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ORIGINAL CONTRIBUTION

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Dietary supplementation of different doses of NUTRIOSE®FB, a fermentable dextrin, alters the activity of faecal enzymes in healthy men

Summary *Background* It is well documented that fermentation of carbohydrates that escape digestion exert several effects supposed to be beneficial for (colonic) health, including an increase in stool volume, a shorter intestinal transit time, production of short chain fatty acids and a decrease of colonic pH (Kritchevsky 1988). NUTRIOSE®FB is a dextrin that is not completely hydrolysed and absorbed in the small intestine, due to many α-1.6 linkages and the presence of non-digestible glucoside linkages (e. g. α-1.2 and α-1.3). To be beneficial for 'colonic' health effective NUTRIOSE®FB must reach the cecum in some form. *Aim of the study* To estimate how much non digested NUTRIOSE®FB is fermented and to determine the fibre-like effect of the wheat dextrin NUTRIOSE®FB by analysing enzymatic activity in faeces. *Methods* In a randomized, double-blind, multiple dose, placebo-controlled, combined cross-over and parallel trial, 20 healthy men (age 31.7 ± 9.1 yrs; BMI 24.5 ± 2.9 kg · m^{-2} received different treatments. One group of ten subjects consumed on top of their diet 10, 30 and 60 g daily of NUTRIOSE®FB or maltodextrin (placebo). The other group of 10 subjects consumed 15, 45 and 80 g daily. Each dose was consumed for 7 days. On the last two days of each of the 7-day period, faeces were collected in which the enzymatic activity and NUTRIOSE®FB residue were analysed. *Results* As expected, the faecal residue of NUTRIOSE®FB non-linearly increased with the dose of NUTRIOSE®FB to approximately 13 % of 80 g/d. Compared with the placebo, 30, 45, 60 and 80 g/d of NUTRIOSE®FB increased the concentration of α-glucosidase significantly. All daily doses of NUTRIOSE®FB (10 g/d to 80 g/d) led to significant changes in concentration of β-glucosidase. *Conclusions* The small amount of the residue of NUTRIOSE®FB in the faeces suggests that approximately 87 % or more of NUTRIOSE®FB is digested or fermented in the gastrointestinal tract. Fermentation of NUTRIOSE®FB led to an increased faecal concentration of α- and β-glucosidase.

Key words NUTRIOSE®FB – dextrin – α-glucosidase – β-glucosidase

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Introduction

Many new prebiotic candidates are available [1] and one of them may be NUTRIOSE®FB, which is a dextrin obtained from wheat starch. In contrast to maltodextrin, NUTRIOSE®FB is not completely hydrolysed and absorbed in the small intestine, due to many α-1.6 linkages and the presence of non-digestible glucoside linkages (e. g. α-1.2 and α-1.3). To be beneficial for 'colonic' health effective NUTRIOSE®FB must reach the cecum in some form. In an *in vivo* experiment 10 non-adapted rats were administered a single dose of 1 g of NUTRIOSE®FB per kg body weight. The 48 hour faeces

collection after consumption of NUTRIOSE®FB for NUTRIOSE®FB residue determination revealed that about 85 % of the product is resistant to enzymatic glucidolytic degradation. These results were in accordance with *in vitro experiments* from which the same results were observed (unpublished results). In man, three quarters of 10 g/d or 15 g/d of NUTRIOSE®FB spread over breakfast, morning and lunch increased breath H_2 excretion as compared with baseline level [2]. Although this is evidence of fermentation of NUTRIOSE®FB, it does not provide information on the true extent of its nondigestion. In the present study we measured the faecal recovery of NUTRIOSE®FB, to estimate how much was resistant to digestion and fermentation.

