**ABSTRACT**

**Background:**

Short-chain fructooligosaccharides (scFOS) have been studied as laxatives in adults, but their effective dose has not been determined for children.

**Objectives:**

The objective of this study was to determine the dose of scFOS at which 50% of children with a history of simple constipation produced a stool with pudding-like or watery consistency.

**Design:**

Fifty-five children (ages 2-5 y) were enrolled into a double-masked, two group, placebo controlled, parallel, multi-center, acute dosage titration study. They were randomly assigned in a 3:2 fashion to receive either scFOS or sucrose after blocking on sex. Following a 3-d baseline period, each child received 0.2 g/kg body weight of scFOS or sucrose once daily at breakfast. The dose was increased in 0.2 g/kg/d increments every other day just until each child produced a pudding-like or watery stool. The maximum possible dosage was 0.8 g/kg/d. Parents recorded bowel function and subjective tolerance.

**Results:**

An intent-to-treat analysis of the data indicated that the effective dose of scFOS was 0.79 g/kg/d (95% CI of 0.58 to 1.12 g/kg/d). The minimum dose at which stool consistency of the scFOS group softened to a greater extent ($P = 0.004$) from baseline compared with the sucrose group occurred at the 0.6 g/kg/d dose. However, administration of scFOS did not change ($P > 0.05$) the frequency of bowel movements from baseline compared with sucrose regardless of dose. Similar results were obtained when data were analyzed from only subjects deemed to be protocol evaluable.

**Conclusions**

Short-chain FOS softened stools in children at a dose comparable to that reported for adults without affecting the frequency of bowel movements.

**Key words:** fructooligosaccharides, nondigestible oligosaccharide, fructan, inulin, oligofructose, dietary fiber, laxative, constipation, osmotic, bowel function, children

## INTRODUCTION

### Prevalence of constipation

Constipation, the infrequent and/or difficult and painful evacuation of hard feces (1), is a widespread problem in the U.S. affecting as much as two percent of the total population (2). Epidemiological data indicate that the frequency of constipation increases with age (2), but this disorder has also been recognized as a common ailment among young children (2-4). In fact, 15% of all constipation-related visits to physicians were seen by pediatricians (5). Constipation also accounted for approximately 3% of visits to pediatric outpatient clinics and 25% of visits to pediatric gastroenterology clinics (6,7).

Inadequate dietary fiber intake has been consistently identified as a contributing factor to childhood constipation (4,8). Dietary fiber, which reduces gastrointestinal transit time and increases the frequency of bowel movements, improves the ease of defecation by helping to produce larger, softer stools (9). Because dietary survey data show that children with chronic constipation consume only half as much fiber as those with normal bowel function (10), increasing the dietary fiber intake should theoretically reduce the frequency of constipation in children. Unfortunately, the goal of increasing dietary fiber intake is not easily achieved in children due to palatability issues.

### Laxative effect of fructooligosaccharides

Short-chain fructooligosaccharides (scFOS) are naturally occurring carbohydrates that are found in many plants such as Jerusalem artichoke (11), asparagus root (11), onion (12), wheat (13,14), rye (14), triticale (14,15), and others (16). Although scFOS are not classified as dietary fiber using traditional analytical methods, these compounds share many of the same physiologic properties as fiber (17). Present evidence indicates that less than 10% of scFOS are digested or absorbed in the stomach or small intestine (18-21). Instead, scFOS pass into the large bowel where they are rapidly and completely fermented to short-chain fatty acids (22,23). Fermentation of scFOS by the bacteria of the large bowel exerts a variety of favorable physiological effects on the gastrointestinal tract (24,25) including: reduced cecal pH (26), increased cecal weight (26), modified fecal flora (27-31), and improved stool consistency (28).

The stool softening effects of scFOS have been well documented in at least two studies using human subjects (32,33). When Hata and Nakajima (33) administered acute dosages of scFOS to 80 healthy adults (51 males and 29 females; ages 20 to 59 y), they found that increasing the dosage of scFOS resulted in softened stool consistency. In addition, they calculated that the dosage resulting in 50% of the subjects experiencing diarrhea (a watery stool during the first defecation following ingestion of scFOS) was approximately 0.8 g FOS/kg body weight. Subsequent studies conducted by Briet et al. (32) in which healthy human adults received acute or chronic dosing with scFOS generated very comparable results; the dosage at which 50% of subjects experienced diarrhea was approximately 0.76 and 0.88 g/kg body weight for acute and chronic dosing, respectively.

**Rationale for the use of FOS as a laxative for children**

Short-chain FOS possess several features that make them an excellent candidate as a laxative for children. For example, scFOS are much more palatable than existing food products, dietary supplements, and over-the-counter medications. In addition, scFOS have been shown to have an excellent safety profile (34) and should therefore carry a lower risk of serious adverse effects compared with existing remedies (35).

