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Interview

with prof. Glenn R. Gibson

From marine sediments to the human gut

In this newsletter we are glad to introduce you to Professor Glenn R. Gibson, the father of the prebiotic concept. Learn more of prebiotics from this authority, who is also a fanatical squash player and football supporter.

An expert also in swimming pools

Professor Glenn R. Gibson (39) did his PhD on marine sediments in Scotland.
"We were looking at sulphate-reducing bacteria that were involved in carbon turnover but also produced a noxious metabolite (sulphide). Sulphate reducers are good metabolisers of hydrogen in such anaerobic ecosystems. From there, I went to Cambridge and worked with John Cummings and George Macfarlane on gas metabolism in the human gut. We were interested in determining why only certain people produced methane in breath or flatus."
"The explanation was that sulphate reducers were also in some persons gut and they could get rid of hydrogen which was the precursor for methane. So, if you had active sulphate reducers you didn't produce methane. Because the sulphate reducers produce a toxic metabolite (sulphide) we started to look at gut disease in relation to their carriage. This involved work on ulcerative colitis which is still ongoing."
"During the course of this, we realised that most bacteria in the gut were in fact harmless and that others could do some good. Probiotics had been frequently used to help this situation but it seemed that targeting indigenous genera through non-viable food components was more worthwhile. We then tested this and introduced the prebiotic concept together with Marcel Roberfroid."
"I then moved to the Institute of Food Research in Reading to look further at the interactions of gut bacteria with dietary components. Following the closure of this laboratory in 1999 I moved to the University of Reading to continue fruitful collaborations with Christine Williams (nutrition) and Bob Rastall (biotechnology). Some of the prebiotic questions outlined above can only be answered with the excellent expertise they and their groups bring to the area."
As a father of two young and energetic children Glenn Gibson not only is an expert on prebiotics, he also is an expert in all local swimming pools, and cinemas around Reading, and of course in Legoland. "On the other hand, I like to fit in as many squash games as possible and I am an ardent supporter of Sunderland Football Club."

"The real value in the use of prebiotics is in better resistance to acute infections such as those caused by pathogenic bacteria or viruses that enter the gut. This is where prebiotics can really come into their own i.e. germ warfare, for improved human health."

► Can you explain, as the 'father' of the prebiotic concept, what it means?

The prebiotic concept has been designed to target certain bacteria in the intestinal tract through the diet. It takes the view that the gut microflora contains genera, or species, seen as beneficial to human health (bifidobacteria are the usual targets, as well as lactobacilli). Whilst we know that some bacteria found in the gut are pathogenic (e.g. through the formation of toxins) the vast majority are harmless and some may even be positive. Most human bacteria reside

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Preface

The BENEO® Programme

by Dr. Anne Franck

In recent years, a growing body of scientific evidence has shown that inulin and oligofructose are associated with nutritional benefits that help to improve well-being and to reduce the risk of disease. Since we started nutritional research on these exciting food ingredients, some 10 years ago, the scientific results we obtain keep surprising us and motivate more and more key scientists to perform innovative work in that field.
Both ingredients selectively stimulate the beneficial bacteria in our digestive system while repressing harmful ones and improve our intestinal function and bowel habits. Furthermore, the latest scientific findings have confirmed that they increase calcium absorption in man. As calcium has a direct effect on bone structure and health - in particular on the incidence of osteoporosis later in life - these data are particularly important.
Scientific work to analyse the possibility that inulin and oligofructose may reduce the risk of cardiovascular disease by decreasing blood triglyceride level and to investigate further the very promising findings about the reduction of colon cancer risk, is under way.
A major new EU-funded research project (SYNCAN) will investigate the potential colon cancer-preventing activity of synbiotic combinations (probiotics and inulin) in human volunteers.
To improve communication of these health benefits to consumers, ORAFTI has launched, first in Belgium, a new initiative, the BENEO® Programme. BENEO® will provide a platform of clear communications to support products containing inulin and oligofructose. "Consumers must be made aware of the scientific benefits of functional foods and this requires clear and informative communications through messages (claims) on products and in accompanying materials," was stated in the European consensus document on Scientific Concepts of

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in the colon where they contribute significantly to the human digestive process, metabolising around 80g of dietary residues per day. Indeed, life would be most uncomfortable without this activity whereby microbial fermentation can result in improved energy generation from the diet.

Prebiotics serve the same purpose as probiotics in that they use foods to target the health-positive components of the flora. Prebiotics are dietary carbohydrates that have a selective effect on the gut flora whereas probiotics incorporate the relevant bacteria themselves into the diet. What this means is that consumers can improve their intestinal microflora composition through the diet. Prebiotics can be incorporated into many everyday food items such as cereals, biscuits, breads, table spreads, drinks, yoghurts... anything that has a carbohydrate base to it is susceptible. I think that this is a very straightforward approach, designed to improve health, that is user-friendly and proven to work through volunteer trials conducted by ourselves and others.

Sceptics may argue that if consumers eat a normal balanced diet, then fortification through prebiotics and other functional foods is not needed.

No one is arguing against a balanced diet and in a perfect world this would be the case. One important issue is that the majority of consumers may know that they have to eat 5-8 pieces (>80g each) of fruit and vegetable per day. However the vast majority do not. What happens with prebiotics and the like is that active ingredients are taken from relevant natural foodstuffs (or deliberately manufactured) and put into more commonly ingested foods. The consumer choice is expanded with functional foods. It is critical that these are backed up by sound scientific principles and mechanistic explanations of effect. This is the case for prebiotics, where minimal operative doses have also been determined.

One of the new potential health benefits of pre- and probiotics may be the prevention of infections.

The health effects of prebiotics and probiotics have been suggested as acting at the local level, i.e. gut (better protection from bowel cancer, irritable bowel syndrome, inflammatory bowel disease), and systemic level (effects on coronary heart disease through reduced blood lipids and on candida infections, improvement of mineral bioavailability). My own feeling is that the real value in their use is in better resistance to acute infections such as those caused by pathogenic bacteria or viruses that enter the gut. It is recognised that the target organisms for prebiotic intake can exert powerful effects against pathogens e.g.