It is well documented that fermentation of carbohydrates that escape digestion exert several effects supposed to be beneficial for (colonic) health, including an increase in stool volume, a shorter intestinal transit time, production of short chain fatty acids and a decrease of colonic pH [3]. In rats fed NUTRIOSE®FB, a higher caeco-colonic production of butyric and propionic acids has been found and a decrease in faecal pH (internal data). Fermentation may also lead to changes in the composition of bile acids in the colon and the activity of faecal enzymes, which in turn may play a role in the pathogenesis of colon cancer [4] or be beneficial for the host by continuing digestion (or hydrolysis) of the matrix of plants in the colonic lumen. Besides analysing the faecal recovery of NUTRIOSE®FB, the aim of the present study was to measure the fibre-like effects of NUTRIOSE®FB by analysing changes in enzymatic activity in faeces. To examine the tolerance threshold of the products, different and increasing dosages of NUTRIOSE®FB were supplied.

Volunteers and methods

Volunteers

At the start 26 men aged between 20 and 45 years were recruited from the pool of volunteers of TNO Nutrition and Food Research and by advertisements in local newspapers. After signing the informed consent forms health was assessed at pre-study screening. This included a medical history, physical examination and routine laboratory tests on blood and urine sampled during the pre-study screening. In the end, 21 healthy men were selected, of whom one was a substitute in case a volunteer would not start the study. Of the twenty men who participated in the study, age ranged between 20 and 44 years (mean age 31.7 ± 9.1) and BMI between 20.1 and 29.5 $kg \cdot m^{-2}$ (mean BMI 24.5 ± 2.9 $kg \cdot m^{-2}$). From one month before the start of the study none of the volunteers used antibiotics or laxatives. The study was approved by the Medical Ethics Committee of TNO and conducted according to the ICH Guideline for Good Clinical Practice. More information about the methods used in this study was published before [2].

Study substances

The test substance NUTRIOSE®FB (Roquette Frères, France) is a purified glucose polymer processed by heating wheat starch at high temperature, adjusted to a low moisture level in the presence of an acid catalyst. The dextrin obtained is then purified with activated carbon and demineralized by exchange resins. Afterwards the product is chromatographed and the high-molecular-weight fraction is retained and spray-dried.

Maltodextrin (Glucidex® 6) was selected as placebo, as NUTRIOSE®FB is originally a glucose polymer as well. The exact composition is given in Table 1.

The study substances were supplied as a powder. The color was caramel. Aspartame was added to abolish any taste differences between the two study substances. A sensory panel found no differences in taste, color or mouth feeling when added to grape juice or fruit yogurt. Therefore, when ingested at the TNO institute, the study substances were added to these food products. The subjects consumed the powder with milk, yogurt or juice at home as well.

Design

The study was designed as a randomized, placebo-controlled, multiple-dose, double-blind trial, with a cross-

Table 1 Composition of NUTRIOSE®FB and Glucidex® 6

	NUTRIOSE®FB	Glucidex® 6
Reducing sugars (%)	2.3	5.7
H_2O (%)	3.5	3.8
Proteins (%)	< 0.5	0
Ash (%)	< 0.5	0
Free glucose (%)	< 0.1	0
Total dietary fibre[1] (%)	53	< 2
1.4 linkages (%)[2]	76	95
1.6 linkages (%)[2]	24	5
Mean degree of polymerization	18	21.5
Mean molecular weight Mw (g/mol)	5344	33075
Median of molecular weight Mn (n)[3]	2480	3480
Weight range index[4]	2.1	9.5

[1] Determined by the AOAC method
[2] Result expressed as the number of 1–4 or 1–6 linkages on the total number of 1–4 plus 1–6
[3] The figure indicates the median of the molecular weight in number (there is the same number of molecules above and below this figure)
[4] Corresponds to Mw/Mn (indicates the repartition of the molecular weights around the mean molecular weight)

over part for treatment and a parallel part for dosage or treatment variation. The duration of the study was eight weeks and consisted of four periods: a run-in period of one week followed by two treatment periods of three weeks each, which were separated by a wash-out period of one week. During the run-in period (day –7 to –1) the subjects received a placebo. A treatment period consisted of three periods of 7 days each (days 1 to 22 and days 29 to 50), during which the dose of the study substances increased enabling the subjects to slowly adapt to the high supplementation dose.