The laxative effect of scFOS have already been studied in the adult population (32,33). Yet, the dosage of scFOS required to elicit a stool softening effect without resulting in diarrhea in children is still unknown. Consequently, the goal of this study was to determine the scFOS dosage required to soften the stools of children with a history of simple constipation.

## SUBJECTS AND METHODS

### Subject Selection

Fifty-five children (boys and girls, ages 2-5 y) were enrolled from four clinical research sites located in Florida, Indiana, and Kansas between February and April 2000. Subject characteristics at study entrance are displayed in Table 1. According to the parents, the children had histories of mild to moderate constipation with constipation defined as “infrequent (less than three bowel movements per week) and/or difficult and painful evacuation of hard feces.” Prior to enrollment, a physician reviewed each child’s medical history. Children who

had fecal impaction, megacolon, diarrhea, fecal soiling, or who were taking any medications that could contribute to constipation were excluded from the study. Similarly, children who were known to have chronic metabolic, gastrointestinal, or neurological diseases or had any impaction or underlying "organic" causes of constipation were also excluded from the study (36). Parents agreed not to administer any laxatives including: over-the-counter products, home remedies, and dietary supplements to the children for the duration of the study. Any child who was taking iron or multivitamin supplements at the time of study enrollment was to remain on the same dosage throughout the study. Children who prematurely terminated from the study had the reason for their withdrawal documented and were not replaced. The research protocol was reviewed and approved by the Institutional Review Board of West Pharmaceutical Services, Inc. (Indianapolis, IN). The legal guardian of each child who participated in the study gave written informed consent.

To be considered compliant, a child must have: 1) consumed every dose of study product in the required sequence without skipping a single dose, and 2) consumed the correct dose of study product (± 1 mL of assigned dose) until producing a bowel movement with stool consistency score of "4" or greater, or reached the maximum possible dose of 0.8 g/kg/d. In addition, children who received oral antibiotics at any time during the study were excluded from the analysis of protocol compliant subjects.

**Study design**

The study was conducted in a double-masked fashion using a parallel design with two study arms consisting of a scFOS group (active treatment) and a sucrose group (placebo). Children were randomly assigned in a ratio of 3:2 to either the scFOS or sucrose groups, respectively, after blocking on sex. Immediately following a 3-d baseline period, each child was given a 0.2 g/kg body weight dose of the respective study product daily at breakfast. The dosage was increased in 0.2 g/kg/d increments every other day just until reaching the study endpoint. The maximum possible dose was 0.8 g/kg/d. A child was considered to have completed the study once he or she: 1) reached the study endpoint by producing a bowel movement with stool consistency score of "4" or greater within 26 h after ingesting the study product, or 2) consumed two doses at the 0.8 g/kg/d dosage rate.

**Study products**

The study products (Table 2) consisted of scFOS (NutraFlora® FOS, Golden Technologies Co., Inc, Westminster, CO) or sucrose (Amalgamated Sugar Co., Ogden, UT) syrups packaged in 125 mL glass bottles. Syrups were flavored and colored to enhance palatability and appearance. Parents dispensed syrup to their children each morning at breakfast using disposable plastic syringes. The amount of syrup given to each child was calculated from the body weight at study entry. Opened bottles of study product were collected at study exit and the contents re-analyzed in order to verify that each subject had received the correct treatment.

**Data collection**

Upon study entry, the parents completed a 3-d bowel function recall that covered the three days just prior to baseline. Beginning at baseline, parents recorded daily the amount of product intake, bowel function parameters, subjective tolerance factors, and any medications that were taken. The sites contacted the parents by telephone each day of study product administration to confirm that the correct dose had been administered and to provide answers to any study-related questions. Parents rated the consistency of their child's stools using the following scale: 1 = hard, dry; pellets, small, hard mass; 2 = hard, formed; dry, stool remains firm and soft; 3 = soft, formed; moist, softer stool that retains shape; 4 = soft, unformed; stool pudding-like; and 5 = watery; liquid that can be poured. Parents noted the severity of burping, flatulence (gassiness), fussiness, and vomiting using a scale of: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

**Statistics**

*Sample size.* A sample size of 25 children completing the study and reaching the study endpoint by the highest scFOS dosage was chosen by assuming that the distribution of responses and the anticipated $ED_{50}$ would be similar to those observed by Briet et al. (32) for healthy adult subjects. Based on the added assumption that as many as 24% of the children could potentially drop out of the study (n=8), a total of 33 children were randomly assigned to the active arm. Because the two groups were not being directly compared for the $ED_{50}$ and because it was anticipated that there would be no response in the placebo group, there was no need to have an

equal allotment of children to the two groups. Therefore, a 3:2 randomization was used to enroll 55 children with 33 assigned to the active and 22 assigned to the placebo arm.

*Statistical analysis.* The primary analysis was an Intent-to-Treat analysis using all available data for each child. The data were also subjected to a subset analysis using data from children who were considered to be compliant. Sites were pooled for analysis due to small cell size.

