

# Inulin-Type Fructans: Functional Food Ingredients<sup>1,2</sup>

Marcel B. Roberfroid\*

Université Catholique de Louvain, B-1348, Louvain-La-Neuve, Belgium

## Abstract

A food (ingredient) is regarded as functional if it is satisfactorily demonstrated to affect beneficially 1 or more target functions in the body beyond adequate nutritional effects. The term inulin-type fructans covers all  $\beta(2 \leftarrow 1)$  linear fructans including native inulin (DP 2–60,  $DP_{av} = 12$ ), oligofructose (DP 2–8,  $DP_{av} = 4$ ), and inulin HP (DP 10–60,  $DP_{av} = 25$ ) as well as Synergy 1, a specific combination of oligofructose and inulin HP. Inulin-type fructans resist digestion and function as dietary fiber improving bowel habits. But, unlike most dietary fibers, their colonic fermentation is selective, thus causing significant changes in the composition of the gut microflora with increased and reduced numbers of potentially health-promoting bacteria and potentially harmful species, respectively. Both oligofructose and inulin act in this way and thus are prebiotic: they also induce changes in the colonic epithelium and in miscellaneous colonic functions. In particular, the claim “inulin-type fructans enhance calcium and magnesium absorption” is scientifically substantiated, and the most active product is oligofructose-enriched inulin (Synergy 1). A series of studies furthermore demonstrate that inulin-type fructans modulate the secretion of gastrointestinal peptides involved in appetite regulation as well as lipid metabolism. Moreover, a large number of animal studies and preliminary human data show that inulin-type fructans reduce the risk of colon carcinogenesis and improve the management of inflammatory bowel diseases. Inulin-type fructans are thus functional food ingredients that are eligible for enhanced function claims, but, as more human data become available, risk reduction claims will become scientifically substantiated. J. Nutr. 137: 2493S–2502S, 2007.

## Introduction

This article served as an introduction to the 5th International ORAFTI Research Conference on Inulin and Oligofructose that took place in Boston, Harvard Medical School, in September 2006. It refers to the concept of “functional food”; it defines inulin-type fructans, the products that were evaluated during the conference; it gives a full description of their chemistry and nomenclature; and it summarizes the data available at the time of the meeting that support the physiological properties of these food ingredients. For full details of these properties, refer to the proceedings of conferences 2, 3, and 4 of this series (1–3), to the specialized articles published in this Supplement, as well as to the book entitled *Inulin-type Fructans as Functional Food Ingredients* (4).

### Concept of functional food

A wide variety of foods are or will, in the future, be characterized as functional food with a variety of components affecting a

variety of body functions relevant to either a state of well-being and health and/or to the reduction of risk of a disease.

In line with the European concept (FUFOSE), the following features characterize a functional food: conventional/everyday food or food ingredient; naturally occurring in foods; proven beneficial effect(s) on target functions beyond nutritive value/basic nutrition; and convincing human nutrition intervention studies demonstrating enhanced well-being and health and/or reduced risk of a disease and/or improved quality of life including physical, psychological, and behavioral performances.

According to the European Consensus on “Scientific Concepts of Functional Foods” (5), a functional food is defined as:

A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially 1 or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either improved stage of health and well-being and/or reduction of risk of disease. A functional food must remain food and it must demonstrate its effects in amounts that can normally be expected to be consumed in the diet: it is not a pill or a capsule, but part of the normal food pattern.

As described in that consensus (5):

The design and development of functional foods is a key issue, as well as a scientific challenge, which should rely on basic scientific knowledge relevant to target

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\* To whom correspondence should be addressed. E-mail: marcel@fefem.com.

functions and their possible modulation by food components. [Emphasis is then put on the importance of] the effects of food components on well-identified and well-characterized target functions in the body that are relevant to well-being and health issues rather than solely on reduction of disease risk.

Achieving such a development, requires identification of potential functional food components and, at least partly, understanding the mechanism(s) by which they modulate target function(s) that are relevant to the state of well-being and health and/or the reduction of a disease risk, formulation of hypotheses to be tested in human nutrition intervention studies aimed at testing the effect of the food components as part of the ordinary diet to be consumed by the general population or large at-risk target groups.

To demonstrate a positive modulation of target functions after (long-term) consumption of the potential functional food components, most of these studies will identify and quantify change(s) in validated/relevant markers. Such a modulation will then be translated into claims that should be based on effects that go beyond what could be expected from the established role of diet. If such effects concern a target function or a biological activity without direct reference to a particular disease or pathological process, claim will be made for an “enhanced function.” But, if the benefit is clearly a reduction of the risk of a disease or pathological process, claim will be made for a “disease risk reduction.”

The large bowel and the composition and its symbiotic microbial ecosystem are major targets for functional food development and are attracting more and more interest from the nutrition community, as shown by the most recent developments in the fields of probiotics, prebiotics, and synbiotics (2,3,6,7). Among these, inulin-type fructans are relatively unique functional food components because of their chemical nature and the combination of their physiological and nutritional effects that affect gastrointestinal functions.

