meet our bodies' needs for prebiotics?

While much can be learnt from the ancient diet, especially its reliance on prebiotic plants and fibre in general, it is not feasible to expect modern people to consume this kind of diets. There is also the issue of farming and food processing methods that reduce plant variety and strip fibre from the resulting products. Given the constraints of the modern food supply, which is dominated by highly processed grains, added sugars and fats, it is unlikely that any significant changes will occur. However, I strongly believe that we will only see significant changes in human health and well-being when the importance of gut bacteria and the role of prebiotics such as inulin and oligofructose are taken more seriously. Until that day, Americans and much of the developing world will continue to suffer obesity and other chronic conditions. It's time to close the pathogenic door and reclaim our health.

State of the Art



Highlights of the 5th ORAFTI Research Conference Inulin and Oligofructose: Proven Health Benefits and Claims

Harvard Medical School was the setting for the latest ORAFTI Research Conference, chaired by experts Professor Glenn Gibson (Reading, UK) and Dr Allan Walker (Boston, US). ORAFTI organised this regular event to provide an ongoing forum for leading scientists working in the field of prebiotics.

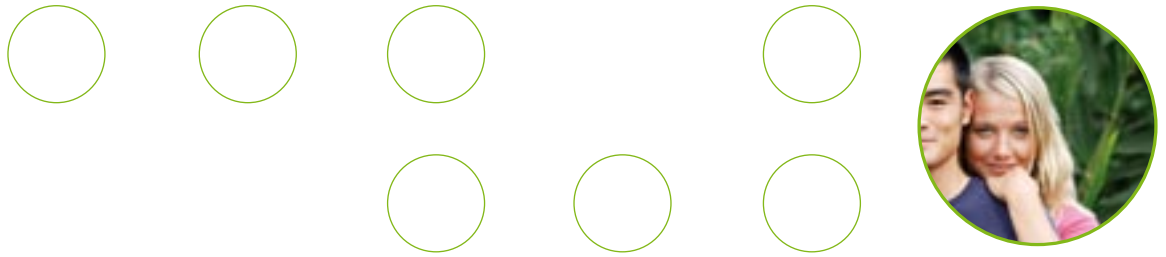
The conference opened with a presentation by Dr Johanna Dwyer, Senior Nutrition Scientist at the US National Institute of Health. Certain functional foods, including prebiotics, have moved into the mainstream of nutrition science due to the availability of high quality studies, she reported. As yet, they don't appear in Food Pyramids or dietary recommendations. Nor is there a legal definition of 'prebiotics'. While consumers are interested in using dietary means to achieve optimal health, there is still some confusion about what gut health claims mean for individuals. Clarifying this is hampered by the sensitivities

of discussing the colon and its microflora. New shifts in thinking are occurring whereby old definitions of fibre are being challenged, and the importance of prebiotics and gut microflora is being recognised.

Gut peptides and energy metabolism

Rising obesity levels worldwide have presented a challenge to scientists, health professionals and policy makers. The role of gastric distension and gut peptides in the regulation of hunger and satiety is understood. Less is known about the contribution of the large intestine and its attendant microflora. Sometimes called 'the second brain',

the gut acts like an endocrine centre, producing a range of important metabolites that are transported via the blood to other key organs, e.g. the liver and brain. As Dr Rémy Burcelin (Toulouse, France) explained, a good example of this is Glucagon-Like Peptide-1 (GLP-1). This is a gut-brain hormone which is secreted by both the brain and the gut in response to oral glucose absorption. GLP-1 may be important in the management of diabetes and insulin resistance because it has the dual effect of enhancing insulin secretion and routing surplus glucose to the liver where it is converted into glycogen for storage. Dr Burcelin



reported research showing that blockage of the GLP-1 receptor with exendin 9-39 in a diabetic mouse model induced glucose intolerance and insulin resistance. In a more recent study, feeding mice with a high-fat diet supplemented with Beneo™ oligofructose stimulated enteric GLP-1 secretion, insulin secretion, lowered food intake and body weight gain and was beneficial for the treatment of diabetes and obesity.

The possible mechanisms for this effect were outlined by Professor Nathalie Delzenne (Brussels, Belgium). Data from a number of animal studies suggest that inulin and oligofructose modulate lipid and glucose metabolism, inhibit food intake, and reduce fat mass development and hepatic steatosis. These effects are seen even in 'at risk' models, such as obese Zucker rats, animals fed high-fat diets, and diabetic rats (treated with streptozotocin to induce diabetes). A likely mechanism is that fermentation of inulin-type fructans in the proximal colon releases by-products that increase the number of GLP-1-secreting cells (L cells) resulting in enhanced levels of GLP-1 in the colon and the portal vein. GLP-1 is an anorexigenic hormone, signalling the feeling of satiety to the brain. This in turn, results in decreased food intake and various beneficial systemic effects related to sugar and lipid metabolism.

Also in humans, evidence indicates so far that inulin and oligofructose are valuable components in glucose and lipid

regulation. A review of the evidence found that 7 of the 11 studies on the impact of inulin-type fructans on blood lipids showed a significant lipid-lowering effect. As Professor David Jenkins (Toronto, Canada) explained, the mechanism probably involves inhibition of hepatic lipogenesis and triglyceride synthesis by metabolites from inulin and oligofructose fermentation, particularly propionate and butyrate. More studies are now required to assess long-term benefits in humans, argued Professor Furio Brighenti (Parma, Italy).

Work on the impact of Beneo™ inulin and oligofructose on energy intake and satiety is evolving in humans too. A

recent study in healthy adults (n=10) involved a two-week single-blind cross-over trial with 8g of Beneo™ oligofructose twice daily compared with a placebo (maltodextrin). As Figure 1 shows, perceived post-meal satiety was maintained following oligofructose supplementation compared with placebo. There was also a significant reduction in energy intake. If this effect persists long-term, it is likely that inulin and oligofructose could contribute to weight management.

Immunity and inflammation

The gut plays a key role in maintaining the body's defences against harmful bacteria and viruses explained Dr Ian Sanderson (London, UK). Central to this

are the natural microflora of the large intestine. As the gut and its bacterial colonies mature during infancy and childhood, so does the immune system. All are subject to programming induced by the introduction of new foods into the diet. Certain food ingredients, such as prebiotics, promote specific beneficial bacterial species, impacting on the balance of species and the metabolites released from prebiotic fermentation. This, in turn, is sensed by the immune system of the gut. There is now evidence suggesting that dietary changes can directly impact on the immune system, with implications for human health.