For continuous demographic variables, such as age of child and blood pressure parameters, the data were analyzed with a Two Sample t Test or the Wilcoxon Rank Sum Test as appropriate. Categorical data including: sex and race of child, did the child have any adverse events, did the child have any deviations from protocol, and reason for study exit were analyzed with a Two Sided Fisher's Exact Test. The estimate of $ED_{50}$ for the active arm was obtained using PROC GENMOD in SAS (37), and the associated 95% CI was calculated using Fieller's Theorem as outlined by D. J. Finney (38). Gastrointestinal symptoms were summarized according to severity of symptoms and percentage of study days for each period of the study for both study arms, but these data were not statistically analyzed.

The data on reaching study endpoint were examined several ways. First, children were classified as to: 1) whether they had reached the endpoint or 2) whether they took all doses and did not reach endpoint. Second, children were classified as to whether or not they reached the study endpoint at each particular dose. These data were analyzed with a Two Sided Fisher's Exact Test. The data for the actual dose at which the endpoint was reached were scored in an ordinal fashion as follows: 1 = 0.2 g/kg, 2 = 0.4 g/kg, 3 = 0.6 g/kg, 4 = 0.8 g/kg, and 5 = did not reach endpoint. These data were analyzed with a Wilcoxon Rank Sum Test. Bowel function data (calculated number of bowel movements per day and average stool consistency per day) were tabulated and summarized with descriptive statistics (mean and SEM) for each period of the study. The study periods were defined as: recall (days -2, -1, and 0), baseline (days 1, 2, and 3), 0.2 g/kg dosage (days 4 and 5), 0.4 g/kg dosage (days 6 and 7), 0.6 g/kg dosage (days 8 and 9), and 0.8 g/kg dosage (days 10 and 11). The average daily number of bowel movements and average daily consistency for each study period were also used to calculate the difference from baseline for each of the four dosage periods. The baseline and calculated changes from baseline for the bowel function data were then analyzed with a Two

Sample t Test or the Wilcoxon Rank Sum Test as appropriate. Only the data up to reaching study endpoint were statistically analyzed. All results were considered statistically significant if the significance level was $\leq$ 5%.

## RESULTS

### Subjects

Of the 55 children enrolled into the study, 47 completed according to protocol (85.45%), seven completed with violations (12.73%), and one was voluntarily dropped at the investigator's request (1.82%). The reason for study exit and the number of children in each treatment group with deviations from protocol were not statistically different between the scFOS and sucrose groups ($P > 0.05$). In all, ten children were deemed not to be protocol evaluable. Nevertheless, results from the Intent-to-Treat analysis were virtually identical to those obtained from the Protocol Evaluable analysis. Therefore, this manuscript will only refer to results from the Intent-to-Treat analysis.

### Frequency of bowel movements

The frequency of bowel movements up until completion of the study is displayed in Figure 1. Although the mean frequencies increased for both groups as the dosage increased, the change in frequency from baseline values during each period did not differ ($P > 0.05$) between the scFOS and sucrose groups.

### Stool consistency

Mean stool consistencies until reaching study completion and changes in stool consistencies from baseline are presented in Figures 2 and 3, respectively. No differences were detected ($P > 0.05$) for the 0.2 and 0.4 g/kg dosages (Figure 3), but the change from baseline was statistically greater ($P = 0.004$) for the scFOS than the sucrose group at the 0.6 g/kg dose. The changes from baseline were not different at the 0.8 g/kg dose ($P = 0.095$).

The estimated $ED_{50}$ to produce a stool with pudding-like or watery consistency was 0.79 g/kg body weight with an associated 95% CI of 0.58 to 1.12 g/kg/d. However, the proportion of children reaching endpoint of producing a pudding-like or watery stool or taking all doses

without reaching the endpoint were not statistically different ($P > 0.05$) between the scFOS and sucrose groups (data not shown). Likewise, there were no statistical differences ($P > 0.05$) in the proportion of children reaching the study endpoint of producing a pudding-like or watery stool at each dose or in the dose at which the endpoint was reached between the scFOS and the sucrose groups.

**Subjective tolerance**

Subjective tolerance ratings were summarized as a percentage of study days and are displayed in Figures 4 through 7. Data were included up until study completion. Even though these data were not statistically analyzed, ratings appeared to be similar between the scFOS and sucrose groups.

**Adverse events**

Seven adverse events occurred in seven different children out of a total of 55 that were enrolled into the study. The adverse events involved either: 1) skin irritations, or 2) respiratory, ear, nose or throat problems. Six of the seven adverse events took place in children who were in the scFOS group and one event took place in a child who was in the sucrose group. However, the frequency of adverse events was not different ($P > 0.05$) between the scFOS and the sucrose groups. Five of the seven adverse events were not attributable to study product consumption, one was attributable to study product consumption, and one was classified as "unknown" regarding its relationship to study product consumption. The adverse event that was attributed by the physician to study product consumption occurred in one of the children who had received the sucrose treatment. The adverse event that was classified as "unknown" occurred in a child who had received the scFOS treatment. This event involved slight reddening of the perineal area was the only adverse event that could potentially be attributed to the ingestion of scFOS. No deaths or serious adverse events occurred during this study.