### Inulin-type fructans: chemistry and nomenclature

Inulin-type fructans are natural components of several edible fruits and vegetables, and the average daily consumption has been estimated to be between 3 and 11 g in Europe (8) and between 1 and 4 g in the United States (9). The most common dietary sources are wheat, onion, banana, garlic, and leek.

Chemically, inulin-type fructans are a linear polydisperse carbohydrate material consisting mainly, if not exclusively, of  $\beta$ -(2 $\leftarrow$ 1) fructosyl-fructose linkages (10). A starting  $\alpha$ -D-glucose moiety can be present but is not necessary.  $G_{py}F_n$  [glucopyranosyl-(fructofuranosyl) $_n$ -fructose] and  $F_{py}F_n$  [fructopyranosyl-(fructofuranosyl) $_n$ -fructose] compounds are included under that same nomenclature; they are both a mixture of oligomers and polymers that are best characterized by the degree of polymerization (DP), either as the average ( $DP_{av}$ ) or the maximum ( $DP_{max}$ ) value.

The plant that is most commonly used industrially for the extraction of inulin-type fructans belongs to the *Compositae* family, i.e., chicory. Native chicory inulin is a nonfractionated inulin extracted from fresh roots (11). Because of the  $\beta$ -configuration of the anomeric  $C_2$  in its fructose monomers, inulin-type fructans resist hydrolysis by human small intestinal digestive enzymes, which are specific for  $\alpha$ -glycosidic bonds. They have thus been classified as “nondigestible” oligosaccharides (12,13).

The DP of chicory inulin varies from 2 to ~60 units with a  $DP_{av} = 12$ . About 10% of the fructan chains in native chicory inulin have a DP ranging between 2 ( $F_2$ ) and 5 ( $GF_4$ ). The partial enzymatic hydrolysis of inulin using an endoinulinase (EC

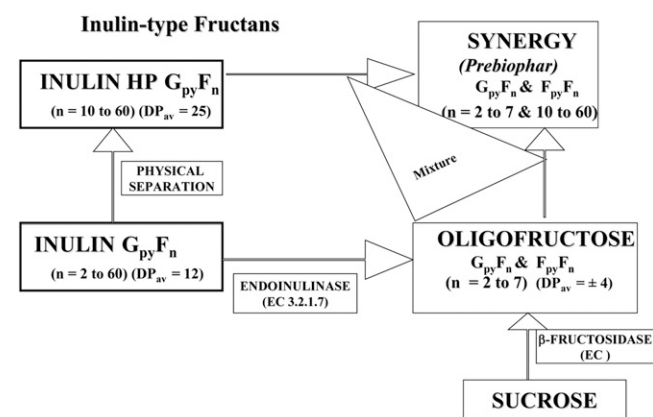
3.2.1.7) produces oligofructose that is a mixture of both  $G_{py}F_n$  and  $F_{py}F_n$  molecules, in which the DP varies from 2 to 7 with a  $DP_{av} = 4$ . It is composed primarily of lower-DP oligosaccharides, namely, 1-kestotriose, 1,1-kestotetraose, and 1,1,1-kestopentaose, as well as inulobiose, inulotriose, and inulotetraose. Oligofructose can otherwise be obtained by enzymatic synthesis (transfructosylation) using the fungal enzyme  $\beta$ -fructosidase (EC 3.2.1.7) from *Aspergillus niger*. In that reaction, in a process similar to the plant biosynthetic pathway, sucrose serves as a substrate to which 1, 2, or 3 additional fructose units are added by forming new  $\beta$ -(2 $\leftarrow$ 1) linkages. In such a synthetic compound, DP varies from 2 to 4 with  $DP_{av} = 3.6$ , and all oligomers are of  $G_{py}F_n$  type. By applying physical separation techniques, it is also possible to eliminate all oligomers with  $DP < 10$  to produce a high-molecular-weight inulin-type fructan or inulin HP, a mixture of  $G_{py}F_n$  molecules with a DP ranging from 10 to ~60 and  $DP_{av} = 25$ . A mixture of 2 distinct populations of the low-molecular-weight oligofructose and the high-molecular-weight inulin is known as oligofructose-enriched inulin or Synergy. It is a unique type of oligosaccharide.

In these proceedings (and as indicated in a footnote at the beginning of each article), the term inulin-type fructan shall apply as a generic term to cover all  $\beta$ -(2 $\leftarrow$ 1) linear fructans when the properties reviewed concern all types of molecules. In any other circumstances that justify the identification of the oligomers vs. the polymers, the terms oligofructose and/or inulin or eventually long-chain or high-molecular-weight inulin (inulin HP) will be used, respectively. Even though the inulin hydrolysate and the synthetic compound have slightly different  $DP_{av}$  (4 and 3.6, respectively), the term oligofructose shall be used to identify both. Indeed, oligofructose and (short-chain) fructooligosaccharides are considered to be synonyms to name the mixture of small inulin oligomers with  $DP_{max} < 10$  (14–18). Moreover, as outlined by Farnworth (19), “although the initial findings (on the effects of inulin) were based on Neosugar (the synthetic or so-called short-chain fructooligosaccharide), it has become evident that many of the conclusions extend to other sources of dietary fructans and especially inulin and inulin derivatives.” Synergy will be used to identify the 30/70 mixture (wt:wt) of oligofructose and inulin HP.