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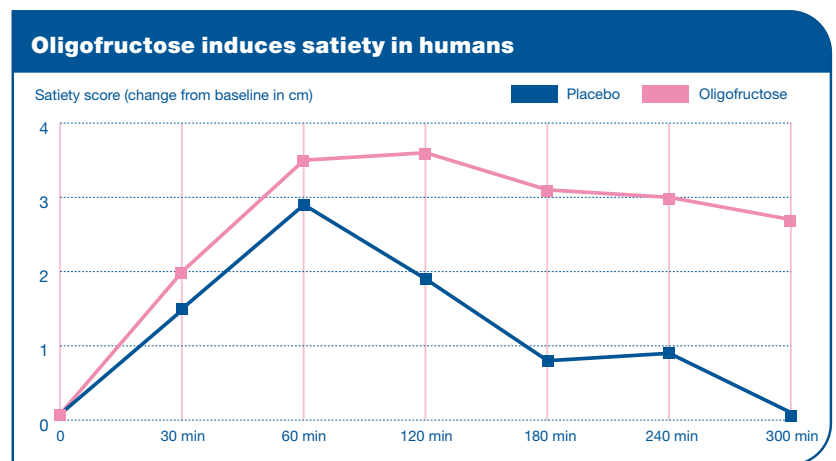


Figure 1

Figure 1 illustrates satiety scores after dinner (measured by Visual Analogue Scale, VAS) in healthy subjects after 2 weeks of supplementation with Beneo™ oligofructose (8 g twice daily) or placebo.

The results are presented as change from baseline scores and are means ± SEM, n=10 subjects for each intervention phase.

Cani PD, Horsmans Y, Delzenne NM (2006) Oligofructose promotes satiety in healthy humans: a pilot study. *Eur. J. Clin. Nutr.* 60: 567-572.

Such implications include the risk of auto-immune inflammatory conditions, such as Crohn's disease and ulcerative colitis which are on the increase in Western countries. The aetiology of inflammatory bowel disease (IBD) involves complex interactions between gut bacteria and the immune system. According to Dr Leo Dieleman (Alberta, Canada), patients with Crohn's disease benefited from the addition of Beneo™ inulin and oligofructose to their diet resulting in a decreased severity of their symptoms. The theory is that a gut bacterial population that lacks sufficient levels of probiotic bacteria combined with adverse dietary stimuli may cause the gut immune system to become intolerant and inflamed. Reversing this situation with prebiotics would seem a logical way to prevent IBD and manage symptoms in those with the disease.

At present, many patients with IBD are treated with elemental diets. However, this is unrealistic in the long-term. Now inulin-type fructans may offer an alternative way to modulate the disease. Mechanistic studies have shown that supplementation with Beneo™ Synergy1 decreases levels of pro-inflammatory and increases immunomodulatory cytokines. Several studies on animal models, as described by Dr Bernhard Watzl (Karlsruhe, Germany), demonstrate that inulin and oligofructose have consistent beneficial effects on immune function. Exposure to Beneo™ Synergy1 was found to increase the phagocytic activity of peripheral blood neutrophils and mono-

cytes, and the proportion of NK-cells in the spleen. Production of the anti-inflammatory IL-4 and IL-10 was also stimulated. The result of these changes would be to modulate the immune function towards a less inflammatory status.

These findings are supported by human studies. A randomized, double-blinded controlled trial examined the use of a synbiotic composed of Beneo™ Synergy1 and *B. longum* in patients with active ulcerative colitis (n=18). Compared with the placebo, patients on the synbiotic regime experienced reduced gut inflammation, reduced markers of inflammation (TNF α and IL-1 α) and increased epithelial regeneration. Also, inulin appears to be effective in treating chronic pouchitis after colectomy.

These benefits may be expanded into more acute settings, suggests Dr Francisco Guarner (Barcelona, Spain). Critically ill patients, particularly those in the post-operative phase, are at risk from bacterial translocation due to depression of the immune function, and drugs that disturb the natural probiotic bacteria that support the gut's mucosal barrier. Oral delivery of synbiotics, based upon inulin and oligofructose, has been found to significantly reduce the rate of post-operative infections in liver transplant patients, and in those who are critically ill.

Colon cancer risk

As populations age, the risk of colo-rectal cancer (CRC) in-

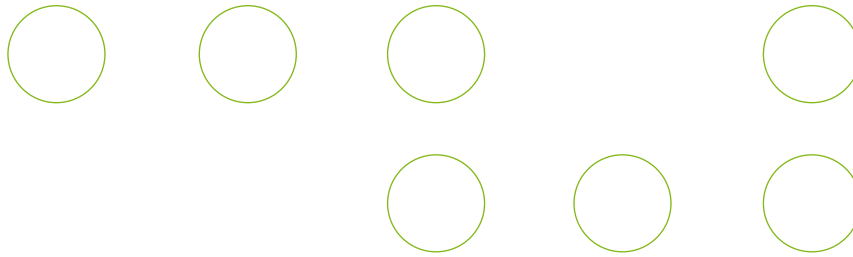
creases. It is already the third most prevalent cancer, with a prevalence of nearly 1 million worldwide, accounting for 12% of cancer deaths. Many experts believe that CRC is preventable due to compelling aetiological links with diet (high energy, low fibre, low fruit & vegetables, high saturated fat), smoking, and low physical activity levels. As in the case of inflammatory bowel disease, interactions between diet, intestinal microflora and gut-associated lymphoid-tissue (GALT) are key in the development of mutations that can lead to polyps and, eventually, CRC.

Early intervention is important, as Dr Kim Young (National Cancer Institute, US) explained. Intervention studies using 13.5g per day dietary fibre diets or 3.5 portions per day of fruit and vegetables do not seem to modulate CRC risk in people with existing polyps. This could either be because the interventions came too late, or because the amounts offered were too low. Certainly, the long lead time in CRC development and the lack of convincing aetiological markers along the way hampers research into dietary components that could lower risk.

Good news comes from studies with inulin and oligofructose, claims Professor Beatrice Pool-Zobel (Jena, Germany). Butyrate and propionate, by-products of inulin and oligofructose fermentation in the gut, have been shown to inhibit the growth of colon tumour cells, encourage apoptosis, and favour normal gene expression, while at the same time,

decreasing levels of potent mutagens, probably due to the action of butyrate. In a number of experimental animal models, including rats fed a high fat 'Western' diet, Beneo™ inulin-type fructans have consistently retarded tumour development and metastasis. A recent development, explained by Professor Pool-Zobel, has been the use of the faecal water (FW) as a biomarker for CRC risk. It appears that the FW from rats that developed colonic tumours (after treatment with the mutagen azoxymethane) was more genotoxic than the FW from rats that did not have tumours. Interestingly, supplementation of diets of those rats having CRC with Beneo™ inulin and oligofructose either alone or as a synbiotic reduced their FW genotoxicity. Since the incidence of tumours and faecal genotoxicity were directly related, the method was deemed to be a useful biomarker in establishing CRC risk in humans too.

Indeed, this methodology was included in the large-scale human study of CRC risk of the EU-funded SYNCAN project. The SYNCAN project, being a multi-centre collaborative trial involved a combination of in vitro, animal and human research. The aims of the project were multiple leading to the identification of new non-invasive risk markers to be used in future prevention studies, and to discover whether supplementation with a synbiotic based on Beneo™ Synergy1 can beneficially modulate several CRC risk biomarkers. In a long-term rat study, administra-



tion of either the prebiotic Beneo™ Synergy1 alone or as a synbiotic prevented the development of azoxymethane-induced colonic tumours and reduced the number of tumours per rat (see Figure 2).