The group of 20 subjects was divided into two subgroups. Ten subjects consumed on top of their diet 10, 30 and 60 g/d of NUTRIOSE®FB or the placebo maltodextrin (i. e. cross-over design). The other 10 subjects consumed a dose of 15, 45 and 80 g/d NUTRIOSE®FB or maltodextrin (also cross-over design). Each dose was consumed for seven days in four portions with breakfast, in the morning, with lunch, and with dinner.

By subtracting the results obtained during the control treatment from the results obtained during the treatment with NUTRIOSE®FB, all dosages of NUTRIOSE®FB could be compared (i. e. parallel design). The study design is shown in Fig. 1.

Data collection

Each volunteer was given an exclusion list of fibre-rich foods and foods containing pre- and probiotics to be avoided during the study period (day –7 up to and including day 49). Each seventh day after a standard breakfast with or without the study substance, the subjects filled in a questionnaire on gastrointestinal symptoms, compliance and food habits.

On day –1, 21 and 49, the volunteers filled in a food frequency questionnaire (FFQ). The FFQ was developed in FOFREX (Food Frequency Expert), a computerized system with data from the second national Dutch food consumption surveys of 1992 [5] and a predefined question matrix. Changes in dietary intakes (total energy, protein, fat, carbohydrates, alcohol, and dietary fibre) over the last three weeks were evaluated.

Faecal sample collection

For the faecal collection the volunteers received a deep-freeze (toilet) at home. We asked the volunteers to collect faeces for 48 h on the last two days of each 7-day period. The volunteer recorded the time of defecation. The faecal samples were weighed at return at the institute and stored at –18 °C. After weighing, the frozen faecal samples were freeze-dried for about 4 days or until dry. The freeze-dried faeces were bulked as 24-h samples, weighed again and ground into powder and homogenized. Portions of approximately 10 g freeze-dried faeces were stored in airtight plastic bottles until analyses.

Faecal analyses

In freeze-dried 24-h faeces of the last day of each 7-d period the enzymatic activity was analysed. The α-glucosidase [EC 3.2.1.20] and β-glucosidase [EC 3.2.1.21] activities were determined enzymatically using respectively p-nitrophenyl a-D and p-nitrophenyl b-D glucopyrannoside as substrates. One glucosidase unit activity corresponded to the amount of substrate hydrolyzed per minute at 37 °C, pH 7, liberating p-nitrophenol quantified at 405 nm. p-nitrophenol was determined thanks to a standard curve from 1.25 to 20 mg/L.

In both 24-h faecal samples, i. e. faeces collected during the last 48 h of each 7-day period, the residue of NUTRIOSE®FB was estimated by the analyses of polymerized glucose. The NUTRIOSE®FB residuals were de-

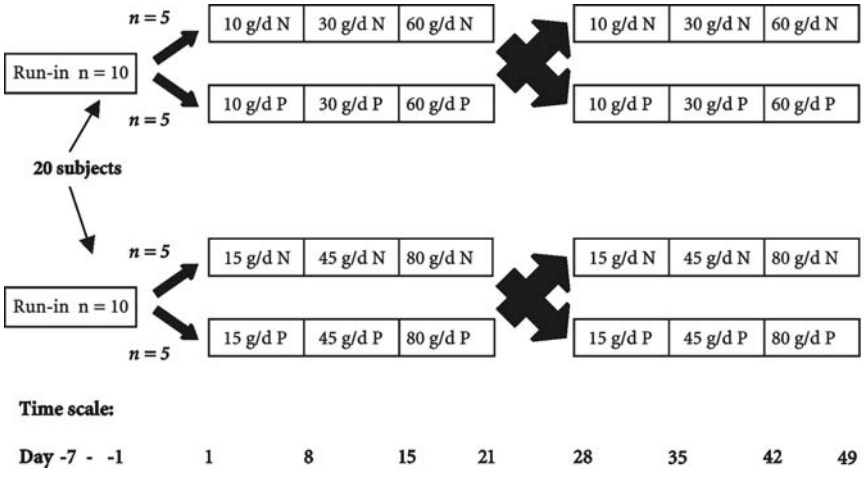

Fig. 1 Study design. Each dose of each three-week treatment was given for 7 days followed by a wash-out period of 7 days. *N* NUTRIOSE®FB; *P* Placebo (Glucidex® 6). Statistical analyses were carried out within the cross-over design and between cross-over designs after correction for the control treatment (i. e. parallel design)