The main structural and molecular features of inulin-type fructans are summarized in Figure 1.

### Inulin-type fructans and the concept of dietary fiber

The 5 basic attributes of a dietary fiber are: components of edible plant cell; carbohydrates (both oligosaccharides and polysaccharides);



**FIGURE 1** Schematic representation of the industrial processes in the preparation of the inulin-derived fructans.

resistance to hydrolysis by human (mammal) alimentary enzymes; resistance to absorption in the small intestine; hydrolysis and fermentation (partial or total) by the bacteria in the large bowel (20).

Inulin-type fructans are plant carbohydrates that, because of the  $\beta$ -(2 $\leftarrow$ 1) configuration of the fructosyl-fructose glycosidic linkages, resist digestion in the upper gastrointestinal tract but are quantitatively fermented in the colon. They are thus undoubtedly part of the dietary fiber complex, and they must be labeled as dietary fiber on consumer food products.

However, because of their specific fermentative properties, inulin-type fructans do have characteristic features different from those of other dietary fibers.

Therefore, they may contribute in a significant way to a well-balanced diet by increasing the fiber content, by improving the diversity of the fiber sources, and by specifically affecting several gastrointestinal functions (composition of intestinal microflora, mucosal functions, endocrine activities, mineral absorption, ...) and even systemic functions (especially lipid homeostasis and immune functions) as well as by reducing the risk of miscellaneous diseases. These effects are summarized in Table 1.

### Inulin-type fructans and modulation of physiological functions

The gastrointestinal functions are primary endpoints that benefit most from inulin-type fructans. One of the most promising effects is modulation of activities of the colon, an organ of the gastrointestinal tract that is recognized more and more as playing a variety of key roles in maintaining health and well-being as well as reducing the risk of diseases (21–25).

The concept of “colonic health” has thus emerged as a major target for functional food development in the area of enhanced function claims (26).

In addition to its important physiological and immunological functions, the colon is also involved in miscellaneous diseases from acute infections and diarrhea or constipation to chronic diseases such as inflammatory bowel diseases, irritable bowel syndrome, or cancer (21). Through modulation of the colonic functions, inulin-type fructans thus also have the potential to reduce the risk of some diseases.

**Concept of balanced colonic microflora.** The composition of the symbiotic colonic microflora is a key player in maintaining the colon (and thus the whole body) health. That composition is largely determined by the flora that establishes at and immediately after birth, is mostly “individual,” can be modulated by

specific compounds in the diet, and may change during the lifetime, becoming more and more complex as we age (27).

To support health and well-being and to reduce the risk of various diseases, we hypothesized that the gut (and especially the colon) microflora must remain a “balanced microflora,” i.e., a microflora composed predominantly (in numbers) of bacteria recognized as potentially health-promoting (such as lactobacilli, bifidobacteria, fusobacteria, ...) to prevent, impair, or control the proliferation of potentially pathogenic/harmful microorganisms (including some species of *E. coli*, clostridia, veillonellae, or *Candida*) (22). Evidently, that hypothesis does not imply that the so-called potentially pathogenic/harmful microorganisms are useless and must be eliminated. Indeed, the colonic microflora is a complex “ecosystem” with a wide variety of potential interactions among the different populations of microorganisms, and it cannot be excluded that some interactions between potentially health-promoting and (a low number of) potentially harmful bacteria and/or microorganisms do in fact play a role in maintaining health and well-being and in reducing the risk of some diseases. It is thus possible that some populations of potentially harmful or even pathogenic bacteria are necessary, provided they remain small compared with the health-promoting species. This is particularly true for the species that are recognized as being both potentially health promoting and potentially harmful. Thanks to the new molecular methodologies now available to analyze its composition in terms of phyla, genera, species, or even strains, we are now in a new phase of exploration of the gut microflora, but we still largely ignore most of the activities of these microorganisms and even more so the interactions, exchanges, and complementarities that exist in that extremely complex microbiota.

By introducing the concept of prebiotics, we hypothesized (22,28) that, through modulation of the composition of the colonic microbiota (i.e., by stimulating the growth of potentially health-promoting bacteria and suppressing, or at least reducing the number of, potentially harmful microorganisms), dietary strategies might be developed to improve colonic health and thus, indirectly, health and well-being of the host as well as the host’s ability to reduce the risk of various diseases.

According to that concept, which was recently revisited: “A prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health” (29).

The classification of a food or a food ingredient as prebiotic requires the scientific demonstration of resistance to gastric acidity, hydrolysis by mammalian enzymes, and gastrointestinal absorption; fermentation by intestinal microflora; and selective stimulation of the growth and/or activity of intestinal bacteria associated with health and well-being (22,29).

Indeed, fermentation of a prebiotic food ingredient must be directed toward bacteria recognized as health promoting, with indigenous lactobacilli and bifidobacteria currently being the preferred targets.