Ultimately, a human study was performed using this synbiotic consisting of 12g per day of Beneo™ Synergy1 plus *Lactobacillus rhamnosus* and *Bifidobacterium lactis*; administered during 12 weeks in a double-blind, placebo-controlled trial in 80 subjects considered to be at risk of CRC. The key results of this intervention trial were presented by Dr Kevin Collins (Coleraine, Northern Ireland) who explained the profound effects of the synbiotic on gut microbial flora composition,

shifting populations towards beneficial species (bifidobacteria and lactobacilli) and away from pathogenic species. Correspondingly, synbiotic administration induced beneficial changes in well-known and newly identified markers indicative of CRC risk, such as reduced crypt proliferation, lower mucosal genotoxic damage, lower genotoxicity of the FW and modulation of immune parameters.

The SYNCAN project clearly shows that Beneo™ Synergy1 beneficially modulates biomarkers involved in CRC risk. More evidence is now required from longer-term studies examining the progression of the disease, tighter with these biomarkers.

This type of study is underway,

reported Dr Asad Umar (National Cancer Institute, US). Patients with polyps, who have a high risk of CRC, will be supplemented with Beneo™ Synergy1 and followed up for a number of years. Beneo™ Synergy1 was selected because it is safe and appropriate for the general population. Based upon the evidence from animal studies and the SYNCAN human trial, it is anticipated that the risk of CRC should be lessened in those receiving Beneo™ Synergy1. Changes in gut microflora and immune function will be investigated too. The human intervention trial will also look at changes in the presence of aberrant crypt foci (ACF), abnormal gut cells that are formed as a result of gene mutation and

which are thought to be a precursor of CRC. A separate study has been set up to identify and classify ACF in around 700 US patients using cutting edge endoscope methodology. It is hoped that the results will provide another reliable biomarker to help identify those at high risk of developing CRC. As Dr Umar explained, there are no effective treatments for advanced CRC, which puts the emphasis on finding good preventative strategies. The evidence so far suggests that inulin and oligofructose are a notable example of this.

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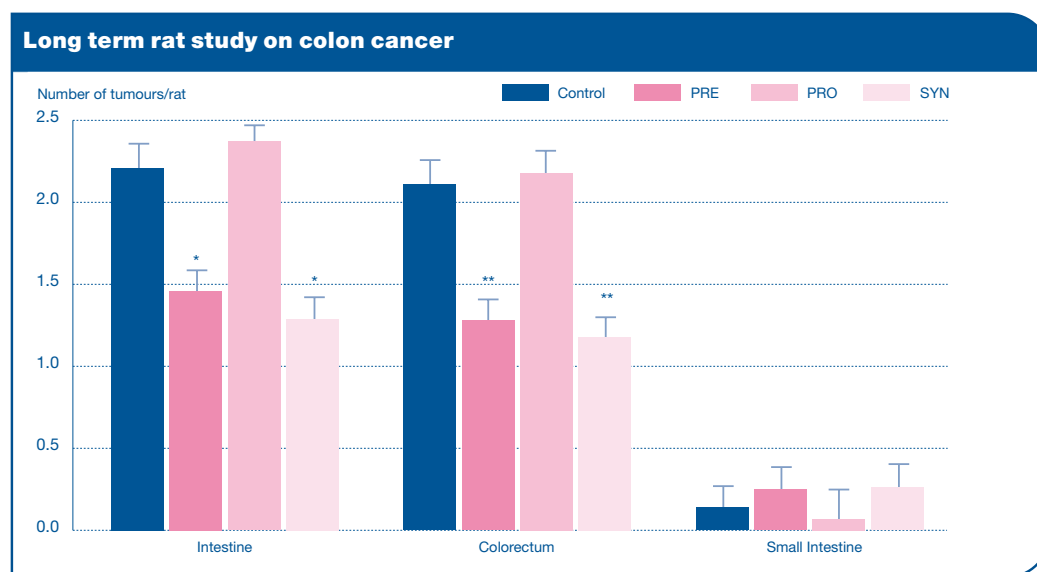


Figure 2

Figure 2 illustrates the number of intestinal tumours in rats (SYNCAN project) fed prebiotics (PRE; Beneo™ Synergy1), probiotics (PRO) or synbiotics (SYN) for 31 weeks * $P=0.001$ - ** $P=0.001$ vs control.

The results are presented as mean numbers \pm SEM, $n=28$ rats in the control, $n=28$ in PRE, $n=27$ in PRO and $n=27$ in SYN groups.

Femia AP, Luceri C, Dolara P, Giannini A, Biggeri A, Salvatori M, Clune Y, Collins K, Paglierani M, Caderni G (2002) Antitumorogenic activity of the prebiotic inulin enriched with oligofructose with the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis* on azoxymethane-induced colon carcinogenesis in rats. *Carcinogenesis* 23: 1953-1960.

Bone health

Osteoporosis is a global health problem that will take on increasing significance as people live longer, began Professor Kevin Cashman (Cork, Republic of Ireland) as he reviewed the issue. This year alone, 1 million osteoporotic fractures will occur in Europe, 80% affecting women. The implications are much more than the cost of treating fractures. Around 25% of hip fracture patients aged 50 or older will die in the year following their fracture. Key lifestyle factors for lowering the risk of osteoporosis are physical activity and adequate intakes of vitamin D and calcium. There is also evidence on the benefits of prebiotics, phyto-estrogens and vitamin K. On the other hand, nutrients that may create an adverse effect on bone include excess amounts of sodium, protein, phosphorus and vitamin A. The traditional Western diet is high in sodium and protein and low in calcium and vitamin D especially for certain sub-groups, particularly girls and young women. Unfortunately, these are exactly the groups that need to achieve adequate intakes to promote optimal peak bone mass (PBM). The issue of obesity also complicates osteoporosis prevention as excess weight increases the risk of childhood fracture and reduces participation in physical activity.

Osteoporosis may affect older adults but it is really a paediatric disease, claimed leading paediatrician Dr Steve Abrams (Houston, US). Influencing PBM in the first three decades of life

and maintaining this for as long as possible is now seen as the best preventative strategy. Yet simply giving more calcium is not the answer. Health promotion programmes to increase calcium and vitamin D have been underway in the US for sometime, with little impact. A better approach is to increase calcium absorption, especially during childhood.

Dr Abrams reported data from several studies looking at the impact of Beneo™ Synergy1 on calcium absorption and bone health. Two 3-week supplementation studies in adolescent girls using 8g per day of Beneo™ Synergy1 found significantly (+20%) higher calcium absorption in the Beneo™ Synergy1 group compared to control. A 1-year intervention study in 100 adolescent boys and girls, found identical results, even showing that the enhancement in calcium absorption persists over time. This study also examined changes in bone mineral content (BMC) and bone mineral density (BMD), finding at 1 year that subjects in the Beneo™ Synergy1 group had a significantly greater whole body BMC and BMD than controls. The difference translated as an extra 31 mg of calcium per day assimilated into the bones. Dr Abrams contended that the magnitude of benefit delivered by Beneo™ Synergy1 was greater than would be expected from calcium supplementation.