termined according to the following procedure. Soluble carbohydrates were extracted from the faeces using a 1 mL chloramphenicol/L water solution. Faeces were washed twice and centrifuged. Free glucose was determined enzymatically on the supernatant with a glucose oxydase Roche kit (Meylan, France). Total glucose was also assessed on the supernatant after acid hydrolysis (HCl 4 N) at 100 °C for 45 min. The difference between total and free glucose concentrations reflected the amount of polymerized glucose assimilated to be NUTRIOSE®FB residues. Results were expressed in mg/g dry faeces matter.

Statistics

The data obtained within the cross-over, parallel designs were statistically analysed using ANOVA. Besides comparisons within each dose, ANOVA for repeated measurements was used to compare the treatment's total dose sequences (10 to 60 g/d or 15 to 80 g/d). Most statistical analyses were carried out using the SAS statistical software package [6]. The ANOVA for repeated measurements was carried out using the Genstat statistical software package [7]. If the parameters did not have a symmetric distribution, natural logarithms of these data were used in the statistical tests. Except for β-glucosidase and faecal weight, the rest of the data was log-transformed to obtain a symmetric distribution. When corrected for the placebo treatment (parallel design), residues of NUTRIOSE®FB (polymerised glucose) also had to be log-transformed to obtain a symmetric distribution. In all statistical tests performed, the null hypothesis (no treatment effect) was rejected at the 0.05 level of probability.

Results

No differences in dietary intake were present between the different treatments. Body weight of the volunteers did not fluctuate significantly during the study period. The maximum difference in body weight was 3 kg.

Table 2 shows that due to 15 g/d of NUTRIOSE®FB the faecal weight (freeze-dried or wet) decreased significantly when compared with the faecal weight during 15 g/d placebo. The percentage dry weight did not change ($p = 0.20$), which means that the amount of faecal water decreased.

Figs. 2–4 show the average values of the concentration of the residue of NUTRIOSE®FB and the faecal en-

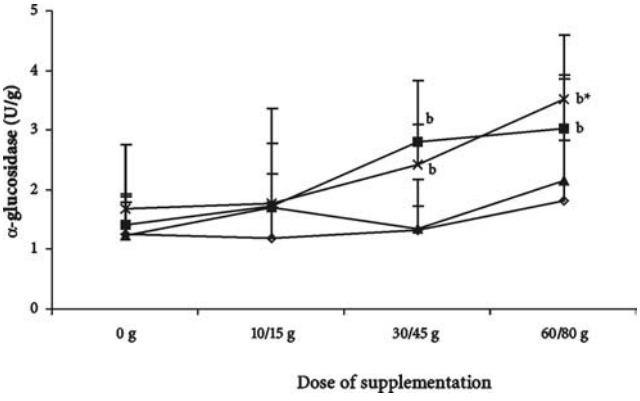

Fig. 2 Concentration of α-glucosidase in faeces (in U/g) collected the last 24 h of seven days on the same dosage of NUTRIOSE®FB or Glucidex® 6. Treatment with 10-30-60 g/d of Glucidex® 6, cross-over (n = 10) is shown with open diamonds (◇) and for the treatment with 10-30-60 g/d of NUTRIOSE®FB a filled square is used (■). Treatment with 15-45-80 g/d of Glucidex® 6, cross-over (n = 10) is shown with filled triangles (▲) and for the treatment with 15-45-80 g/d of NUTRIOSE®FB a cross is used (x). Each dose was given for 7 days and presented on the x-axis. * Indicates a difference in course over time between NUTRIOSE®FB and Glucidex® 6 (same dosage sequence); 'b' indicates a significant difference between NUTRIOSE®FB and Glucidex® 6 within one cross-over design