Functional Foods in Europe (Diplock et al., 1999). New market research conducted in Europe showed that consumers are interested in foods that can help to improve health, including intestinal well-being. There was a good knowledge of the importance of diet in maintaining healthy intestinal function, with some knowledge of the importance of a balanced intestinal microflora. Beneficial ingredients that can be incorporated into everyday foods, thus increasing nutritional profile, were appealing because they make it easier for consumers to eat healthily. Ingredients derived from chicory, a plant that people traditionally associate with health-giving properties, also were appealing.
In addition, this research showed that consumers respond best to clear and straightforward messages about nutritional benefits and claims.
The exclusive BENEO® Programme is a co-operative initiative that is built on skills and experience from complementary scientific disciplines. It combines the latest developments in nutritional science and the creativity of the food industry. The BENEO® symbol will appear on foods and drinks that contain sufficient inulin or oligofructose to have a beneficial effect. Communications for BENEO® will explain what it does, where it comes from, what it is and why it is 'good for you'.
An independent BENEO® Scientific Committee has been set up to establish the criteria that a product needs to meet to become part of the BENEO® Programme. These criteria include guidelines about the dosages required and appropriate wordings. The Scientific Committee, which is chaired by Prof. em. Marcel Roberfroid (Catholic University of Louvain) continuously monitors scientific developments around inulin and oligofructose to identify nutritional benefits. At present these are the stimulation of beneficial intestinal bifidobacteria, the positive effects on digestive function and bowel habits and the increase in calcium absorption. Together with you, we can bring these positive messages to consumers.

Diplock A.T., Aggett P.J., Ashwell M., Bornet F., Fern E.B. & Roberfroid M.B. (1999), Scientific Concepts of Functional Foods in Europe: Consensus Document, British Journal of Nutrition, 81(S1), S1-S27.

through competition for nutrients and colonisation sites, acid excretion and formation of antimicrobial peptides.

Improved gut health that better resists infectious agents that may be present in the food should have a large impact on the consumer. Not many people think they will suffer from colon cancer or coronary heart disease. Unfortunately many are wrong, but the use of foods to protect from these disorders could have limited, although extremely important, marketing impact. On the contrary, people are worried about the safety of their food and almost everyone suffers from acute gastroenteritis caused by food poisoning at some time in his or her life. A lot of effort is being expended on cleaning up the food chain from farm to fork (or plough to plate). However, there are too many variables along the way to do this successfully. Also, the agents involved in food poisoning have their effects after the fork (or plate). We can therefore argue that this is even more important than tracking a pathogen to the gut. So, why not use diet to better fortify the natural resistance? Given that bifidobacteria are useful inhibitors of common food safety-relevant bacteria it seems rational that increasing their numbers in the gut will help in this regard. This is where prebiotics can really come into their own i.e. germ warfare, for improved human health.

Is there some evidence for this hypothesis?

As supporting evidence, I would add that the elderly have reduced resistance to infections (e.g. those caused by campylobacter and *E. coli*) and numbers of indigenous (protective) bifidobacteria and lactobacilli are reduced in this population group. My own research group has completed a challenge in vitro with a laboratory gut model and in vivo experiments with a primate colony that tend to confirm these observations. To do this kind of challenge is obviously impossible in humans but we are now looking at the use of prebiotics for more predictive gut infections i.e. *Helicobacter pylori* (peptic ulcers), sulphate-reducing bacteria (ulcerative colitis) and Clostridium difficile (pseudomembranous colitis).

What do you expect for the near future in this field?

For the near future I expect to see a much wider use of prebiotics in common foods, much further use in combination with probiotics (i.e. as synbiotics) and defined health outcomes with mechanisms of effect. For the research side prebiotics that have multi-functional activities are now being developed (i.e. stimulate bifidobacteria/lactobacilli but also contain regions that inhibit or attenuate pathogens). Also, prebiotics that act at the species, rather than genus, level are possible. ■

Introducing the BENEO® Scientific Committee

Chairman is prof. Marcel Roberfroid (Belgium). He is Emeritus Professor at the Catholic University of Louvain in Brussels, where he has conducted research in biochemistry, toxicology, food and nutrition, and cancer. Throughout his career, prof. Roberfroid has been very active internationally. He undertook a post-doctoral research fellowship at the National Institutes of Health in the United States, he has served on the executive committee of the European Association for Cancer Research, he has been president of the International Life Science Institute in Europe, and he is founding member of the European Research Group for Alternatives to Toxicity Testing.

Members

Prof. Glenn Gibson (UK) is Professor of Microbiology and Head of the Food Microbial Sciences Unit at the University of Reading. Prior to that he was with the Institute of Food Research, Reading and Dunn Clinical Nutrition Centre, Cambridge. His research interests include various aspects of the human gut flora in health and disease. In particular, he has introduced and developed the prebiotic concept, with prof. Roberfroid, which enables gut flora to be managed through diet.

Prof. Beatrice Pool-Zobel (Germany) is Professor of Nutritional Sciences at the Institute of Nutrition, Friedrich Schiller University, in Jena, and Head of the Department of Nutritional Toxicology. Prior to that she was with the German Cancer Research Centre in Heidelberg and the Federal Centre for Nutrition in Karlsruhe. Her research interests include understanding the molecular basis of the causes of colon cancer and the interactions of risk factors with phytoprotectants. In addition she is developing new biomarker techniques to be used during nutritional intervention trials to assess preventative strategies.

Prof. Margareta Nyman (Sweden) is Associate Professor in Food Chemistry and Assistant Head at the Department of Applied Nutrition and Food Chemistry at Lund University. Her research interests have been focusing on nutritional effects of dietary fibre and other indigestible carbohydrates in the diet. An important aim during her work has been to relate physical and chemical properties of carbohydrates to their physiological effects and to be able to understand their important nutritional parameters, such as bulking effect, formation of short-chain fatty acids and metabolic effects.

Dr. Anne Franck (Belgium), Director of Science and Technology at ORAFTI, provides the scientific secretariat of the BENEO® Scientific Committee. In her position she directs ORAFTI's extensive scientific research programme to understand and demonstrate the nutritional benefits of inulin and oligofructose.