**DISCUSSION**

**Effective dose**

When children were given scFOS, the minimum dose at which stool consistency was softened to a greater extent from baseline compared with the sucrose group occurred at the 0.6 g/kg/d

dose. Further analysis of the data indicated that the effective dose of scFOS was 0.79 g/kg/d. These results are consistent with those obtained using healthy human adult subjects. For example, a dose titration study conducted by Briet et al. (32) indicated that the $ED_{50}$ for scFOS to induce diarrhea in healthy adults was 50 g/d (0.76 g/d on a per kg body weight basis) when consumed once per week. Similar results were observed if the dose was gradually escalated over a period of up to 18 days. Likewise, Hata et al. (33) also estimated an $ED_{50}$ for scFOS of 0.8 g/kg among men and women using an acute dosing scheme.

In the present study, the dose at which children reached the endpoint of producing at least one stool with pudding-like or watery consistency varied considerably. Some subjects reached the endpoint at 0.2 g/kg/d while others did not attain the endpoint even at dosages as high as 0.8 g/kg/d. In fact, half of the children did not reach the endpoint even after reaching the 0.8 g/kg/d dose. Dosage variations were also reported in other studies where indigestible carbohydrates were provided to apparently healthy adult subjects (32,33,39,40). Thus, the dosage rate of scFOS, as with other dietary fiber supplements, will need to be adjusted for each individual in order to achieve the desired result.

The large variation in the amount of scFOS required to elicit stool softening may be attributed to variation in the inherent ability of the colonic microbiota to dispose of carbohydrates. In a study using 12 healthy Caucasian volunteers between the ages of 27 and 56 y, Clausen et al. (40) classified subjects into low, medium, and high responders based on the quantity of oligofructose or lactulose required to elicit a laxative response with high responders requiring the least amount of carbohydrate to elicit a stool softening effect. Because high responders had lower fecal pH, higher concentrations of fecal short-chain fatty acids, and residual unfermented carbohydrate remaining in the feces, the authors postulated that high responders had a more limited capacity to ferment carbohydrate in the proximal colon. This lower capacity to ferment carbohydrates in the proximal colon resulted in more fermentation occurring in the distal colon and any excess carbohydrate drawing water into the feces.

**Subjective tolerance**

Studies in which scFOS or other indigestible oligosaccharides were fed to adults have frequently reported gastrointestinal symptoms at the higher dosages (31,32,39). Common complaints include diarrhea, abdominal cramps, bloating, excess flatus, and borborygmus. Interestingly enough, according to data collected by the parents, children partipating in the present study experienced few tolerance problems even at the highest scFOS dose of 0.8 g/kg/d.

**Frequency of bowel movements**

Not surprisingly, the present study showed that the ingestion of scFOS had little effect on the frequency of bowel movements in children with a history of mild to moderate constipation. Tominaga et al. (41) examined the effect of scFOS on stool frequency by administering 3 g of scFOS or a placebo daily to healthy female volunteers. Stratification analysis of the data according to stool frequency observed during the non-intake (baseline) period of the study showed that only subjects who had lower than normal stool frequencies experienced an increase in frequency upon ingestion of scFOS. Subjects classified as being within the normal range of stool frequency (i.e., > 5 times per week) were not affected by ingestion of scFOS.

During the present study, children in the scFOS and sucrose groups experienced an average of $0.72 \pm 0.08$ and $0.76 \pm 0.10$ bowel movements per day during the baseline period. Converted to a weekly basis, these figures correspond to 5.0 and 5.3 bowel movements for the scFOS and sucrose groups, respectively. Based on these data and the Rome II Criteria for defining functional constipation (42), most of the children participating in the present study were already within the normal range of stool frequency.

**FOS as a laxative for children**

Toddlers and children of 2 y of age or older are most prone to “functional” stool retention whereby chronic constipation develops due to behavioral reasons such as poor dietary habits, toilet training, school anxiety, birth of a new sibling, or fear of having a bowel movement outside of the home. Therapy for functional constipation in children is a multi-step process. The initial phase involves oral clean out or manual disimpaction. This step is followed by 6 to

12 months of maintenance involving oral laxatives, dietary changes, behavioral modification, and positive reinforcement (43).

Even though numerous potentially efficacious options are available for the treatment of constipation, over-the-counter laxative preparations may not be ideally suited for use in children. Common remedies such as mineral oil and milk of magnesia must be cleverly disguised in foods so that they are acceptable to children. Other therapies may be undesirable due to inconvenience of administration or they may have been removed from the market due to safety concerns. Ideally, increasing dietary fiber intake using "real food" could solve the problem. However, in reality, the choice of laxative depends on which one the child will best tolerate (43).