While the focus of osteoporosis prevention is childhood, risk factors can still be modulated in older people. Animal models of osteoporosis offer insight into

the benefits that could be expected from inulin and oligofructose supplementation and what mechanisms may be at work, explained Dr Katharina Scholz-Ahrens (Kiel, Germany). Studies in ovariectomised rats, a model simulating hormonal changes that occur in post-menopausal women, demonstrated improvements in calcium absorption, BMC and BMD with Beneo™ inulin and oligofructose supplementation. Addition of a medium dose of inulin and oligofructose to a high calcium diet increased bone quality (e.g. trabecular area and perimeter), due to a greater number of trabecules. This implies that a combination of calcium with inulin and oligofructose may produce stronger bones.

Several mechanisms have been suggested by which inulin and oligofructose increase calcium absorption among which one is an improvement in passive calcium absorption due to the pH-lowering action of organic acids produced during prebiotic fermentation, which may increase mineral solubility. Options are that prebiotics enhance the mucosal expression of calcium-transport proteins, thus stimulating active calcium absorption. Certainly, there is new evidence that Beneo™ Synergy1 increases calcium absorption across the whole intestine, with a major part taking place into the colon.

Dr Véronique Coxam (INRA, France) highlighted a mechanistic concept involving interactions between prebiotics and plant isoflavones. It is clear that

phyto-estrogens can be converted by the colonic microbiota into the bone modulating isoflavone-derivate, equol. Rat studies now suggest that inulin and oligofructose can enhance this process by stimulating key enzymes involved in converting daidzein to equol. Thus inulin and oligofructose improve equol production and its bioavailability, thereby exacerbating its bone sparing effects. Indeed, a study in post-menopausal women confirmed that a supplement of soy together with oligofructose shifted the colon microflora towards those species able to facilitate production of equol.

Benefits for specific target groups

Other speakers at the conference demonstrated how inulin and oligofructose could benefit consumers from birth to old age, and presented new data on the use of prebiotics for animal feed.

Infants and small children

Dr Nanda Nanthakumar (Harvard, US) gave an overview of how the gut matures from birth to adulthood. Born with a sterile gut, newborns quickly acquire bacteria from their mothers birth canal and during the process of feeding. There is now good data showing that the gut microflora of breast-fed infants is more skewed towards probiotic bacteria than that of bottle-fed infants. This has implications for the developing immune system due to 'cross talk' between gut microflora and the immune cells residing along the intestinal



tract. Another big shift in the gut microflora arises due to weaning when solid foods are introduced in the diet. Finally, as humans age, their microflora move away from the probiotic 'infant model', often towards higher prevalence of pathogenic bacteria if prebiotics are lacking in the diet.

Infants and young children are prone to infections and gut problems, especially if they were not breast-fed, suggests Dr Gigi Veereman (Antwerp, Belgium). Prebiotic intake can modulate the gut flora to favour probiotic species, thus improving intestinal health and defence to invading pathogens. In a study of healthy children attending day-care, 21 days of Beneo™ oligofructose supplementation was found promote levels of bifidobacteria and decrease levels potential pathogens, particularly clostridia. Infants in the prebiotic group also experienced significantly less flatulence, diarrhoea, vomiting and fever compared with the placebo group. These clinical effects confirm earlier observations in studies in infants and young children. More recently, another benefit linked with prebiotic supplementation is the lower risk of atopy, surely an important finding given the increased prevalence of allergy, asthma and eczema in developed countries.

Elderly

There are around 580 million people in the world aged 60 years and over, according to WHO, explained Dr Kieran Tuohy (Reading, UK). Many of

these suffer unnecessary ill-health due to gastro-intestinal (GI) conditions. Indeed, older people are more likely to die from GI infections than younger adults. As the gut microbiota changes during old age, the risk of bacterial overgrowth increases, allowing pathogenic bacteria to gain a foothold. Studies with inulin and oligofructose supplementation in elderly people have previously found reduced constipation, lower levels of pathogenic bacteria and higher levels of bifidobacteria. Dr Tuohy also reported findings from the EU-funded CROWNALIFE project which involved two arms of research. The baseline study aimed to seek microbial diversity in the elderly. In the intervention study the impact of a synbiotic based upon 10g of Beneo™ Synergy1 per day and *Bifidobacterium animalis* was studied on health markers. Using cutting-edge molecular methodology on faecal samples from across Europe, it was found that elderly people tended to have more enterobacteria and sometimes fewer bifidobacteria. Numbers of other species, e.g. *Eu.rectale*, Bacteroides and Atopobium groups varied depending upon the country of origin. Data from the intervention study so far suggest that supplementation with the synbiotic increased levels of bifidobacteria and lactobacilli. The health indicators are still being assessed, including biomarkers of colo-rectal cancer.

Animal nutrition

The benefits of inulin and oligofructose extend beyond humans

to the animal world. This has implications for animal health, food safety and human nutrition, claimed Dr Jan Van Loo (ORAFI, Belgium). His wide-ranging presentation reviewed research showing advantages for both farm and companion animals when prebiotics were added to feedstuffs, increasing animal welfare and farming efficiency. Studies in various animals (pigs, calves, broilers and fish) showed improved utilisation of feed, resulting in better growth with inulin and oligofructose. Interestingly in calves, addition of oligofructose resulted in an equal weight gain compared with antibiotic treatment. In laying hens, egg yield improved as did shell hardness, probably due to enhanced calcium absorption. Also, the cholesterol level in the egg yolk decreased. Beneficial effects were also seen in cats and dogs with inulin and oligofructose (e.g. reduced urinary nitrogen output, increased calcium and magnesium absorption, and modulation of lipid parameters).

Conclusion

The list of biological functions that are beneficially modulated by inulin and oligofructose is long; including gut peptides and energy metabolism, immunomodulation and inflammation, biomarkers of colonic cancer risk, calcium absorption and bone health, as well as lipid and sugar metabolism; which, when considered all have a common aetiological component. The gut has been described recently as the 'second brain', while others have termed the gut microbiota 'the forgotten organ'.

Many intestinal conditions, such as inflammatory bowel disease, atopy or gastro-enteritis may have their origins either in a maladapted immune response to endogenous bacteria or pathogens, or in failure of the gut to repel invading pathogens. Others could relate to the interaction between the microbiota and endothelial cells creating changes in expression of genes, as in the case of colo-rectal cancer. The intestinal cells absorb nutrients from foods and any conditions that affect intestinal metabolism might affect nutrient absorption, e.g. calcium and magnesium; but also cholesterol. In addition, metabolites and peptides produced in the gut resulting from inulin and oligofructose fermentation might have effects beyond the gut, e.g. influencing appetite and lipid and sugar metabolism. At the end of the day, all of these physiological factors are influenced in some way by the complex balance of the microbiota in the large intestine and that is where inulin and oligofructose have their effect. By skewing the composition of the microbial flora in the colon towards probiotic species, prebiotics optimise the metabolic processes occurring in the intestines.

While research is still ongoing to study more the beneficial effects of Beneo™ inulin and oligofructose in the human body and to elucidate the mechanisms by which this happens, it is clear from the high quality evidence presented at the 5th ORAFI Research Conference that the benefits of inulin and oligofructose are logical and significant.

Questions and Answers

Is inulin a drug?

No, inulin and its hydrolysed form, oligofructose, are food ingredients.