State of the Art:

Colorectal cancer is the second cancer in term of frequency (15% of all cancers), after lung cancer in men and breast cancer in women. Only 50% of those who develop colon cancer live longer than 5 years after diagnosis. Epidemiological studies indicate that increased consumption of fruits and vegetables and high total dietary fibre intake reduce the risk of development of colon cancer. Human metabolic studies suggest that beneficial effects of dietary fibre in relation to colon cancer development depend on the composition and physical properties of fibre. Animal studies also demonstrate that tumour-inhibitory properties of dietary fibre depend on their composition. In this article we will review a number of recent animal studies on the potential inhibitory properties of inulin and oligofructose on (colon) carcinogenesis.

Non-digestible oligosaccharides and the risk of colon cancer

Reddy et al. (1997) added 10% high performance inulin (RAFTILINE®HP) or oligofructose (RAFTILOSE®P95) to the diet of rats. After adaptation, the animals were injected with azoxymethane (AOM). For both types of fructan, a statistically significant reduction in the number of colonic ACF (aberrant crypt foci) was observed. ACF are considered to be early precursor lesions of colon tumours in rodents and humans. The degree of ACF inhibition was more pronounced in animals fed inulin than in those fed oligofructose, which is probably due to the slower fermentation rate of high performance (or long chain) inulin allowing it to be fermented in the more distal part of the colon.

Molck et al. (1999) and Poulsen et al. (1999) also found that inulin is a more potent inhibitor of ACF formation in rats than oligofructose.

Inhibitory effects of fructans on (colon) carcinogenesis

The tumour-inhibitory effect of inulin and oligofructose seems to be dose related. Verghese et al. (1999) added 2.5%, 5% and 10% inulin (RAFTILINE®HP) to the diet of mature rats (52 weeks old) treated with AOM to induce colonic ACF. They observed a significant, dose-dependent reduction of ACF: minus 25% ACF with the 2.5% diet, minus 51% ACF with the 5% diet and minus 65% ACF with the 10% diet. They observed a significant increase in caecal weight and a decrease in caecal pH from 7.17 in the control group to 6.87, 6.61 and 5.76 in the inulin groups.

Also the time of administration of the fructans may be an important factor. In a long-term experiment (45 weeks) with colon tumours as end-points, Verghese & Rao (1999) and Rao et al. (1999) added 10% inulin (RAFTILINE®HP) to the diet of rats during initiation, promotion or both phases of carcinogenesis. They observed a significant inhibition of the incidence and yield of colon tumours, especially when inulin was given during the promotion phase.

Hughes et al. (2000) studied apoptosis (programmed cell death) and bacterial metabolism as a possible mechanism involved in the protective effects of oligofructose (RAFTILOSE®P95) and inulin (RAFTILINE®HP).
They fed 18 rats for a three-week period with either a basal diet (44% energy as fat), or a basal diet with 5% oligofructose or with 5% inulin. All animals were then dosed with 1,2-dimethylhydrazine and sacrificed after 24h.
The mean number of apoptotic cells per crypt was significantly higher in the colon of rats fed fructans compared to those fed the basal diet alone.
The apoptotic index was slightly higher in animals fed inulin.

Pierre et al. (1997) observed a significant reduction in the number of spontaneously developing tumours (mainly in the small intestine) in Min-mice after an oral intake of oligofructose (58 g/kg diet). This study also provided evidence of a concomitant development of the gut-associated lymphoid tissue.

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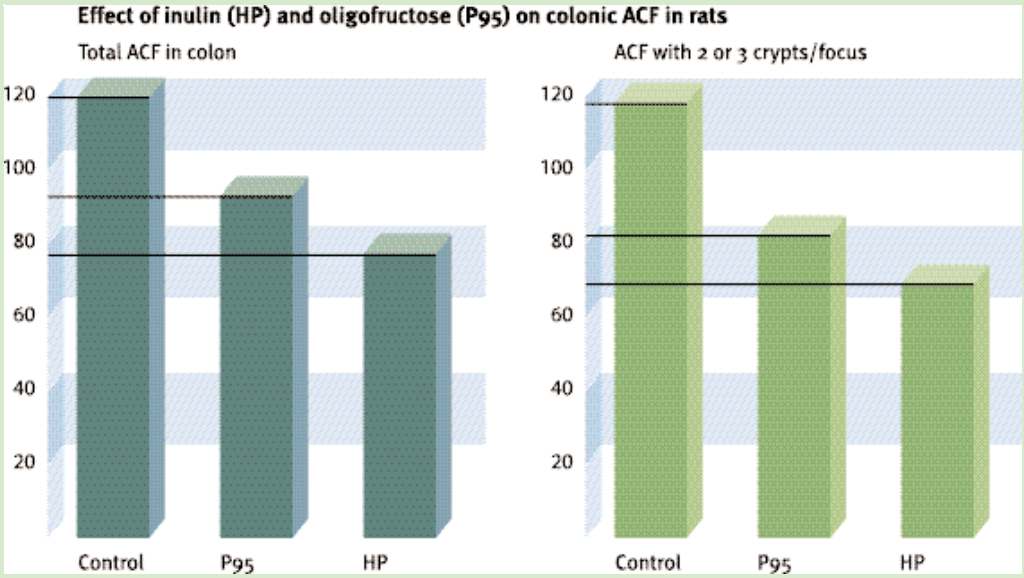

Synbiotics and colon cancer risk in humans

the SYNCAN project

The consensus report from the EU-funded ENDO project (Van Loo et al., 1999) concluded that the available animal studies are sufficient to claim preliminary evidence for interaction of non-digestible oligosaccharides with colon carcinogenesis and that these experimental data therefore support the investment for performing human nutrition studies.

A new EU-funded project called SYNCAN started in January 2000 to investigate the potential colon cancer-preventing activity of synbiotic combinations (probiotics and inulin) in human volunteers (a group of cancer patients and a group of polypectomised patients). Several biomarkers for monitoring the anticancer activities of the synbiotic combinations will be measured in the volunteers. Hypothesised mechanisms of action will be studied by means of in vitro and in vivo animal models. It is expected that this strategy will result in the identification of a range of probiotic and prebiotic (synbiotic) combinations with the potential to influence gut ecology and reduce colorectal cancer (CRC) risk. It should also help identify the likely stages of the cancer process which are affected. In a first phase of the project, synbiotics will be developed combining increased competitive advantages in the intestinal ecosystem and synergistic anticancer properties, and also targeting distal parts of the colon, the place where colorectal cancers most frequently occur. ORAFTI initiated and coordinates this project in which research centres in Ireland, Italy, UK, Sweden, Germany and Finland are collaborating (University College Cork, University of Firenze, University of Ulster, Karolinska Institute, University of Jena, Federal Research Center for Nutrition BFE, as well as Valio).