Results from this study indicate that scFOS has good potential for improving the treatment of childhood constipation. These carbohydrates act as an effective stool softeners at dosages comparable to those found in adults without causing serious gastrointestinal tolerance issues. Perhaps even more importantly, the high palatability of scFOS would increase the likelihood of successfully treating childhood constipation due to increased compliance and convenience. The authors caution the extrapolation of this data to other sources of fructooligosaccharides because Clausen et al. (40) have shown that laxation is highly related to the osmotic effect of the indigestible sugar being fed.

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**TABLE 1.** Subject characteristics at study entrance[1]

| Characteristic | Treatment | | $P^2$ |
|---|---|---|---|
| | scFOS ($n$ = 34) | Sucrose ($n$ = 21) | |
| Age (y) | 3.76 ± 0.20 | 4.29 ± 0.23 | NS |
| Sex (M/F) | 15/19 | 10/11 | NS |
| Subject ethnicity (%) | | | NS |
| Caucasian | 20 (58.8%) | 12 (57.1%) | -- |
| Latino | 13 (38.2%) | 8 (38.1%) | -- |
| African American | 1 (2.9%) | 0 (0%) | -- |
| Asian/Pacific Islander | 0 (0%) | 1 (4.8%) | -- |
| Height (cm) | 100.23 ± 1.68 | 103.76 ± 1.78 | NS |
| Weight (kg) | 16.62 ± 0.68 | 17.65 ± 0.73 | NS |
| Body temperature ($^{o}$C) | 36.68 ± 0.05 | 36.58 ± 0.07 | NS |
| Blood pressure (mm Hg) | | | |
| Systolic | 87.27 ± 1.48 | 90.82 ± 2.01 | NS |
| Diastolic | 57.67 ± 1.02 | 58.59 ± 1.50 | NS |
| Pulse rate (beats/min) | 106.06 ± 1.84 | 97.81 ± 3.35 | 0.023 |
| Respiratory rate (breaths/min) | 20.85 ± 0.47 | 20.38 ± 0.60 | NS |

[1]Includes data from all randomized subjects. Mean ± SEM.
[2]All $P > 0.05$ regarded as NS.

**TABLE 2.** Composition of the study products[1]

| Carbohydrate | Grape scFOS | Grape Sucrose | Cherry scFOS | Cherry Sucrose |
|---|---|---|---|---|
| | g/100 g Syrup | | | |
| Glucose | 0.295 | 0 | 0.305 | 0 |
| Fructose | 1.47 | 0 | 1.68 | 0 |
| Sucrose | 1.78 | 65.2 | 1.99 | 63.8 |
| GF2 | 20.64 | 0 | 20.72 | 0 |
| GF3 | 29.68 | 0 | 29.44 | 0 |
| GF4 | 4.44 | 0 | 4.44 | 0 |
| Total scFOS[2] | 61 | 0.43 | 60.8 | 1.43 |
| Total solids | 65.1 | 66.8 | 65.0 | 66.2 |

[1]Values were obtained from analysis of study products 2 months prior to the start of study enrollment. Products were also re-analyzed 2 months after the last subject was completed, and test results were found to be within 6% of the original analysis. GF2, 1-kestose; GF3, nystose; GF4, 1-β-fructofuranosyl nystose.
[2]Total scFOS also includes fructans that do not analyze as GF2, GF3 or GF4.