According to the EC-Regulation of the European Parliament and of the Council (178/2002, published in 2002): a 'food' (or 'foodstuff') means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. This includes drinks, chewing gum and any substance (including water) intentionally incorporated into the food during its manufacture, preparation or treatment. Also, 'food' shall not include: feed, cosmetics, tobacco, etc. and medicinal products (also called 'drugs'). The latter is defined as any substance or combination of substances presented for treating or preventing disease in human beings (Directive 2001/83/EC of the European Parliament and of the Council, published in 2002). Therefore, from a legal point of view, the difference between a 'food' (and/or food ingredient) and a 'drug' is clear. Additionally, inulin and oligofructose are 'functional' food ingredients. Functional foods (and ingredients) are foods or dietary components that may provide a health benefit beyond basic nutrition. In other words, you can take greater control of your health and well-being through the food

choices you make, knowing that some foods provide specific nutritional and health benefits. Examples include beta-carotene which bolsters cellular antioxidant defences, lutein which may contribute to the maintenance of healthy vision, as well as inulin and oligofructose which improve gut health (among other benefits). The benefits of functional foods are clearly different from those of a drug, the latter aiming to treat disease rather than to improve health and well-being.

Currently, in the European Union, it is not allowed to correlate the effect of a (functional) food (and/or ingredient) to a disease. However, in the near future, with the new EU Regulation on Health Claims making progress, it will be allowed under certain conditions to make claims relating to some foods (and/or food ingredients) and their impact on the reduction of disease risk. This will only be allowed if the effect is clearly substantiated by sound scientific evidence. This new European claim regulation will open new perspectives for food companies in the development of functional foods with proven health benefits.

Monitor

Infant formulae supplemented with oligofructose are safe and well-tolerated

A prospective, blind, multi-centre trial was undertaken to document the safety of infant formulae supplemented with oligofructose in healthy term infants of less than 14 days of postnatal age. The study included a total of 297 infants enrolled in 17 outpatient physician offices in the United States. Term infants were randomly assigned to 1 of 3 infant formulae, being a bovine milk-based control formula or the same formula supplemented with either 1.5 g/l or 3.0 g/l oligofructose (Beneo™P95) for 12 weeks. Anthropometric measurements of weight, length and head circumference were measured at baseline and regular intervals. Primary outcomes for safety assessment were adverse events (AE) and the infants' acceptance and tolerance of the formulae which were frequently recorded during the study period. Secondary outcomes were chemistry measures (albumin, creatinine, triglycerides, low-density lipoprotein, and cholesterol) and were obtained at baseline and at the end of the study.

All infants enrolled in the study had appropriate mean weight, length and head circumference gains over the whole study period compared to the control and the reference range according to the Centres for Disease Control and Prevention. All infant formulae were judged to be safe and well-tolerated by the infants based on growth, laboratory data and AE profiles. Interestingly, constipation was less frequent in the group that re-

ceived the 3.0 g/l oligofructose formula ($P=0.0333$).

To conclude, supplementing infant formulae with oligofructose appears to be safe and supports normal infant growth. The nutritional efficacy of the supplemented formulae is similar to that of the control.

Bettler J, Euler AR (2006) An evaluation of term infants fed formulae supplemented with fructo-oligosaccharides. *Int. J. Prebiotics and Probiotics* 1: 19-26.

Human study shows lower food intake and increased satiety with oligofructose

Studies in different animal models have clearly demonstrated that the addition of inulin-type fructans to various diets lowers food intake and body weight gain. This was especially true in rats put on a high-fat diet (Cani et al., 2004 *Obesity Res.* 13: 1000-1007) and in diabetes-induced hyperphagia (Cani et al., 2005 *J. Endocrin.* 185: 457-465). The aim of this study was to find

out whether these findings were supported in humans too. A placebo-controlled human pilot intervention study was performed including 10 healthy men and women (aged 21-39 yrs.). Female and male volunteers with normal body mass index values were randomised in a cross-over manner and supplemented with 8g oligofructose twice daily (8g of Beneo™ P95 at breakfast and dinner) or placebo (maltodextrin). Each intervention phase lasted for 2 weeks and in between a 2-week wash-out period was included. At the beginning and end of each intervention phase subjects were invited to a day of free-choice buffets during which their food and drink intakes were monitored. Appetite ratings of hunger, satiety and fullness after the meals were recorded by visual analogue scales (VAS).

The energy intake at breakfast and lunch was significantly lower with oligofructose as compared to the placebo treatment

($P<0.05$). This resulted in a significant reduction in total energy intake during the day in the volunteers supplemented with oligofructose compared to the placebo ($P<0.05$) (Figure). After breakfast, oligofructose significantly increased satiety as compared to the placebo treatment ($P<0.05$). After the dinner meal, higher levels of satiety were also obtained and maintained in volunteers supplemented with oligofructose compared to the placebo subjects ($P<0.05$). In addition, supplementation with oligofructose reduced hunger ($P<0.05$) and prospective food consumption compared to the placebo ($P<0.05$). To conclude, the results of this pilot study are in line with the data obtained in animal models and show that supplementation of the diet with oligofructose limits food intake by inducing satiety.

Cani PD, Horsmans Y, Delzenne NM (2006) Oligofructose promotes satiety in healthy humans: a pilot study. *Eur. J. Clin. Nutr.* 60: 567-572.

continued on page 12

Oligofructose reduces energy intake in humans



The figure represents the % energy intake relative to placebo at breakfast, lunch, dinner and over the day in healthy subjects after 2 weeks of oligofructose supplementation (8 g twice daily). Values are means \pm SEM, $n=10$ subjects.

Monitor

Fast growth of *Lactobacillus paracasei* on both inulin and oligofructose

Numerous human studies have shown that inulin and oligofructose selectively stimulate the growth and/or activity of bifidobacteria and lac-

tobacilli in the colon. This property is well described; however, less is known on the fermentation of inulin and oligofructose on the strain level.

Therefore, an in vitro study was undertaken to investigate the capacity of certain lactobacilli strains to ferment long-chain

inulin (Beneo™HP), oligofructose (Beneo™P95) and oligofructose-enriched inulin (Beneo™ Synergy1) in batch cultures. The study showed that *L.acidophilus* IBB 801 and *L.paracasei subsp. paracasei* 8700:2 grew fast on both oligofructose and Synergy1. *L.paracasei subsp. paracasei* 8700:2 also grew very well on the long-chain inulin. Lactic acid was the main metabolic end-product. The *L.paracasei subsp. paracasei* 8700:2 rapidly degraded the inulin and oligofructose fractions through the presence of an extracellular β -fructosidase enzyme, since fructose, inulobiose (F2) and kestose (GF2) did rapidly accumulate in the medium. The short fractions could then be taken up by the bacteria for further intracellular hydrolysis into energy.

To conclude, it appears that some lactobacilli strains have the capacity to ferment both (long-chain) inulin and (short-chain) oligofructose.

Makras L, Van Acker G, De Vuyst L (2005) *Lactobacillus paracasei subsp. paracasei* 8700:2 degrades inulin-type fructans exhibiting different degrees of polymerisation. *Appl. Environ. Microbiol.* 71: 6531-6537.