**The prebiotic properties of inulin-type fructans.** Inulin and oligofructose are the most studied and well-established prebiotics. As previously mentioned, they escape digestion in the upper gastrointestinal tract and reach the large intestine virtually intact, where they are quantitatively fermented and act as prebiotics. Indeed, in the studies (30–44) that investigated the effects of inulin and oligofructose on the human gut microbiota, a selective stimulation of growth of the beneficial flora, namely bifidobacteria, to a lesser extent lactobacilli, and possibly other

**TABLE 1** Nutritional effects and potential health benefits of inulin-type fructans

Enhanced functions
Composition and activities of the gut microflora
Stool production
Absorption of Ca and other minerals
Production of gastrointestinal endocrine peptides
Immunity and resistance to infections
Lipid homeostasis
Reduction of disease risks
Intestinal infections
Irritable bowel diseases
Colon cancer
Osteoporosis
Obesity

species such as the *Clostridium coccooides-Eubacterium rectale* cluster known to be butyrate producers has been reported (45,46). According to these data, and even though all inulin derivatives (see Fig. 1) induce a significant stimulation of growth of bifidobacteria, they do not have, qualitatively, the same effects in the different segments of the large bowel, which might be differently influenced.

The bacterial flora colonizing surfaces in the large intestine, especially the mucosa, the mucus layer, or eventually the particulate materials in the colonic lumen (47), is a topic of growing interest. Indeed, studies using either biopsies or resected samples have demonstrated the presence, in the mucus layer, of a microflora with a specific composition, different from the luminal colonic microflora (48), and it has been speculated that this mucosal microflora could play specific roles in the protection of the mucosal epithelium and that changes in the composition of that intestinal environment could influence the miscellaneous functions of the epithelium. In an ex vivo protocol in which 15 healthy volunteers selected from the colonoscopy waiting list had been asked to supplement their usual diet with Synergy (15 g/d) for 2 wk, preliminary data have shown increases in both bifidobacteria and lactobacilli counts in the mucosa (+1 and 0.5 log<sub>10</sub> cfu/g of mucosa, respectively) (49). Using the model of rats harboring a human fecal flora, Kleessen et al. (50) have similarly reported that feeding an inulin-supplemented diet significantly increased (16-fold) mucosal bifidobacteria (cells/mm<sup>2</sup> mucosal surface) even though the stimulation was not significant in the intestinal lumen. Thus, the prebiotic effect of inulin-type fructans concerns both the luminal and the mucosa-associated microflora.

Concerning the quantitative aspects of the prebiotic effect, 2 questions have attracted (too much!) attention (mostly for marketing purposes!): Are the different inulin-type fructans equally effective? Can a dose-effect relation be established?

As discussed previously (4,51), the daily dose of a prebiotic does not correlate with the absolute numbers of “new” bacterial cells that have appeared as a consequence of the prebiotic treatment ( $r = 0.06$  and  $-0.09$ , respectively; NS). The daily dose of an inulin-type fructan is thus not a determinant of its prebiotic effect, even if, in 1 group of volunteers with relatively similar initial counts of fecal bifidobacteria, a limited dose-effect relation has been established (52). The reason is that an important parameter, i.e., the initial number of bifidobacteria, is usually not taken into account. In the first report of a prebiotic effect, Hidaka et al. have already argued that the initial numbers of bifidobacteria influence the prebiotic effect after observing an inverse correlation between these numbers and their “crude” increases after oligofructose feeding (53). Rao (41), Roberfroid et al. (54), and Rycroft et al. (55) have reached essentially the same conclusion. At the population level, it is the fecal flora composition (especially the number of bifidobacteria before the prebiotic treatment) characteristic of each individual that determines the efficacy of a prebiotic but not necessarily the dose itself. The ingested prebiotic stimulates the whole indigenous population of bifidobacteria to growth, and the larger that population is, the larger is the number of new bacterial cells appearing in feces. The “dose argument” (often used as a marketing argument) is thus not straightforward, and it cannot be generalized because, as supported by the scientific data, the factors controlling the prebiotic effect are multiple. The “dose argument” can thus be misleading for consumers and should not be allowed.

One important question remaining unanswered is the effect of prebiotic, especially inulin-type fructans, not on the numbers

of bacteria, especially bifidobacteria, but rather on activities associated with these bacteria. Indeed, the health benefits for the host are part of the definition (“confers benefits upon host well-being and health”) (22,29), and these benefits are directly dependent on what these bacteria do, how they interact with the others, and how they modulate intestinal functions. Miscellaneous bacterial enzyme activities such as glucuronidase, glycosidases, nitroreductase; metabolites such as SCFAs; or endproducts of the fermentation of amino acids, mucins, or sterols (especially primary and secondary bile acids) have been measured and shown to vary (increase or decrease) after feeding of prebiotics. But the relevance of these parameters still remains to be established, especially in terms of their value as biomarkers of colonic and eventually host health and well-being or disease risk reduction. In that context, the effects of inulin-type fructans on these parameters reported so far are contradictory and difficult to interpret (37,38,56).