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Synbiotic effect

Rowland et al. (1998) and Rumney et al. (1998) have shown that the combined administration of *Bifidobacterium longum* and 5% inulin (RAFTILINE®HP) resulted in more potent ACF-inhibition (80% inhibition of small ACF) than with the pro- or prebiotic alone, thus providing good evidence for a synbiotic effect. Furthermore, the combined synbiotic administration decreased the incidence of large ACF by 59%. Since the dietary treatment started 1 week after the carcinogen dose, these results suggest that inulin and *B. longum* may affect the early promotion phase of the carcinogenic process.

Furthermore, consumption of diets with inulin and/or *B. longum* were also associated with decreases in beta-glucuronidase activity and ammonia concentration in the caecal contents, two factors associated with carcinogenesis of the colon.

A similar synbiotic effect was described by Gallaher et al. (1997 & 1999) who combined several oligosaccharides (oligofructose, soybean oligosaccharides and wheat bran oligosaccharides) with bifidobacteria. The synbiotic effect on the number of ACF in the distal colon of rats was observed only for the combination with oligofructose, not for the other combinations. This study failed to show a significant reduction in ACF number in rats given either oligofructose or bifidobacteria alone.

Mechanism

It is likely that the protective effect of fructans proceeds through the selective modulation of microflora (increase of bifidobacteria and decrease of bacteroides, clostridia and fusobacteria and/or Gram-positive cocci). The colonizing cells of bifidobacteria produce lactic acid, thereby lowering the pH, and create a bacteriocidal environment for putative enteropathogens, thus developing a favourable micro-environment in the gut. This may also involve the modulation of specific bacterial enzymes such as beta-glucuronidase. In addition, prebiotics increase the production of short-chain fatty acids (SCFA) in the colon, especially butyrate, by microbial fermentation. Butyrate may inhibit the genotoxic activity of nitrosamides and of hydrogen peroxide in human colon cells and induce a more differentiated phenotype including colorectal tumour cells (Reddy, 1998 & 1999; Pool-Zobel, 1998). Also Roland et al. (1994 & 1996) observed an effect of different sources of dietary fibre, including inulin, on hepatic and intestinal cytochrome P-450, glutathione-*S*-transferase and UDP-glucuronosyl-transferase in rats inoculated with a human whole faecal flora.

Hughes et al . (2000) studied apoptosis as a possible mechanism involved in the protective effects of oligofructose and inulin, but failed to determine mechanisms for the upregulation of apoptosis. No significant dietary effect on bacterial enzyme activities or ammonia concentration during the fructan diets was shown in the study. Pierre et al. (1997) reported that the intestinal immune system of mice was stimulated by oligofructose, concomitant with a reduction in the development of (small) intestinal tumours. ■

Gallaher D.D., Stalings W., Blessing L.L., Busta F.F. & Brady L.J. (1996), Probiotics, cecal microflora, and aberrant crypts in the rat colon, Journal of Nutrition, 126, 1362-1371.

Gallaher D.D. & Khil J. (1999), The Effect of Synbiotics on colon Carcinogenesis in Rats, Journal of Nutrition, 129 (7S), 1483S- 1487S.

Hughes R. & Rowland I.R. (2000), Investigation of apoptosis as a possible mechanism involved in the protective effects of two prebiotic chicory fructans against colon cancer, submitted.

Molck A.-M., Poulsen M. (1999), Different effect of fructooligosaccharides and inulin on carcinogen-induced aberrant crypt foci in rats, Abstract presented at the International Conference on Diet and Prevention of Cancer, Tampere Finland, May 28-June 2, 1999.

Pierre, F., Perrin P., Champ M., Bornet F., Meflah K. & Menanteau J. (1997), Short-Chain Fructo-oligosaccharides Reduce the Occurrence of Colon Tumours and Develop Gut-Associated Lymphoid Tissue in Min Mice, Cancer Research, 57, 225-228.

Pool-Zobel B.L. (1998), Potential of pro- and prebiotics to prevent colon cancer by antigenotoxic and other mechanisms, Abstract presented at the International Symposium on Probiotics and Prebiotics, Kiel Germany, June 11-12, 1998.

Poulsen M. & Molck A.-M. (1999), Effect of fructooligosaccharides and inulin on large intestine parameters related to aberrant crypt foci in rats, Abstract presented at the International Conference on Diet and Prevention of Cancer, Tampere Finland, May 28-June 2, 1999.

Reddy B.S., Hamid R. & Rao C.V. (1997), Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition, Carcinogenesis, 18 (7), 1371-1374.

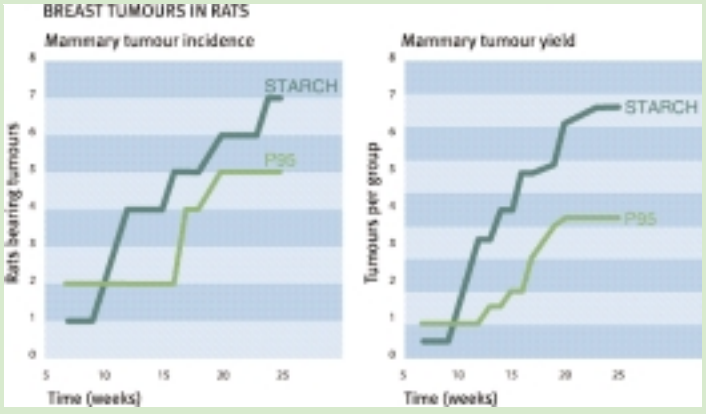
Animal studies on other cancers

Roberfroid et al. (1994) and Taper et al. (1994) studied the effect of 15% oligofructose (RAFTILOSE®P95) on breast tumours induced by methyl-nitroso-urea (MNU) in female rats. They observed a much lower incidence of mammary tumours (-50%) in the rats fed with oligofructose in comparison with placebo (starch).
Taper et al. (1996, 1997, 1998) also showed that the growth of transplantable mouse tumours (of liver or mammary origin) was significantly inhibited by the supplementation of the basal diet of mice with 15% of either inulin (RAFTILINE®HP) or oligofructose (RAFTILOSE®P95).
For solid tumours, tumour growth was nearly 50% lower than in the control group, and for ascitic tumours the increase in life span of the mice was 16%. The dietary treatment was performed starting at day 7 before tumour transplantation and continued until the end of observation.