Prebiotics reduce incidence of allergy in infants at risk

The prevalence of atopic disease (AD) has increased steadily during the last decade. Evidence is increasing about the role of the intestinal flora in the maturation of the immune system and its role in the occurrence of allergic diseases. Inulin and oligofructose have been shown to exert immuno-modulating effects in the gastro-intestinal tract.

Therefore, the aim of this study was to assess the effect of a prebiotic infant formula on the incidence of allergy in infants at risk. A total of 259 infants with high risk of atopy were randomised into a double-blind, randomised, placebo-controlled (parallel) study. They were randomly assigned to one of two (hydrolysed protein) formulae groups with either 0.8 g/100 ml (reconstituted milk) of prebiotics - which consisted of a mixture of galacto-oligosaccharides and long-chain inulin (Beneo™HP) - or placebo (maltodextrin) for 6 months.

During the 6-month period, only 10 infants (9.8%) in the prebiotic group and 24 infants (23.1%) in the placebo group developed AD ($P=0.014$). In the infants with AD, the severity of the symptoms was not different between groups. Stool frequency was significantly higher in the prebiotic group ($P<0.01$ vs. placebo at 3 and 6 months). Consistency of the stools, on the other hand, was significant lower in the prebiotic group ($P<0.0001$ vs. placebo at 3 and 6 months). In a subgroup of infants ($n=94$), faecal bifidobacteria and lactobacilli were plated and counted, and a significant increase in bifidobacteria (not lactobacilli) was observed in the prebiotic group ($P<0.0001$ vs. placebo at 3 and 6 months).

To conclude, this study suggests that supplementation of infant formulae with prebiotics reduces the cumulative incidence of AD during the first 6 months of life.

Moro G, Arslanoglu S, Stahl B, Wahn U, Boehm G (2006) A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch. Dis. Child* 91: 841-849.

Inulin increases calcium and magnesium absorption in animals at all ages

Numerous studies in animal models have demonstrated that inulin and oligofructose increase calcium and magnesium absorption. These data have been confirmed in human intervention trials in children and the elderly. Although the beneficial effects of inulin and oligofructose on mineral absorption have been well described amongst different age groups, less is known about the efficiency variation with age.

Therefore, the objective of this study was to evaluate the effect of inulin on calcium and magnesium absorption in rats of various ages. 80 rats of four different ages (2, 5, 10 and 20 months) were randomised into an inulin-supplemented group (7.5% of Beneo™) or a control group for 3 weeks. Calcium and magnesium absorption were significantly lower in the aged rats (10 and 20 months) than in the young and adult rat groups. Inulin intake significantly increased calcium and magnesium absorption in all four rat groups. The relative increase in calcium absorption with inulin intake was 41.5% in the younger animals (2 and 5 months) and 84.5% in the older rats (10 and 20 months). The increase in magnesium absorption with inulin was 53.5% and 54.5% in the younger and older rats, respectively.

To conclude, it was again confirmed that inulin intake stimulates the absorption of calcium and magnesium. Furthermore, the stimulatory effect of inulin on calcium absorption was greater in older rats than in the younger ones.

Coudray C, Rambeau M, Feillet-Coudray C, Tressol JC, Demigne C, Gueux E, Mazur A, Rayssiguier Y (2005) Dietary inulin intake and age can significantly affect intestinal absorption of calcium and magnesium in rats: a stable isotope approach. *Nutrition Journal* 4: 2-8 (www.nutritionjournal.com/content/4/1/29).



Oligofructose normalises glycaemia and insulinaemia in diabetic rats

It has been found that the addition of oligofructose (BeneoTMP95) to the diet of rats improved glucose homeostasis and insulin sensitivity (Cani et al. 2004 J.Nutr. 128:1099-1103). This was associated with an increased production of the glucagon-like peptide-1(7-36) amide (GLP-1). GLP-1 is a peptide that is strongly involved in the regulation of food intake (suppression of hunger) and hence in body weight modulation. It appears that GLP-1 also functions in maintenance of glucose homeostasis.

In this perspective, the aim of the present study was to evaluate whether the administration of oligofructose could have a normalising effect on sugar metabolism in rats suffering from diabetes and whether GLP-1 could have a role in this. To induce postprandial hyperglycemia, the rats were injected (iv.) with streptozotocin (STZ). A group of normal (non diabetic) rats was kept as well and used as control (CT). STZ-treated rats were randomised to receive either a standard diet (STZ-CT) or a diet enriched with oligofructose (10% of BeneoTMP95) (STZ-OF) *ad libitum* for 6 weeks.

A subset of rats were subjected to an oral glucose tolerance test (OGTT) after 4 weeks receiving the diets. The glucose response (area under the curve, AUC) in the diabetic rats receiving the oligofructose (STZ-OF) was significantly lower compared with the control diabetic rats (STZ-CT rats) ($P < 0.05$), but still higher

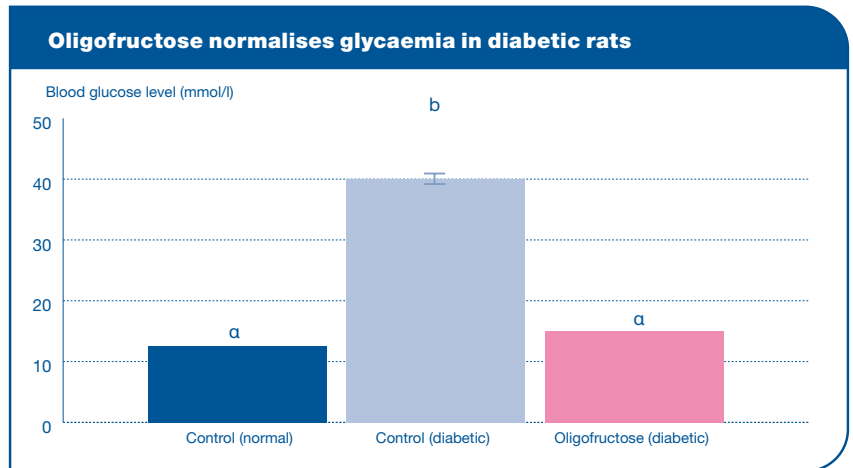
than in normal (non diabetic) rats (CT) ($P < 0.05$). The insulin response (AUC for insulin) in the diabetic rats receiving the oligofructose (STZ-OF) was normalised (e.g. higher as in the control diabetic rats, $P < 0.05$) and equal to the response seen in the normal (non diabetic) rats (CT).