Table 2 Mean values of the faecal parameters per treatment[4] (standard deviations between brackets)

Glucidex® 6[1] (g)				NUTRIOSE®FB[1] (g)				Glucidex® 6[2] (g)				NUTRIOSE®FB[2] (g)			
0	10	30	60	0	10	30	60	0	15	45	80	0	15	45	80
Freeze-dried faecal weight (g/48 h)															
80 (33)	80 (25)	78 (20)	79 (22)	72 (23)	66 (20)	79 (39)	80 (29)	71 (29)	87a (26)	80 (19)	83 (29)	72 (34)	61b (25)	99 (33)	95 (47)
Freeze-dried faecal weight (%)[3]															
25.9 (5.6)	24.4 (5.7)	25.5 (6.2)	23.2 (4.5)	24.4 (3.4)	25.4 (4.8)	24.6 (5.2)	24.3 (4.6)	22.6 (3.3)	20.5 (4.0)	21.9 (3.7)	22.2 (4.0)	21.6 (4.6)	22.3 (4.0)	22.4 (2.9)	24.2 (3.6)

[1] First cross-over design, n = 10, treatments are 10-30-60 g per day of NUTRIOSE®FB or Glucidex® 6, each dose given for seven days
[2] Second cross-over design, n = 10, treatments are 15-45-80 g per day of NUTRIOSE®FB or Glucidex® 6, each dose given for seven days
[3] Freeze-dried faecal weight (%) is the ratio of the freeze-dried fecal weight and wet fecal weight collected over 48 h
[4] Statistical analyses: unequal letters indicate a significant difference due to NUTRIOSE®FB within one of the cross-over designs ($p < 0.05$). Because no carry-over effect was present of the intake of the prior dose, the effect of the earlier dose is not taken into account, i. e. each dose is statistically analysed as being an individual dose

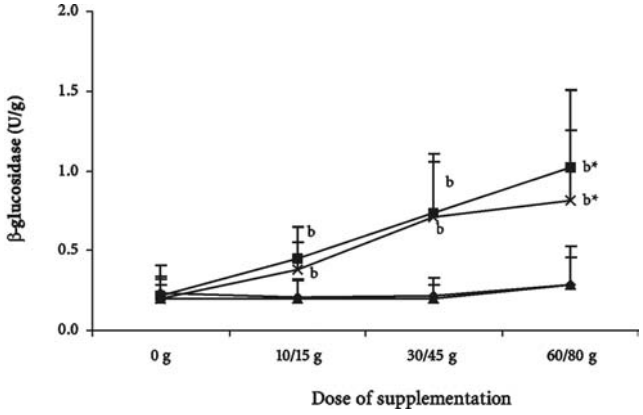

Fig. 3 Concentration of β-glucosidase in faeces (in U/g) collected the last 24 h of seven days on the same dosage of NUTRIOSE®FB or Glucidex® 6. Treatment with 10-30-60 g/d of Glucidex® 6, cross-over (n = 10) is shown with open diamonds (◇) and for the treatment with 10-30-60 g/d of NUTRIOSE®FB a filled square is used (■). Treatment with 15-45-80 g/d of Glucidex® 6, cross-over (n = 10) is shown with filled triangles (▲) and for the treatment with 15-45-80 g/d of NUTRIOSE®FB a cross is used (x). Each dose was given for 7 days and presented on the x-axis. * Indicates a difference in course over time between NUTRIOSE®FB and Glucidex® 6 (same dosage sequence); 'b' indicates a significant difference between NUTRIOSE®FB and Glucidex® 6 within one cross-over design