Furthermore, Taper et al. (1999 & 2000a) studied the effect of 15% inulin (RAFTILINE®HP) or oligofructose RAFTILOSE®P95) in combination with several anti-cancer drugs on transplanted ascitic tumours in mice. In experiments with anti-metabolite drugs the combination had a statistically significant synergistic character and increased the life span of mice up to 47%. The fructans did not increase the general and organ toxicity induced by the cytotoxic drugs used.

Taper et al. (2000b) also investigated the effect of 15% inulin (RAFTILINE®HP) or oligofructose (RAFTILOSE®P95) on lung metastases developed from transplantable liver tumours in mice. 47 days after tumour transplantation, 59% of mice in the control group were bearing lung metastases, in comparison to only 36% in the inulin fed group and 35% in the oligofructose fed group. The total number of lung metastases was 37 in the control group, 18 in the inulin fed one and only 6 in oligofructose fed mice.

Several hypothetical mechanisms may be involved in this tumour growth inhibition, like calorie restriction, alteration of colonic microflora, decrease of the level of serum glucose, insulin and insulin-like growth factor, decrease of de novo lipogenesis, or immunity-mediated effects.



Reddy B.S. (1998), Prevention of colon cancer by pre- and probiotics: evidence from laboratory studies, British Journal of Nutrition, 80, Suppl.2., S219-S223.

Reddy B.S. (1999), Possible Mechanisms by Which Pro- and Prebiotics Influence Colon Carcinogenesis and Tumour Growth, Journal of Nutrition, 129 (7S), 1478S- 1482S.

Rao D.R., Verghese M., Chawan C.B., Shackelford L.A. (1999), Suppression of Azoxymethane-induced colon and small intestinal tumours in rats by inulin, Abstract presented at the International Conference on Diet and Prevention of Cancer, Tampere Finland, May 28-June 2, 1999.

Roberfroid M., Delzenne N. & Taper H. (1994), Negative modulation of MNU-induced rat mammary carcinogenesis by fructo-oligosaccharides from chicory, Abstract presented at the XVI International Cancer Congress, New Delhi India, October 30-November 5, 1994.

Roland N., Nugon-Baudon L., Flinois J.-P. & Beaune P. (1994), Hepatic and intestinal cytochrome P-450, Glutathione-S-Transferase and UDP-Glucuronosyl-Transferase are affected by six types of dietary fiber in rats inoculated with human whole fecal flora, Journal of Nutrition, 124, 1581-1587.

Roland N., Rabot S. & Nugon-Baudon L. (1996), Modulation of the Biological Effects of Glucosinolates by Inulin and Oat Fibre in Gnotobiotic Rats Inoculated with a Human Whole Faecal Flora, Food and Chemical Toxicology, 34, 671-677.

Rowland I.R., Rumney C.J., Coutts J.T. & Lievense L.C. (1998), Effect of bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats, Carcinogenesis, 19 (2), 281-285.

Rumney C., Coutts J., Lievense L., Rowland I. (1998), The influence of Bifidobacterium longum and inulin (Raftiline HP) on colonic neoplastic lesions and gut bacterial metabolism: probiotic, prebiotic and synbiotic effects, in: Sadler M.J. & Saltmarsch M.(ed.); Functional Foods, the Consumer, the Products and the Evidence, British Nutrition Foundation.

Taper H.S., Delzenne N.M., Roberfroid M.B. (1996), Growth inhibition of two transplantable mouse tumour lines by dietary administration of non-digestible carbohydrates, Abstract presented at the International Meeting on Cancer Chemoprevention, Molecular Basis, Mechanisms and Trials, Heidelberg Germany, September 9-11, 1996.

Taper H.S., Delzenne N.M., Roberfroid M.B. (1997), Growth inhibition of transplantable mouse tumours by non-digestible carbohydrates, Int. J. Cancer, 71, 1109-1112.

Taper H.S., Lemort C., Roberfroid M.B. (1998a), Inhibition effect of dietary Inulin and Oligofructose on the growth of transplantable mouse tumour, Anticancer Research, 18, 4123-4126.

Taper H.S., Delzenne N.M., Roberfroid M.B. (1998b), Tumour Growth Inhibition by Inulin and other Non-Digestible Carbohydrates, Abstract presented at the 7th Inulin Seminar, Leuven Belgium, January, 1998.

Taper H.S. & Roberfroid M. (1999), Influence of Inulin and Oligofructose on Breast Cancer and Tumour Growth, Journal of Nutrition, 129 (7S) 1488S-1491S.

Taper H.S. & Roberfroid M. (2000a), Non-toxic potentiation of cancer chemotherapy by dietary oligofructose or inulin, Nutrition and Cancer, in press.

Taper H.S. & Roberfroid M. (2000b), Inhibitory effect of dietary inulin or oligofructose on the development of cancer metastases, Anticancer Research, in press.

Van Loo J., Cummings J., Delzenne N., Englyst H., Franck A., Hopkins M., Kok N., Macfarlane G., Newton D., Quigley M., Roberfroid M., van Vliet T. & van den Heuvel E. (1999), Functional food properties of non-digestible oligosaccharides: a consensus report from the ENDO project (DGXII AIRII-CT94-1095), British Journal of Nutrition, 81, 121-132.

Verghese M., Chawan C.B., Rao D.R., Van Loo J. (1999), Long chain inulin suppresses AOM-induced aberrant crypt foci in colon of retired male Fisher-344 rats, Abstract presented at AICR Meeting, Washington USA, December 2-3, 1999.

Monitor

In the following pages we offer you the latest nutritional information on chicory inulin and oligofructose, summarized from key articles in major scientific journals.