All diabetic rats in the control group (STZ-CT) showed hyperphagia during the whole treatment and this because of their diabetic condition. On the other hand, the diabetic rats receiving the oligofructose (STZ-OF) had normal food intakes and ate the same amount of food as the normal (non diabetic) rats (CT) during the whole study. Postprandial glycaemia at the end of the study was normalised in the oligofructose-fed diabetic rats (STZ-OF) (e.g. significantly lower than in their diabetic controls, $P < 0.05$) and similar to the level of glycaemia in normal rats (CT)

(see Figure). Also, a normalisation of the postprandial insulin levels occurred in the rats receiving the oligofructose feeding (STZ-OF) meaning that their levels were higher (vs. diabetic controls, $P < 0.05$; which have low levels because of their diabetic insulin resistant condition) and similar to the normal rats (CT). After examination, it was shown that diabetic rats had drastically reduced insulin contents in their pancreas (STZ-CT) when compared to the normal rats. Interestingly, this condition was not seen in the diabetic rats receiving the oligofructose. Pancreatic insulin levels and the beta-cell mass were significantly elevated when rats were fed the oligofructose (STZ-OF) ($P < 0.05$ vs. STZ-CT). In addition, GLP-1 levels in the portal blood were significantly higher in the rats fed the oligofructose (STZ-OF) ($P < 0.05$ vs. STZ-CT).

To conclude, it appears that the addition of oligofructose normalised glycaemia and insulinaemia in diabetic rats. Key in this effect was the improvement in the levels of insulin in the pancreas and the restoration of the beta-cell function. Even interesting were the corresponding high levels of GLP-1. The exact role of this peptide needs further investigation. This opens new perspectives for the use of oligofructose as a nutritional adjuvant in the management of diabetes and insulin resistance.

Cani PD, Daubioul CA, Reusens B, Remacle C, Catillon G, Delzenne NM (2005) Involvement of endogenous glucagon-like peptide-1(7-36) amide on glycemia-lowering effect of oligofructose in streptozotocin-treated rats. *J. Endocrin.* 185: 457-465.



The figure represents the (plasma) levels of glucose in diabetic rats after 6 weeks of supplementing the diet with oligofructose (10%) or not (diabetic controls). The glucose levels in non-diabetic rats (normal controls) are given as well.

Values are means \pm SEM, $n=5$ rats per group. (a-b) represents significant differences between groups when bars are marked with different superscripts, $P < 0.05$.

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Anti-diabetic mechanism of oligofructose elucidated

Animal studies have shown an anti-diabetic effect and an increased secretion of the glucagon-like peptide-1(7-36) amide (GLP-1) with oligofructose.

The aim of this study was to further investigate the role of GLP-1 and its receptor-dependent mechanisms for the systemic effects on glycaemia and insulinaemia observed with oligofructose. The study used two independent experimental approaches. In the first one, mice were fed a high-fat diet for 28 days supplemented with oligofructose (10% BeneoTMP95), or not (control), in the presence or absence of a GLP-1 receptor antagonist (exendin, Ex 9-39). The high-fat diet induced a typical type-2 diabetic condition. In those diabetic mice, oligofructose improved glucose tolerance, fasting blood glucose, glucose-stimulated insulin secretion as well as insulin sensitive hepatic glucose production, and it reduced body weight gain. Treatment with the receptor antagonist (Ex 9-39) totally prevented the beneficial effects seen with oligofructose. Addition of oligofructose also reduced the levels of intracellular inflammatory effectors (e.g. nuclear factor- κ B and inhibitor of κ B kinase β) in the liver. This latter effect was not abolished by Ex 9-39.

For their second approach, the authors used GLP-1 receptor knock-out mice (GLP-1R $-/-$). GLP-1R $-/-$ mice were put on a high-fat diet for 28 days and, interestingly, were completely insensitive to the anti-diabetic actions of oligofructose. The present data demonstrate that oligofructose reduced the impact of high-fat feeding on the occurrence of diabetes and obesity in a GLP-1 receptor dependent manner. These findings highlight the potential role of oligofructose for the prevention of weight gain and development of type-2 diabetes with high-fat diets through its impact on GLP-1 secretion.

Cani PD, Knauf C, Iglesias MA, Drucker DJ, Delzenne NM, Burcelin R (2006) Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes* 55: 1484-1490.

Synbiotic administration improves intestinal motility in old rats

Ageing is often accompanied by gastro-intestinal dysfunction. The interdigestive intestinal motility, more specifically the migrating myoelectric/motor complex (MMC), is one physiological mechanism that prevents bacterial overgrowth and translocation in the gut. There appears to be a relationship between the intestinal motility and the composition of the intestinal microflora. The objective of the present study was, therefore to determine whether dietary induced changes in the composition of the intestinal microflora would have an effect on the motility response. 30 elderly rats were randomised into either a synbiotic group, receiving *Lactobacillus* GG, *Bifidobacterium lactis* Bb12 and oligofructose-enriched inulin (8% of BeneoTM Synergy1), or a control group for 21 days. Rats were implanted with electrodes recording the duodenojejunal electromyography (EMG) to evaluate small intestinal motility. The synbiotic altered the composition of the microflora in the gastro-intestinal tract and significantly increased the number of bifidobacteria and decreased the number of enterobacteria when compared to the controls ($P < 0.05$). The synbiotic also stimulated a more regular occurrence of intestinal contractions of high amplitude which are more effective in propelling the residual food, debris, secretions and bacterial cells.

To conclude, this study demonstrated that the administration of the synbiotic improved the interdigestive intestinal motility func-

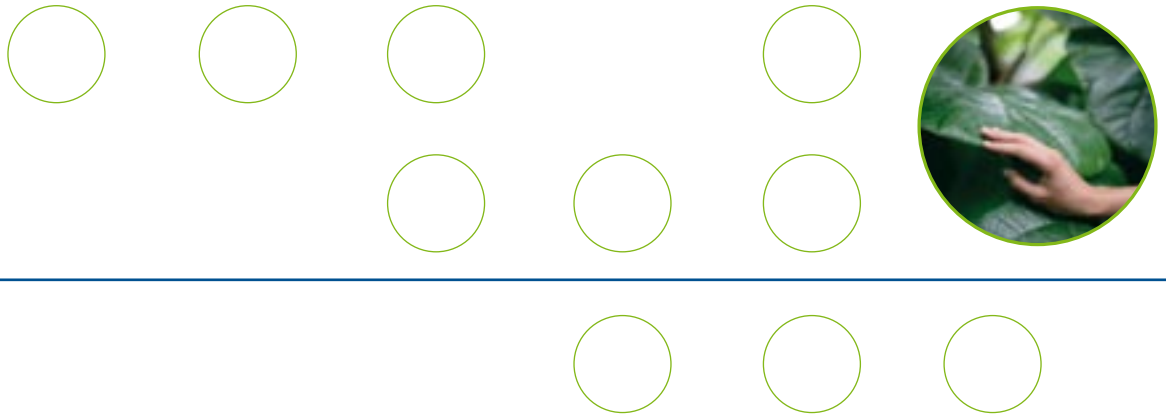
tion in old rats which might be of relevance for the treatment of gastro-intestinal dysfunction, especially related to ageing.

Lesniewska V, Rowland I, Laerke HN, Grant G, Naughton PJ (2006) Relationship between dietary-induced changes in intestinal commensal microflora and duodenojejunal myoelectric activity monitored by radiotelemetry in the rat in vivo. *Experimental Physiology* 91: 229-237.

Active transport is involved in the mechanism of increased calcium absorption with oligofructose

Most of the ingested calcium is absorbed in the proximal intestine. However, the increase in calcium absorption observed with inulin and oligofructose is most likely to occur mainly in the colon. Although, the beneficial effects of inulin and oligofructose on calcium absorption and retention are well known, the molecular mechanisms by which these enhance calcium absorption remain to be further clarified.