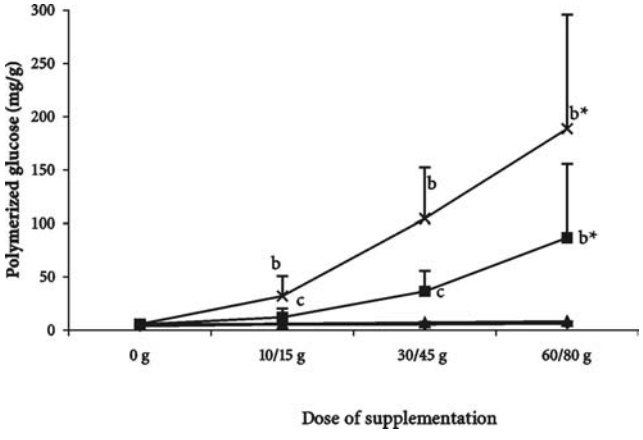

Fig. 4 Concentration of polymerized glucose (mg/g) in faeces collected the last 48 h of seven days on the same dosage of NUTRIOSE®FB or Glucidex® 6. Treatment with 10-30-60 g/d of Glucidex® 6, cross-over (n = 10) is shown with open diamonds (◇) and for the treatment with 10-30-60 g/d of NUTRIOSE®FB a filled square is used (■). Treatment with 15-45-80 g/d of Glucidex® 6, cross-over (n = 10) is shown with filled triangles (▲) and for the treatment with 15–45–80 g/d of NUTRIOSE®FB a cross is used (x). Each dose was given for 7 days and presented on the x-axis. * Indicates a difference in course over time between NUTRIOSE®FB and Glucidex® 6 (same dosage sequence); 'b' indicates a significant difference between NUTRIOSE®FB and Glucidex® 6 within one cross-over design. The 'c' indicates a significant difference between the effect of 10 and 15 g/d, 30 and 45 g/d or 60 and 80 g/d of NUTRIOSE®FB, after correction for the control treatment

zymes in freeze-dried faeces. As expected, the residue of NUTRIOSE®FB reflected by the amount of polymerised glucose, increased with the dose of NUTRIOSE®FB as compared with the control treatment. Compared with the control treatment, a significantly increased concentration of α-glucosidase was found during the 7-day treatment periods with 30, 45, 60 and 80 g/d of NUTRIOSE®FB. The concentration of β-glucosidase increased significantly for all doses of NUTRIOSE®FB (10 g/d to 80 g/d), as compared with the placebo.

The results of the ANOVA for repeated measurements showed a significant interaction between treatment (both dosage sequences) and time for the concentration of β-glucosidase and the residue of NUTRIOSE®FB. For the dosage sequence 15–45–80 g/d a significant interaction was also present for the concentration of α-glucosidase. These interactions suggest that the course in time of the parameter is different between the treatments (see Figs. 2–4). So, the earlier dose affects the outcome of a parameter for a particular dose.

Discussion

The NUTRIOSE®FB test substance studied was very well tolerated, as discussed elsewhere [2]. During the highest dosages (60 and 80 g daily) some bloating and increased flatulence was reported, but no diarrhea was reported.

NUTRIOSE®FB is not completely resistant to hydrolysis by the human digestive enzymes α-glucosidase, maltase-isomaltase, sucrase, which are specific for α-glycosidic linkages. Based on rat and *in vitro* experiments we assume that only 85 % arrives quantitatively in the colon (internal data), where it is (partly) fermented by the bacterial flora. NUTRIOSE®FB recovered in faeces as polymerised glucose, represented the non-digested and non-fermented part of NUTRIOSE®FB. In several human feeding studies, faecal recovery of inulin or FOS was measured and found to be zero [1]. Assuming a constant excretion of NUTRIOSE®FB in faeces per 24 h, we can calculate that about 2 to 13 % of 10 to 80 g/d of NUTRIOSE®FB, respectively was recovered in the faeces. If we assume that the results of the rat-experiment (internal data) can be extrapolated to man, we can estimate that about 75 % or more of NUTRIOSE®FB was fermented.