Gastrointestinal function and general health status of infants consuming a weaning food supplemented with oligofructose

This double-blind randomized controlled study examined the effects of a pediatric weaning food supplemented with oligofructose (OF) in 123 non breast-feeding infants aged 4 tot 24 months and attending daycare. One group received a standard infant cereal for 6 months, the second group received the same cereal supplemented with 0.55 g OF per 15 g cereal (the average daily intake was 1.2g OF). There were no significant differences between the groups in frequency of diarrhea, bowel movement frequency, stool consistency, diaper rash or flatulence. Consumption of OF-supplemented cereal was interestingly associated with a decrease in severity of diarrheal disease and an improvement of general gastrointestinal status with decreased perceived bowel movement discomfort, vomiting and regurgitation. Furthermore, consumption of OF resulted in adequate growth and was associated with reduction in febrile events and cold symptoms, antibiotic use and day care absenteeism.

Saavedra J., Tschernia A., Moore N., Abi-Hanna A., Coletta F., Emenhiser C., Yolken R. (1999), Gastro-intestinal function in infants consuming a weaning food supplemented with oligofructose, a prebiotic, J. Pediatr. Gastroenterol. Nutr., 29 (4), A95.

Tschernia A., Moore N., Abi-Hanna A., Yolken R., Coletta F., Emenhiser C., Saavedra J. (1999), Effects of long-term consumption of a weaning food supplemented with oligofructose, a prebiotic, on general infant health status, J. Pediatr. Gastroenterol. Nutr., 29 (4), A58.

Fn-type chicory inulin hydrolysate has a prebiotic effect in humans

This study demonstrated that, as is the case with GFn-type oligofructose, a preparation of chicory oligofructose (RAFTILOSE® L60) containing 90% of Fn-type molecules selectively stimulates the growth of colonic bifidobacteria in human volunteers, as evidenced by the significant increase in faecal number. The volunteers consumed 8g/d of an Fn-rich product for up to 5 weeks. Changes in stool frequency (+12%) as well as in the appearance (softer) and the amount of stools showed a tendency to confirm the bulking effect reported earlier. Only six mild complaints of intestinal side-effects were reported from 224 meals.

Menne E., Guggenbuhl N., Roberfroid M. (2000), Fn-type chicory inulin hydrolysate has a prebiotic effect in humans, American Journal of Clinical Nutrition, 67, 1197-1199.

Effects of inulin on faecal bifidobacteria in human subjects

The partial replacement of dietary fat by chicory inulin (up to 34g/d) in an otherwise isoenergetic diet which was consumed by 8 healthy subjects for a period of 64 days distinctly promoted the growth of faecal bifidobacteria. The administration of inulin did not affect significantly any of the following variables: total, HDL and LDL cholesterol and triacylglycerols in serum, total faecal short-chain fatty acids (SCFA), molar ratios of faecal SCFA. The study concludes that a high-dose long-term application of inulin is practicable.

Kruse H.-P., Kleessen B., Blaut M. (1999), Effects of inulin on faecal bifidobacteria in human subjects, British Journal of Nutrition, 82, 375-382.

Effect of high-performance inulin on constipation

This placebo controlled study investigated the effect of long-chain inulin on bowel function in 6 healthy volunteers with low stool frequency (1 stool every 2 to 3 days). Subjects were administered 15g/d inulin (RAFTILINE® HP) for 2 weeks. There was a significant increase in stool frequency and faecal bulking, but no effects on other parameters such as oro-caecal transit time or intestinal permeability.

The study concludes that inulin can be added to the normal nutrition to obtain effective levels of e.g. 4 to 5g/d and that it is suitable for tube-feeding formulae.

Den Hond, E., Geypens B., Ghoos Y. (2000), Effect of high performance chicory inulin on constipation, Nutrition Research 20 (5), 731-736.

Effects of a breakfast cereal containing inulin on healthy males

This subject-blinded but not randomized study was planned to test the effects of consumption of a ready-to-eat breakfast cereal containing inulin on lipid metabolism and on colonic milieu in healthy young men.

Twelve healthy male volunteers consumed daily for 3 periods of 4 weeks, first 50g of a rice-based cereal (placebo) in substitution of their habitual breakfast, then the same cereal containing 18% chicory inulin (9g/d), and then they returned to their habitual diet (wash-out). No changes in body weight, dietary habits, faecal and bile acid output, faecal short-chain fatty acids (SCFA) and faecal pH were observed at the end of each period. Plasma total cholesterol and triacylglycerols (TAG) significantly decreased at the end

of the inulin period. TAG levels remained significantly low after 1 month of cessation of inulin supplementation. Inulin enhanced breath H_2 excretion as well as faecal concentration of L-lactate. Total facultative anaerobes significantly decreased and bifidobacteria increased after correction for total anaerobes, upon inulin ingestion. Changes in blood lipids were negatively correlated with bifidobacteria counts and positively with secondary bile acid excretion.

Brighenti F., Casiraghi M.C., Canzi E., Ferrari A. (1999), Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers, European Journal of Clinical Nutrition, 53, 726-733.

Dietary oligofructose lessens hepatic steatosis in obese rats

The addition of 10% oligofructose (OF, RAFTILOSE® P95) to the diet of obese fa/fa Zucker rats slowed the increase in body weight without modifying serum triglycerides or glucose levels after 7 weeks of treatment. A fat load (2g glucose and 5g corn oil/kg body weight) increased triglyceridemia more in OF-fed rats than in controls, suggesting either a higher capacity to absorb lipids from the intestinal tract and/or a greater secretion of endogenous VLDL from the liver. After 10 weeks of treatment, OF decreased the hepatic concentration of triglycerides by 57% relative to controls. The less severe steatosis was confirmed by histologic analysis. Among the key enzymes involved in fatty acid synthesis and esterification, only malic enzyme activity was significantly lower in OF-fed rats. Also the epididymal fat mass was significantly lower. No modifications of glycemia during OF treatment were detected, but a lower serum glucose concentration was observed in the portal and cava veins at the end of the sudy. This effect was accompanied by a higher concentration of insulin. The study concludes that OF can counteract both the fat mass development and the hepatic steatosis that occur in obese Zucker rats. This effect was not shown in previous experiments with non-obese rats.

Daubioul C.A., Taper H.S., De Wispelaere L.D., Delzenne N.M. (2000), Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese Zucker rats, Journal of Nutrition, 130, 1314-1319.