In the article introducing the concept of prebiotics, Gibson and Roberfroid also suggested that combining a prebiotic with a probiotic in a “synbiotic” approach could open new perspectives (22). Indeed, in experiments in vitro designed to test the inhibitory effect of probiotics on the growth of human intestinal pathogens (*E. coli*, *Campylobacter jejuni*, *Salmonella enteritidis*), Fooks and Gibson showed that, as compared with other carbohydrates (lactulose, lactitol, dextran, starch), inulin-type fructans (alone or combined with xylooligosaccharides) were observed to strongly support the inhibitory activity (57). In a rat model, Bielecka et al. showed that combining a probiotic (10<sup>9</sup> *Bifidobacterium* spp. per rat) and oligofructose (5% wt:wt in diet) did not improve the prebiotic effect (58). A few other synbiotic protocols have also been used in experimental rat carcinogenesis in the human EU-funded SYNCAN project (59) and in the development of animal feed. These data are discussed in other review articles covering these topics (60,61).

### Inulin-type fructans and enhancement of colonic functions

The enhancing effects of inulin-type fructans on colonic functions have been reviewed recently (2–4), and they are extensively reviewed in different articles in the present Supplement.

**Inulin-type fructans and stool production.** As dietary fiber, inulin-type fructans have positive effects on basic physiological functions of the colon, i.e., stool production and fecal excretion. A recent meta-analysis (J. Cumps, personal communication) of the published data (36,62–65) reveals that consuming inulin-type fructans significantly ( $P = 0.008$ ) increases fecal biomass. This also regularizes bowel habit, a classical physiological effect of dietary fiber (36,38).

**Inulin-type fructans and mineral bioavailability.** A number of food constituents have attracted attention as potential enhancers of mineral absorption, such as lactose, casein phosphopeptides (66,67), and nondigestible oligosaccharides, especially inulin-type fructans (68,69; this Supplement). In experimental animals (mostly rats), a large number of publications demonstrate that inulin-type fructans significantly increase mineral absorption, essentially Ca and Mg (70; K. E. Scholz-Ahrens and J. Schrezenmeir, this Supplement). All inulin-type fructans (native inulin, oligofructose, inulin HP, or Synergy 1) were effective in modulating mineral absorption, although some qualitative differences appear when the effects of different types of inulin are compared. Indeed, in a study aimed at comparing oligofructose, inulin HP, and Synergy 1, Coudray et al. have

shown that the latter product is more active than oligofructose or inulin HP alone in enhancing Ca and Mg absorption (71). It has also been shown that the beneficial effects of inulin-type fructans on mineral absorption still persist after ovariectomy in female rats. Thus, it can be hypothesized that, in females, such effects are hormone-independent and that inulin-type fructans might also be beneficial in postmenopausal women [for a review, see Coxam (72) and V. Coxam, this Supplement].

In humans, inulin-type fructans have no effect on mineral absorption in the small intestine, and their effects on Ca and Mg absorption are likely to be mediated via changes in the lower part of the gut that are mediated by the activity of the microflora (see S. A. Abrams, this Supplement). The most convincing data have been obtained in adolescents (73–76) and in postmenopausal women (72,77–79), but 1 study has confirmed these effects in adult men (80). An interesting conclusion of the studies in adolescence is the inverse correlation between the relative increase in absorption caused by inulin-type fructans and the basal absorption capacity as measured before the intervention. The same correlation was demonstrated in analyses of the animal data. That would indicate that, with regard to mineral absorption, consuming inulin-type fructans would benefit more the adolescents who have a low basal level. Because genetic polymorphisms are known to account for differences in Ca absorption, it has been speculated that some genotypes could be more likely to benefit from consumption of inulin-type fructans and especially Synergy (75).

Both experimental and human data already support the hypothesis that the beneficial effects of inulin-type fructans target not only the mineral absorption phase but also other aspects of bone health, especially bone mineralization, bone density, and bone accretion and resorption, i.e., bone turnover (72). See also reviews by S. A. Abrams, V. Coxam, and K. E. Scholz-Ahrens (this Supplement).

***Inulin-type fructans and body defense mechanism.*** The defense functions of the body are multiple, involving different organs and different mechanisms and targeting different potential aggressors. One of the main objectives of functional food science is to identify food components that have the capacity to positively modulate defense functions so as to help individuals to strengthen, restore, or rebalance them. Data already support the hypothesis that inulin-type fructans are among the potential functional food ingredients capable of playing such roles. Indeed, they beneficially affect a series of gastrointestinal functions by modulating both the structure and composition as well as miscellaneous activities of the mucosa and the microflora. They also affect intestinal epithelium by improving mucosal morphology and thickening and improving the composition of the mucins. As a consequence, they improve colonization resistance and prevent bacterial translocation (at least when tested in an appropriate model), and finally, they contribute to improving both chemical and enzymatic safeguard functions in the gastrointestinal tract. Inulin-type fructans also beneficially affect the immune system, especially the intestinal immune functions by targeting the gut-associated lymphoid tissue and especially the Peyer's patches, and consequently they have been shown to reduce the risk of diseases related to dysfunction of the gastrointestinal defense's functions, an indirect but strong evidence for a beneficial effect (81,82) (see also Guarner and Watzl et al., this Supplement).