Due to fermentation of fermentable carbohydrates, biomass increased. Van Loo and co-workers [8] have reported the bulking effect, expressed as an increase in daily faecal mass, to range between 1.5 and 2 g/d per g of ingested inulin or fructo-oligosaccharides. The bulking effect of isomaltose-oligosaccharides (3 g increase of stool per g isomaltose-oligosaccharide) was greater than that of FOS [9]. Unexpectedly, the opposite was found in the present study. Supplementation with NUTRIOSE®FB decreased wet and dry weight of faeces for both lowest dosages of NUTRIOSE®FB supplied. However, the percentage dry matter did not change, and so the amount of faecal water probably decreased (see Table 2 for the 10 and 15 g NUTRIOSE®FB dosage). This agreed with the subjective judgment of the volunteers,

i. e. thicker faeces during the last 24 h on 15 g/d of NUTRIOSE®FB, as described earlier [2]. A lower amount of faecal water may be due to a high SCFA absorption. A high SCFA absorption is associated with a high water and salt absorption, which may reduce the incidence of diarrhea [10]. Further study is needed to support the hypothesis that NUTRIOSE®FB leads to a high production and absorption of SCFA in man, as the effect on faecal weight disappeared with a higher dose of NUTRIOSE®FB. Internal studies conducted on rats showed a high production of caecal SCFA and a decrease in the faecal pH.

NUTRIOSE®FB increased the faecal concentration of α-glucosidase and β-glucosidase in healthy men. According to the results of McBain and Macfarlane [11], changes in β-glucosidase activity are explained by substrate-induced modulation of bacterial metabolism. In rats fed 5 % transgalacto-oligosaccharides or inulin with or without *Bifidobacterium breve* [12, 13] or indigestible plant cell-wall components derived from 100 g cabbages or carrots/kg [14], a high activity of β-glucosidase was found in the caecal content. In rats inoculated with a human faecal flora, 10 g/kg of α-gluco-oligosaccharides led to a nonspecific enzymic induction of caecal β-glucosidase and α-glucosidase activities. The diets containing β-fructo- and β-galacto-oligosaccharides did not modify the activity of the enzymes [15].

In human studies contrasting results are found. In elderly constipated persons, a gradual increase of 20 to 40 g/d of inulin during 19 days did not change the β-glucosidase or β-glucuronidase activity expressed as μmol/min/mg dry faeces [16]. During two 4 week periods on a high-resistant starch diet, in twelve healthy volunteers bacterial β-glucosidase (mg/h/g) decreased by 26 % [17]. Expressed as IU/g dry faeces, the intake of 15 g/d of inulin, transgalacto-oligosaccharides or fructo-oligosaccharides did not affect faecal β-glucosidase activity in healthy men [18]. A fermentable dairy product containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, however, did increase faecal β-glucosidase activity in nine healthy volunteers after three weeks [19]. Like Van Dokkum [18] and Marteau [19] and colleagues we expressed the enzymes as IU/g dry faeces. In the present study, both α- and β-glucosidase increased due to NUTRIOSE®FB dose-dependently. The increase in α-glucosidase activity could be considered as beneficial for the host. The α-glucosidase activity can improve the fermentation of NUTRIOSE®FB leading to SCFA and lactic acids that are a source of energy for the tissues [20]. An increase in β-glucosidase could potentially be regarded as an advantage for health by releasing flavonoids with antimutagenic, antioxidative, anticarcinogenic, and immune stimulatory effects [21], although some others state that lowering of β-glucosidase activity is beneficial with regard to colon carcinogenesis prevention [22]. The hydrolysis of plant glycosides reveals release of mutagenic aglykones; however, some have anticarcinogenic activity as well [23]. Therefore, the functional implication is still under debate. For this study it is relevant that increased β-glucosidase activity is dose dependently related to NUTRIOSE®FB supplementation. In this way more hydrolysis of the NUTRIOSE®FB residue takes place in the colon, resulting in more energy for the microbes and probably liberation of microconstituants from food matrix. These effects were obtained with vegetables which are rich in cellulosic and hemicellulosic compounds [14].

In conclusion, the small amount of residue of NUTRIOSE®FB in the faeces suggests that approximately 87 % of NUTRIOSE®FB is digested or fermented in the gastrointestinal tract. A daily dose of 30 g of NUTRIOSE®FB or more increased the concentration of α-glucosidase and 10 g/d or more increased the concentration of β-glucosidase, which may be considered as beneficial health effects.

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