Health benefits of inulin in hypercholesterolemic men

Daily intake of 20g of chicory inulin for three weeks significantly reduced serum triglycerides by 40 mg/dl in hypercholesterolemic men. The study was a randomized, double-blind, crossover design with no washout period. Twelve men were randomly assigned to 2 controlled diets (with 1 pint of vanilla ice cream with either sucrose or inulin). A trend toward a reduction in serum cholesterol and toward short-chain fatty acids (SCFA) profile changes were observed. Subjects with serum cholesterol levels higher than 250 mg/dl tended to have the greatest reduction after inulin supplementation. Insulin and glucagon levels were increased at 1-hour post glucose load. This may be the result of the effects of elevated SCFA on proglucagon mRNA and thus glucagon expression and secretion. Transit time did not differ significantly, although most of the subjects showed decreased transit times during the inulin phase.

Causey J.L., Feirtag J.M., Gallaher D.D., Tungland B.C., Slavin J.L. (2000), Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men, Nutrition Research 20 (2), 191-201.

Fluorescence in situ hybridization for the quantification of human faecal bacteria

This study compared conventional cultivation of faecal samples on anaerobic selective media with fluorescence in situ hybridization (FISH) using rRNA-based probes for the detection and enumeration of human colonic bacteria in different faecal sub-populations. Artificial variation was introduced in the samples by incubation for 2 days at 37°C and by addition of pure cultures. The results showed that plate counts of total anaerobes, bifidobacteria, lactobacilli and bacteroides were approximately 10-fold lower than the corresponding FISH counts. Numbers of clostridia were higher using the plating method, probably because the clostridia probe used in FISH analyses was designed to detect only part of the genus Clostridium. For accurate and fast identification the FISH methodology is probably more appropriate since it is based on molecular markers. An added value of the approach is that stored samples can be used for analysis.

Harmsen H.J.M., Gibson G.R., Elfferich P., Raangs G.C., Wildeboer-Veloo A.C.M., Argaiz A., Roberfroid M.B., Welling G.W. (1999), Comparison of viable cell counts and fluorescence in situ hybridization using specific rRNA-based probes for the quantification of human faecal bacteria, FEMS Microbiology Letters 183, 125-129.

Actions of non-digestible carbohydrates on blood lipids

This article reviews in detail recent research on the influence of different non-digestible carbohydrates (NDC) (fructans, resistant starch, cellulose and soluble fibres like pectin, guar gum and beta-glucans) on lipid metabolism and circulating blood lipids. Feeding NDC leads to modest reductions in blood lipids in human subjects and in animal models. The major effect of soluble fibres appears to be on the total and LDL cholesterol fractions (largely through inhibition of bile acid absorption and metabolism), whereas the fructans and resistant starch appear to affect the triglyceride-rich fractions (through effects secondary to fermentation in the large bowel). The

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variable blood lipid responses observed in human volunteer studies may be due, in part, to the influence of other dietary components. In particular, triglyceride-lowering effects of fructans and resistant starch may best be observed in subjects on high carbohydrate diets, whilst cholesterol-lowering effects are best observed in the presence of high dietary cholesterol.

Delzenne N., Williams C.M. (1999), Actions of Non-Digestible Carbohydrates on Blood Lipids in Humans and Animals, in: Gibson G.R. & Roberfroid M.B. (ed.); Colonic Microbiota, Nutrition and Health, Kluwer Academic Publishers, 213-231.

Gastrointestinal effects of fructooligosaccharides

As is the case with other dietary fibres, the chicory fructans inulin and oligofructose are resistant to digestion in the upper part of the intestinal tract and are subsequently fermented in the colon to produce short-chain fatty acids, which acidify the colon content and are absorbed and metabolized in different parts of the body. They also modify the composition of the gut microflora, especially by stimulating the growth of bifidobacteria that are beneficial for health, while the growth of potentially pathogenic species, such as clostridia and Escherichia coli *is inhibited. They are thus model type prebiotics. The health benefits of such a change are still to be established however. Moreover, this fermentation induces a bulking effect (between 1.5 and 2 g/g of ingested inulin or oligofructose). Another typical dietary fibre effect is the increase in stool frequency. None of the molecules of fructose and glucose that form inulin and oligofructose appear in the portal blood. Chicory fructans also show beneficial effects on calcium absorption, on the biochemical mechanisms controlling triacylglycerol metabolism, and possibly on the reduction of risk in developing precancerous lesions in the colon.*

Roberfroid M.B. (2000a), Fructo-oligosaccharide malabsorption: benefit for gastrointestinal functions, Current Opinion in Gastroenterology, 16, 173-177.

Roberfroid M.B. (2000b), Chicory fructo-oligosaccharides and the gastrointestinal tract, Nutrition, 16 (7/8), 677-679.

Prebiotics in consumer products

This article gives an overview of the actual use of prebiotics, mostly non-digestible oligosaccharides (NDO), as food ingredients because of their nutritional advantages (low caloric value, prebiotic properties, stool bulking effect, etc.), their technological properties or both. The use of NDO as fibre-like ingredients can lead to an improved taste and texture, they can give increased crispness and expansion to extruded snacks and cereals, they may help maintain breads and cakes moist and fresh. Their solubility allows incorporation into fluid systems such as drinks, dairy products and table spreads. They are increasingly used in functional foods as prebiotic agents to stimulate the growth of beneficial intestinal bacteria. Because of specific gelling characteristics, inulin allows the development of low-fat table spreads, butter-like products, cream cheeses and processed cheeses, meat products, sauces and soups. In low-fat dairy products, the addition of inulin improves flavour and gives a creamier mouthfeel, in dairy mousses it improves processability and upgrades organoleptic quality. In frozen desserts, inulin provides easy processing, excellent melting properties as well as freeze-thaw stability. In several food products it may also replace certain stabilisers.

Fructose-based oligosaccharides are applied in yoghurts, fermented milks, fresh cheeses, dairy drinks, desserts and meal replacers. Their incorporation into baked goods allows replacement of sugar, fibre enrichment and good moisture retention properties. They also offer binding characteristics in cereal bars.

Franck, A. (2000), Prebiotics in Consumer Products, in: Gibson G.R. & Roberfroid M.B. (ed.); Colonic Microbiota, Nutrition and Health, Kluwer Academic Publishers, 291-300.