***Inulin-type fructans and enteroendocrine activities.*** Over the last 2 decades, data have accumulated that demonstrate the

key role of the gut in producing a variety of enteroendocrine-derived peptides that control and modulate miscellaneous metabolic and physiological processes and create a link between the gut and the brain (83,84). Among these, glucagon-like peptide-1 (GLP-1) and ghrelin have been particularly investigated and shown to participate in appetite regulation, being anorexigenic and orexigenic, respectively (85–87). Experimental data are now accumulating that demonstrate the modulation of GLP-1 and ghrelin production by inulin-type fructans with, as one consequence, appetite regulation. Preliminary human data tend to confirm such an effect, which still needs further and more extensive investigation (88). See also Burcelin et al. and Delzenne et al. (this Supplement).

### **Inulin-type fructans and enhancement of systemic functions**

Among the systemic functions, the effect of inulin-type fructans on lipid homeostasis has attracted most of the research interest up to now.

***Inulin-type fructans and lipid metabolism.*** Modulation of either the digestion/absorption or the metabolism of lipids is another physiological effect of inulin-type fructans that affect triglyceridemia and cholesterolemia as well as the distribution of the lipids among the different lipoproteins in favor of a pattern more beneficial for health (89).

Indeed, a series of animal studies demonstrate that inulin-type fructans affect the metabolism of the lipids primarily by decreasing triglyceridemia in both the fasted and the postprandial state. The effect on cholesterolemia is less constant, being statistically significant in only some of the studies so far reported. These decreases are caused by a reduction in the number of VLDL particles with the same composition in lipids and the same size. The human data confirm the animal experiments. They demonstrate mainly a reduction in triglyceridemia and only a relatively slight decrease in cholesterolemia in both normo- and (slightly) hypertriglyceridemic conditions. In human nutrition intervention trials, inulin appeared to be more effective than oligofructose in reducing triglyceridemia, whereas in animals (especially in rats), both products were equally active. With respect to the mechanism, adding inulin-type fructans to a rodent's diet reduces liver lipogenesis by reducing the expression of the genes coding for the lipogenic enzymes. In humans, a similar mechanism is likely to operate. Indeed, Letexier et al. have demonstrated a reduced hepatic lipogenesis but not cholesterol synthesis in subjects receiving 10 g/d of inulin (90). However, and especially in the presence of more severe dysbalances in lipid homeostasis, other mechanisms might also operate through enhanced catabolism of triglyceride-rich lipoproteins.

Whatever the mechanism is, the question of the links between the gastrointestinal site of the fermentation (and thus the disappearance) of inulin-type fructans and their effect on lipid homeostasis inside the body (the so-called systemic effect) still remains open. Various hypotheses have been tested to tentatively answer that question. 1) Modifications of glucose and/or insulin levels have been suggested, but the effects of inulin-type fructans on glycemia and insulinemia are not yet fully understood, and available data are still conflicting, indicating that they may depend on physiological (fasting vs. postprandial state) or disease (diabetes) conditions (91–93). 2) Modifications of the absorption of macronutrients, especially carbohydrates, may occur, either by delaying gastric emptying and/or shortening small intestinal transit time (94). It must be emphasized,

however, that inulin-type fructans do not have the high viscosity of other nonstarch polysaccharides, a physical property that is usually correlated with their effect on absorption of macronutrients. 3) Increased production of fermentation end products may result, especially propionate, which is absorbed via the portal vein (95), where its concentration is increased by >2-fold in oligofructose-fed rats (16) to reach a concentration shown to inhibit the carrier-mediated acetate uptake and to decrease the concentration of FAS mRNA in cultured isolated hepatocytes (89). 4) Increased concentration of polyamines, especially putrescine, as has been observed in the cecum of oligofructose-fed rats (96). 5) Changes in the production of enteroendocrine peptides (see above).

### **Inulin-type fructans and reduction of risk of diseases**

In addition to their enhancing effects on miscellaneous physiological functions, inulin-type fructans have also shown promising properties in reducing the risk of diseases, especially irritable bowel diseases (IBD) and colon cancer. Their effects on GLP-1, syndrome X, and related disease are also presently topics of active research programs.

#### *Inulin-type fructans and the risk and management of IBD.*

As reviewed in details by Dieleman et al. (this Supplement), experiments have been performed in different animal models of IBD (ulcerative colitis and Crohn's disease) to test for the effects of inulin-type fructans. All tests demonstrate beneficial effects that include reduction in clinical symptoms and in global and histological scores of inflammation as well as reduction in the production of miscellaneous proinflammatory molecules and increase in the secretion of antiinflammatory cytokines. In some of these experiments, such changes correlate with increase in colonic bifidobacteria and lactobacilli (prebiotic effect). Such experimental data are already confirmed in preliminary human clinical studies, especially in Crohn's disease, ulcerative colitis, and pouchitis. Further clinical tests are presently in progress to extend these data (81) (see also Guarner, this Supplement).