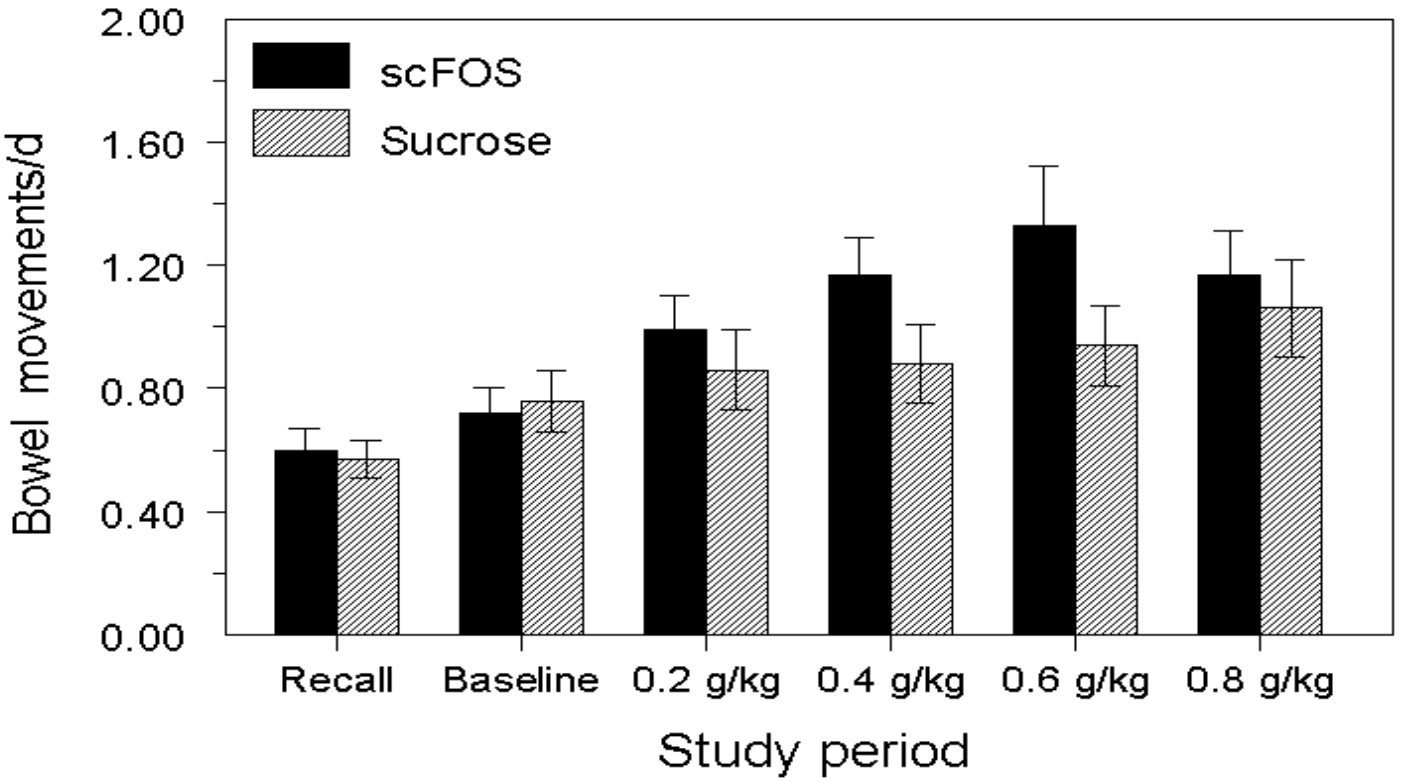


**Figure 1.** Mean frequency of bowel movements (± SEM) for scFOS and sucrose groups, respectively, during recall (*n* = 32, 17), baseline (*n* = 34, 21), 0.2 g/kg (*n* = 34, 21), 0.4 g/kg (*n* = 30, 21), 0.6 g/kg (*n* = 26, 18), and 0.8 g/kg (*n* = 21, 16) study periods. All data were included up until reaching the study endpoint.