New developments in prebiotics

Non-digestible oligosaccharides (NDO) have been shown to be of particular interest because of their prebiotic properties. To establish the prebiotic nature it is critical to measure as many components of the gut microbiota as possible during fermentation studies. Simple stimulation of bifidobacteria and/or lactobacilli is insufficient without determining effects on other gut micro-organisms, as it is the selectivity that determines classification as a prebiotic. Pure bacterial studies are of very limited use in this respect, unless they are supported by mixed culture work. The prebiotic effect should also be determined in vivo with human volunteers. As most colonic disorders originate in the left (distal) side, prebiotics that exert an effect in this region of the large intestine may have added benefits.

Oligosaccharides with anti-adhesive properties that mimic the interaction between certain patogenic micro-organisms and carbohydrate receptors might reduce colonisation with pathogenic species. More research is needed on the synergistic effect of the combination of probiotics and prebiotics.

A very important research target for the future is the development of convenient and reliable molecular methods of identification of gut bacteria, e.g. bifidobacteria.

Gibson G.R., Rastall R.A., Roberfroid M. (1999), Prebiotics, in: Gibson G.R. & Roberfroid M. (ed.); Colonic Microbiota, Nutrition and Health, Kluwer Academic Publishers, 101-124.

FAQ

This page is entirely reserved for your FAQs. It is meant to give answers to the most important questions that may arise.

Can inulin cause an allergic reaction?

Recently, Gay-Crosier et al. (2000) reported about a man showing anaphylactic reactions to foods containing inulin. They described the case of a 39-year old man who had four episodes of anaphylaxis a few minutes after ingestion of salsify, artichoke leaves, a margarine and a candy containing inulin. Skin-prick testing with inulin extract and intradermal tests also were positive. However, there was no reaction to the ingestion of oligofructose.
This is to our knowledge the first case of allergic reaction to foods containing inulin, an ingredient present in several hundreds of consumer food products worldwide. Every year, thousands of tons of inulin are used by the food industry and millions of people consume it, mainly for its beneficial health effects. In more than 10 years of this activity, no other case of allergic reaction to this ingredient has been reported. Inulin has been used as a diagnostic agent for renal clearance tests since the early 1900s. Nobody has ever reported an allergic or other adverse reaction to such intravenous injections of inulin.

Similar to starch, inulin is present in significant amounts in the daily diet of the whole population of the planet. Commercial inulin is a complex carbohydrate, obtained from chicory roots (*Cichorium intybus*). Since inulin is a polysaccharide and allergens are usually proteins, the allergic reaction might, in principle, be due to the presence of protein residues from the source material. However, only two publications have reported allergic reactions to chicory (Cadot et al., 1996 and Helbling et al., 1997).
The first study reports a case of occupational allergy to chicory (Belgian endive) in a vegetables wholesaler. Symptoms occurred after oral, cutaneous and inhalatory exposure. The patient also reported reactions after ingestion of botanically related endive (Cichorium endivia) and lettuce (*Lactuca sativa*). No cross-reactivity was found with mugwort (*Artemisia vulgaris*), ryegrass (*Lolium perenne*) or birch (*Betula verrucosa*) pollen, which suggests that the vegetable was the primary allergenic material. The responsible allergen was identified to be a 48-kDa protein, confined to the non-illuminated parts of the plant.

The second report documents a systemic reaction after ingestion of chicory (Belgian endive) in a 26-year old female cook with a history of summertime rhinoconjunctivitis. The mechanism involved may be IgE-mediated, as demonstrated by the positive skin prick test and immunoblot findings. No endive-specific IgE could be detected. Sensitization may have occurred as a result of the handling of salads. This seems very unlikely, however, because the skin of the study subject was not affected. More likely, the inhalation of airborne allergens could have fostered an alimentary hypersensitivity caused by cross-reactive episodes. Sensization to grass pollen, which is associated with hypersensitivity to various foods, may be the source of cross-reactive epitopes, which then resulted in allergy to Belgian endive.

So, chicory is rarely allergenic and our experts have concluded that the risk of allergic reactions to inulin seems exceedingly small. Compared to other allergenic foods like peanuts, milk, soy, shellfish and wheat ... to which an estimated 15 million people are allergic in the Western world, inulin clearly has a significantly lower allergenic potential.

Cadot P., Kochuyt A.M., Deman R., Stevens E.A.M. (1996), Inhalative occupational and ingestive immediate-type allergy caused by chicory (Cichorium intybus), Clin. Exp. Allergy, 26, 940-944.

Gay-Crosier F., Schreiber G., Hauser C. (2000), Anaphylaxis from Inulin in Vegetables and Processed Food, New England Journal of Medicine, May 2000, 1372.

Helbling A., Reimers A., Walti M., Borgts R., Brander K.A. (1997), Food allergy to Belgian endive (chicory), J. Allergy Clin. Immunol., 99, 854-856.

Agenda

Arolla, Switzerland
August 16-20, 2000

Fourth International Fructan Symposium

The symposium with 8 plenary sessions, poster viewing and round-table discussions will bring together scientists from various disciplines involved in fructan research:
plant and microbial physiologists, geneticists, taxonomists, molecular biologists, biotechnologists, scientists from human and animal nutritional and medical research.

Keynote speakers include:
Andrew J. Cairns (UK), Rita de Cassia L. Figueiredo-Ribeiro (Brazil), Lazaro Hernandez (Cuba), David P. Livingston (USA) and Diederick Meyer (The Netherlands).

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Geneva, Switzerland
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European Health

This forum organised by Leatherhead Food Research Association, is dedicated to examining the potential benefits of health claims and furthering the understanding of this emerging trend.

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The conference will discuss inulin and oligofructose in relation to gut function, gut flora, calcium metabolism, cancer risk, lipid metabolism and immunology, as well as their technological functionality and their place in baby food, in pet food and in feed applications.
Chairmen of the conference are Prof. G. Gibson and Prof. M. Roberfroid.

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Colophon

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ORAFTI produces inulin (RAFTILINE®), oligofructose (RAFTILOSE®) and fructose syrups (RAFTISWEET®) from chicory roots.
The commercial department of ORAFTI is based in Tienen and operates worldwide in 50 countries through own sales offices and distributors.
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