The objective of this study was to determine whether the regulation of calbindin-D9k gene expression was involved in the process by which oligofructose enhances calcium absorption. Also, the mechanisms of this oligofructose-mediated impact on gene expression were explored by investigating its effect on two distinct transcription factors. The calbindin-D9k is an intracellular protein that binds calcium and brings it to basolateral membrane where it is transported into the blood. The expression of this protein involves the action of the vitamin-D receptor (VDR), which also acts as a transcription factor



(VDRE). Another transcription factor that positively regulates calbindin-D9k expression is the caudal-related homeodomain protein *cdx-2*.

Rats (n=36) were divided into three groups receiving either a diet with 10% oligofructose (FOS) for 5 days, or the same diet for 10 days, or a non-supplemented (control) diet for 10 days. Thereafter, the rats were sacrificed and mRNA of the calbindin-D9k, VDR and *cdx-2* were extracted from the proximal intestine and colorectal segments. In the small intestinal segment, oligofructose modulated the transcription of calbindin-D9k, VDR and *cdx-2*. In the colorectal segment, a significant increase in the expression of calbindin-D9k, VDR and *cdx-2* was observed with oligofructose both after 5 and 10 days. The good correlations between gene expression of the calbindin-D9k vs. VDR ($r=0.73$, $P<0.01$) and the calbindin-D9k vs. *cdx-2* ($r=0.52$, $P<0.05$) suggest that both transcription factors are involved in the regulation of calbindin-D9k expression in the colorectal segment and one of the mechanisms by which oligofructose enhances calcium absorption.

To conclude, it appears that the modulation of the transcellular active transport of calcium through the up-regulation of the calbindin-D9k protein and its associated transcription factors VDR and *cdx-2* is involved in the mechanism by which oligofructose increases calcium absorption.

Fukushima A, Ohta A, Sakai K, Sakuma K (2005) Expression of calbindin-D9k, VDR and *Cdx-2* Messenger RNA in the process by which fructo-oligosaccharides increase calcium absorption in rats. *J Nutr Sci Vitaminol* 51: 426-432.

Inulin and oligofructose increase bifidobacteria and lactobacilli in infants after antibiotic treatment

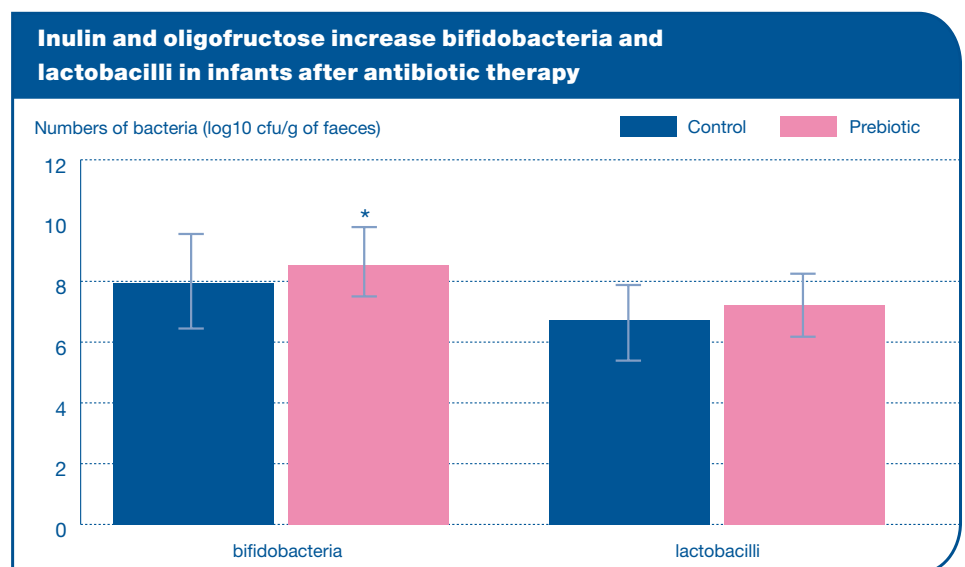
Treatment of infants with antibiotics dramatically disturbs the resident microbiota in the gut which favours the growth of potentially pathogenic micro-organisms. Through eradication of susceptible commensal micro-organisms some opportunistic bacteria might proliferate and occupy ecological niches previously unavailable to them. The objective of this study was to evaluate the effect of supplementing infant formula with inulin and oligofructose on the recovery of the intestinal microbiota in infants after antibiotic treatment. 140 infants of 1 to

2 years of age with acute bronchitis were randomised in a double-blind manner into 2 groups after treatment with the antibiotic amoxicillin. The infants received for 3 weeks an infant formula supplemented with 4.5 g/l of inulin and oligofructose (Beneo™) (30% inulin and 70% oligofructose) or a control formula (without prebiotics). Both infant formulae were well tolerated. Administration of the antibiotic disturbed the microflora to a major extent resulting in a 30% decrease in the counts of total faecal bacteria. The prebiotic infant formula significantly increased the levels of bifidobacteria compared with the control ($P=0.029$). The differences in the *Lactobacillus* population between the two for-

mulae showed a similar tendency towards higher levels with the prebiotic supplementation ($P=0.057$) (see Figure). Levels of other bacteria remained unchanged.

To conclude, infant formulae supplemented with inulin and oligofructose are well-tolerated. Feeding them to infants early after antibiotic therapy increased the levels of bifidobacteria and lactobacilli and in this way contributes to the re-establishment of the homeostasis of the gut microbiota in infancy.

Brunser O, Gotteland M, Cruchet S, Figueroa G, Garrido D, Steenhout P (2006) Effect of a milk formula with prebiotics on the intestinal microbiota of infants after an antibiotic treatment. *Pediatric Research* 59: 451-456.



The figure represents the faecal levels of bifidobacteria and lactobacilli in infants receiving the prebiotic infant formula (4.5 g/l of inulin and oligofructose) or control formula for 1 week after antibiotic treatment.

Values are means \pm SEM, n=70 infants/group.

* Represents significant difference with control group, $P<0.05$

Agenda



Brasil, Florianopolis November 12-16, 2006

Subject 14° CLN Congresso Latinoamericano de Nutrição (SLAN)

Speaker Wim CAERS, ORAFTI

Content An update of the last studies on intestinal health

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Belgium, Gent November 30, 2006

Subject Vierde Voedingscyclus

Speaker Paul COUSSEMENT & Anne FRANCK, ORAFTI

Content ORAFTI's Innovation Strategy

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France, Montpellier March 30-31, 2007

Subject 3° Congrès Interprofessionnel de Médecine Intégrée:

Le Système intestinal, Carrefour de la maladie et de la guérison

Speaker Prof. Marcel ROBERFROID

Content Prébiotiques et Médecine : quelles perspectives ?

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Hungary, Budapest April 20-21, 2007

Subject Early Nutrition Programming & Health Outcomes in Later Life: Obesity and Beyond (EARNEST)

Speaker Dr. T. Decsi and Dr. D. Molnár

Content Importance of early nutrition on long-term effects on development and health

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