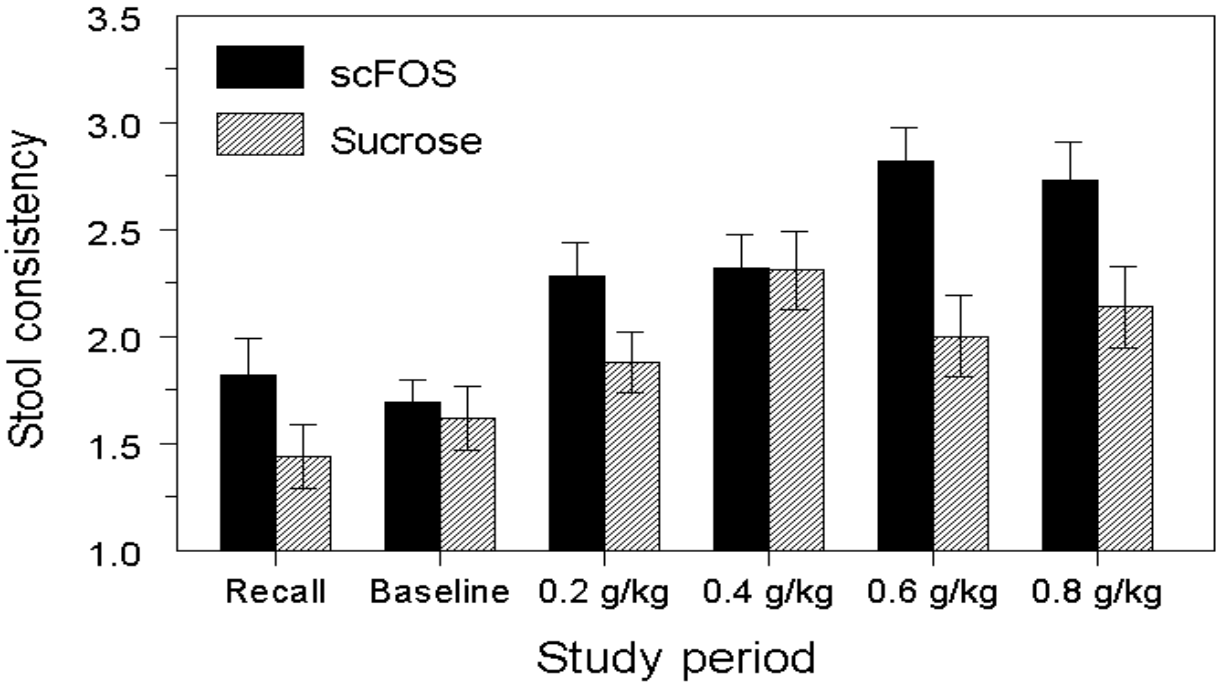


**Figure 2.** Mean daily stool consistency (± SEM) for scFOS and sucrose groups, respectively, during recall (*n* = 29, 16), baseline (*n* = 32, 20), 0.2 g/kg (*n* = 31, 18), 0.4 g/kg (*n* = 29, 18), 0.6 g/kg (*n* = 23, 16), and 0.8 g/kg (*n* = 20, 16) study periods. Stool consistencies were scored by parents using the following scale: 1: hard, dry; pellets, small hard mass; 2: hard, formed; dry, stool remains firm and soft; 3: soft, formed; moist, softer stool that retains shape; 4: soft, unformed; stool pudding-like; 5: watery; liquid that can be poured. All data were included up until reaching the study endpoint.

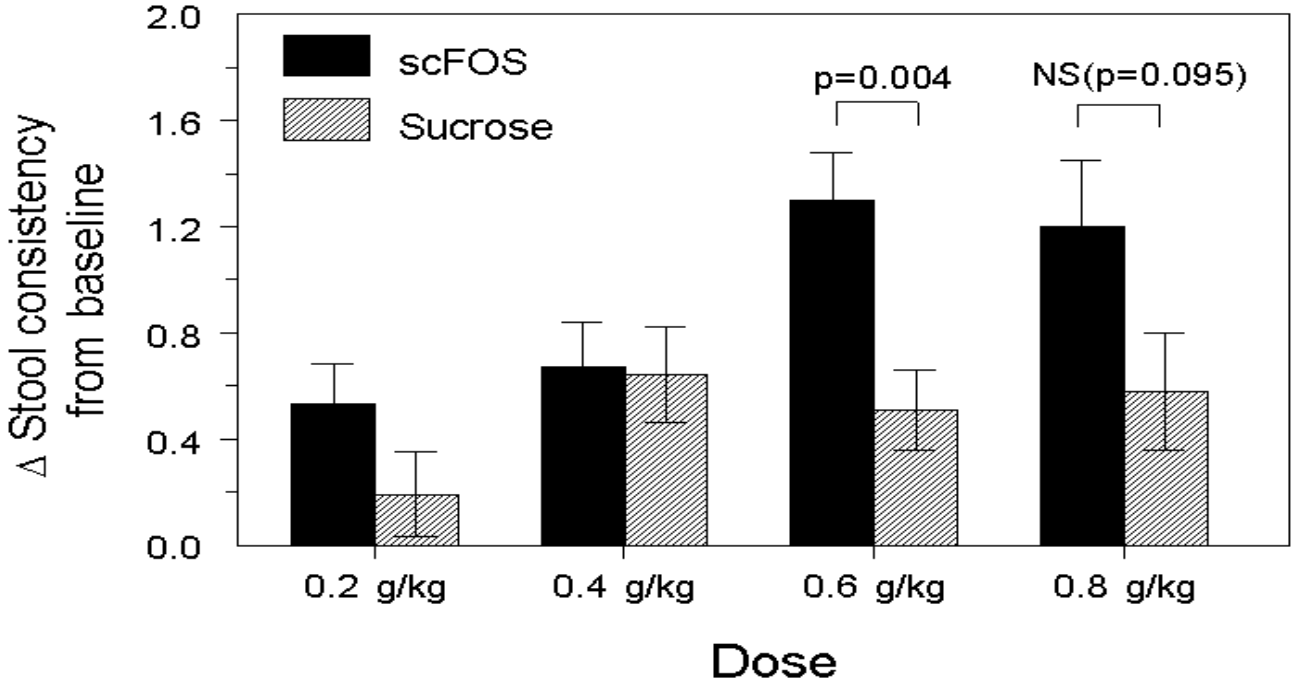


**Figure 3.** Mean change in daily stool consistency (± SEM) for scFOS and sucrose groups, respectively, from baseline during the 0.2 g/kg (*n* = 29, 18), 0.4 g/kg (*n* = 28, 17), 0.6 g/kg (*n* = 22, 16), and 0.8 g/kg (*n* = 19, 16) study periods. Stool consistencies were scored by parents using the following scale: 1: hard, dry; pellets, small hard mass; 2: hard, formed; dry, stool remains firm and soft; 3: soft, formed; moist, softer stool that retains shape; 4: soft, unformed; stool pudding-like; 5: watery; liquid that can be poured. An Intent-to-Treat analysis was conducted using data collected until each child reached the study endpoint. At the 0.6 g/kg dosage, a greater degree of stool softening (P = 0.004) was observed in the scFOS than in the sucrose groups compared with baseline values (Wilcoxon Rank Sum Test).