*Inulin-type fructans and the risk of colon cancer.* Regarding the risk of colon cancer, inulin-type fructans have the capacity to suppress chemically induced colon carcinogenesis in both mice and rats, and such an effect is likely to be potentiated in synbiotic preparations with lactic acid bacteria (97,98) (see also Pool-Zobel, this Supplement). It has been hypothesized that inulin HP and Synergy are more active than oligofructose because the long-chain molecules are likely to be more slowly fermented in the large bowel, thus prolonging their effects in the transverse and distal colon (99,100). Indeed, the shortest oligomers of oligofructose are already rapidly and quantitatively fermented in the proximal colon and thus never arrive in the distal colon. Inulin HP and Synergy act mostly during the promotion phase of the carcinogenic process, and their effect is on the incidence, the yield, as well as on the multiplicity of aberrant crypt foci, tumors, and even cancers. Not only do they reduce the number and the size of lesions but they also reduce the risk of progression of these lesions toward malignancy. Based on these convincing experimental data, inulin-type fructans and especially Synergy have been tested in both cancer and polypectomized patients in a multicenter human intervention nutrition trial that was funded by the European Union (EU project QLK1-1999-00346 DG XII Research, EU) (60) (see also Pool-Zobel, this Supplement). Data show that Synergy reduces proliferation of colorectal mucosa and the capacity of fecal water to induce necrosis in eukaryotic cells as well as mutations in colonic biopsies and improves

modulation of secretion of cytokines. This preliminary information has justified the inclusion of Synergy in a protocol approved by the U.S. National Cancer Institute to evaluate the efficacy of different treatments to reduce the risk of colon cancer.

Inulin-type fructans thus are classified as negative modulators of the carcinogenic process. The mechanisms proposed to explain these beneficial effects include changes in the composition and/or activity of colonic microflora (the prebiotic effect) and in the composition of the pool of SCFAs and especially an increased relative proportion of butyrate as a result of their anaerobic fermentation. These effects fit well with the concept of changes in metabolic and proliferative homeostasis in the large bowel and especially the colonic mucosa. In addition inulin-type fructans strengthen and stimulate gastrointestinal defense functions and especially the intestinal immunity, 2 effects that certainly improve resistance to cancer development (60,97,98).

In addition to their effects (both direct and indirect) on the risk of diseases related to dysfunction of the gastrointestinal defense functions, inulin-type fructans have also been shown to possibly contribute to reducing the risk of diseases related to dysfunction of systemic functions. Essentially, this has been shown using experimental models of systemic infection, chemically induced mammary carcinogenesis, growth and metastasis of implanted tumor, and cancer therapy. Moreover, and because hypertriglyceridemia is recognized as an independent risk factor for cardiovascular disease and arteriosclerosis, the confirmation of the hypertriglyceridemic effect of inulin-type fructans in humans with slight dyslipidemia might, in the future, support their use in the prevention of these diseases (88,101).

What makes a food "functional" is the scientific demonstration that it beneficially affects functions in the body beyond what could be expected from basic nutrition. Concerning inulin-type fructans and by reference to the strategy for functional food development, this conclusion thus concentrates on basic scientific knowledge and experimental data to identify potential functional effects as well as to formulate hypotheses to be tested in human nutrition intervention studies and results of human nutrition intervention trials to substantiate claims (mainly type A but also a few type B).

As summarized, the effects of inulin-type fructans have been investigated in different domains of interest using a wide variety of experimental models and human trials. These domains can be divided into the following categories:

*Category 1:* Experimental results exist that have been evaluated and used to justify human intervention studies; confirmatory human data of these human trials are available to substantiate claims. The domains included in this category are dietary fiber and bowel functions, gut microflora, gastrointestinal absorption of minerals, and lipid (triglycerides) metabolism (Table 2).

*Category 2:* Data from different experimental models are convincing, preliminary human data are available, and sound hypotheses exist, but more human nutrition trials are necessary to substantiate claims. The domains included in this category are cholesterol metabolism, gut-associated immune functions, IBD, and colon cancer (Table 3).

*Category 3:* Recent experimental investigations have generated promising results that justify more extensive studies including, in some cases, preliminary tests in human volunteers. The domains that are included in this category are bone health, gastrointestinal endocrinology, cancer therapy, and behavior and cognitive performance (Table 4).

The claims that are or might become scientifically substantiated are that inulin-type fructans are fermentable dietary fiber

**TABLE 2** Experimental and human data that substantiate claims on inulin-type fructans: summary presentation

Property or target function	Supportive evidence	Claims: Inulin-type fructans...
Dietary fiber	Oligo/polysaccharide Resistant to digestion Fermentation	Are dietary fiber
Bowel functions Stool production	Bulking effect Regulation of stool production Improved stool consistency	Regularize bowel functions
Colonic microflora	Substrates for anaerobic saccharolytic fermentation Selective stimulation of growth of health-promoting bacteria (e.g., bifidobacteria)	Are prebiotic
Bioavailability of Ca and Mg	Increased absorption of Ca/Mg Increased bone mineral content/density	Increase Ca/Mg absorption Increase bone mineral content/density in adolescents
Lipid homeostasis	Reduction of triglyceridemia Mechanistic data	Reduce triglyceridemia in slightly hypertriglyceridemic individuals

and help improve gut functions, especially by improving regularity, by increasing stool frequency, and by fecal bulking; inulin-type fructans are bifidogenic and prebiotic; inulin-type fructans increase calcium absorption; and inulin reduces triglyceridemia in hyperlipidemic individuals.

Inulin-type fructans are thus classified as functional food ingredients that target gastrointestinal functions but also, most likely via their effects on the gut and the gut microflora, systemic functions that are known to be closely related to health and well-being.

In that context, gastrointestinal functions and especially colonic functions (e.g., control of the colonic environment, regulation of hormone-dependent metabolic processes, modulation of the brain-gut axis, systemic impact of gut fermentation products, and activity of the immune system) deserve special attention. Indeed, disturbances of colon's functions may lead to

dysfunction not only in the gut but also in the whole body. The classical view that the human colon is an organ (or a "tube") in which salts and water are absorbed and waste products of digestion are neatly disposed of is no longer appropriate. Indeed, the colon has a major role in digestion (as achieved by the microbial fermentation) through the salvage of energy. But it also contributes to absorption of nutrients such as minerals and vitamins; it plays a key role in protecting the body against translocation of bacteria; and finally, it is active as an endocrine (via the gastrointestinal peptides) as well as an immune organ. It is also involved in miscellaneous diseases from acute infections and diarrhea or constipation to chronic diseases such as IBD, irritable bowel syndrome, or cancer (21,23–25).

The reason the colon plays such important physiological roles originates in its unique composition that associates pluricellular eukaryotic epithelial tissue and a population of unicellular (mostly prokaryotic) microorganisms that collaborate in maintaining health and well-being. Indeed, the microflora that symbiotically colonizes the large bowel is a key player in keeping the colon (and thus the whole body) healthy as well as keeping the individual feeling well. But that population of unicellular microorganisms is complex and highly diversified. To better understand the microflora and its symbiosis with the intestine, we hypothesize that, "stimulated" by the complexity of its host's pluricellular tissue, the intestinal microflora has itself developed during evolution and continues to develop during individual life, as a population of myriads of unicellular microorganisms belonging to hundreds of genera, species, and strains that not only live close together but actively collaborate to reach a (sometimes precarious) balanced activity that has become essential not only for health and well-being but simply for life. It can even further be speculated that it is in fact 2 "pluricellular" worlds (1 eukaryotic and 1 mostly prokaryotic) that live together and cooperate in the large bowel. Such a hypothesis would suggest that, like the different eukaryotic cells of a tissue (especially the immune system, which is composed of mostly isolated specialized cells that interact and cooperate to neutralize and eliminate antigens), the various genera, species, and strains of microorganisms that colonize the digestive tract are specialized cells that form a complex tissue-like structure in which the different types of "specialized" (most of which have still to be identified!) cells interact to perform a series of physiological functions. Intestinal health and well-being would then result from interactions within and between these 2 pluricellular worlds, the interaction between the 2 worlds being

**TABLE 3** Data on inulin-type fructans that support hypotheses to be tested in human nutrition and clinical intervention studies: summary presentation

Target functions or disease risk	Supportive evidence
Lipid homeostasis Immunostimulation	Reduced cholesterolemia Improved resistance to common infections in children Improved response to vaccination
Gastrointestinal endocrinology	Stimulation of production of intestinal hormonal peptides (GIP, GLP-1, PYY, ghrelin...) Regulation of appetite
Inflammatory bowel diseases (IBDs)	Improved management of the diseases Improved clinical symptoms Improved biomarkers
Colon cancer	Animal data in different experimental models + SYNCAN + NCI comparative trial

**TABLE 4** Data on inulin-type fructans that require more experimental research to support hypotheses to be tested in human nutrition and clinical intervention studies: summary presentation

Property or target functions	Supportive evidence
Gastrointestinal absorption of minerals	Increased absorption of Fe, Cu, Zn
Lipid homeostasis	Reduction of lipid pool in obese rats
Defense mechanisms	Improved barrier functions Improved resistance to intestinal infections
Cancer development	Slowing of tumor growth Reduction of risk of metastasis Improved efficacy of cancer therapies

referred to as “crosstalk” (102). The multicellular prokaryotic tissue-like entity would benefit from but would also provide benefits to the intestinal mucosa (i.e., the whole and complex pluricellular tissue) and vice versa. A major determinant of these interactions would be the composition of these 2 worlds, especially that of the prokaryotic population, which establishes very early in life immediately after birth but can also be modulated later in life by the diet, and may change during a lifetime becoming more and more complex but also perhaps more fragile as the body ages. Through modulation of the composition of the colonic microbiota, it thus becomes possible to influence large bowel functions but also to act, indirectly, on systemic functions and finally on the host’s health and well-being. Inversely, it cannot be excluded that systemic dysfunction elsewhere in the body’s organs influences the composition of the colonic flora and, as a consequence, the activities and the colonic functions. For example, and as reported recently, that seems to be the case in obesity (103).

By their specific effects, inulin-type fructans have the capacity to improve the composition, the activity, and the functionality of both the colonic microflora and the intestinal mucosa and to optimize the interactions between the “pluricellular” tissue and tissue-like structures, thus creating the conditions for better intestinal health and well-being. As prebiotics, inulin-type fructans act essentially via a modification of the endogenous intestinal microflora, and it is that modified microflora that directly or indirectly is at the origin of most if not all their effects. Such an effect is best characterized as “ecological” in the sense that it preserves the individual composition of the microflora but strengthens its physiological functions.

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