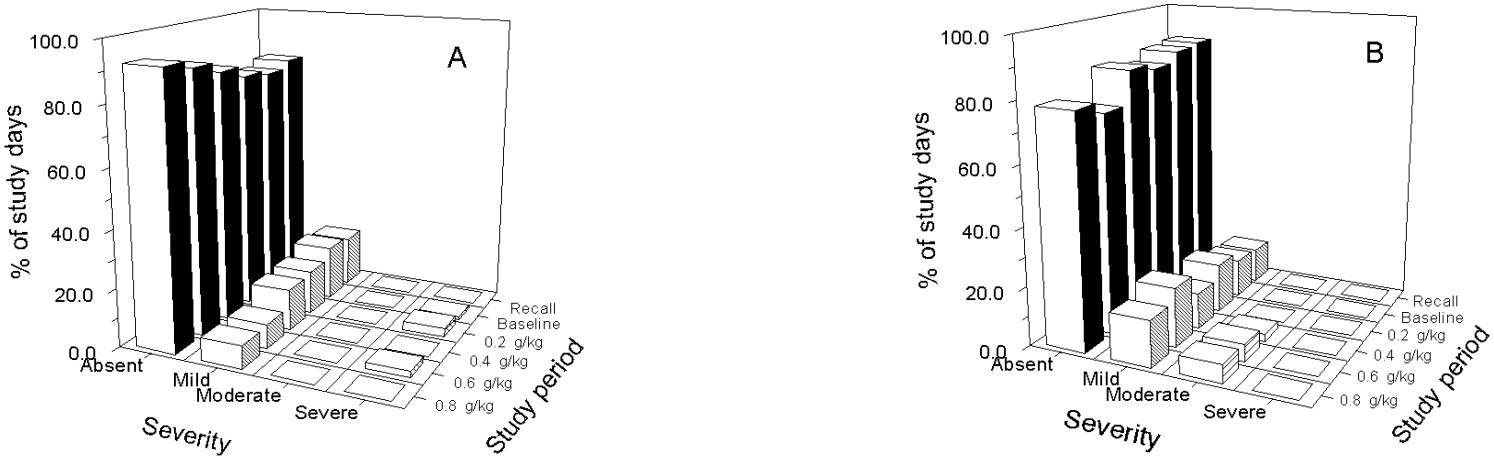


**Figure 4.** Percentage of study days where burping was noted in children given scFOS (A) or sucrose (B). The severity of burping was recorded daily by the parents and rated as: absent, mild, moderate, or severe. All data were included up until reaching the study endpoint.

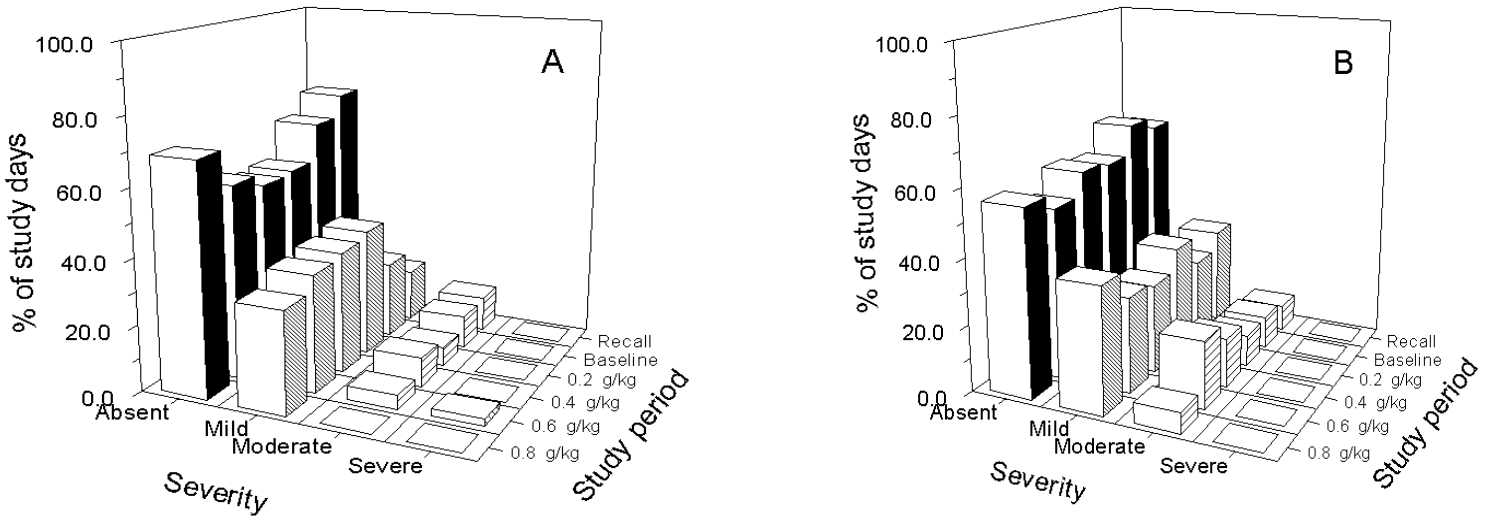


**Figure 5.** Percentage of study days where flatulence was noted in children given scFOS (A) or sucrose (B). The severity of flatulence was recorded daily by the parents and rated as: absent, mild, moderate, or severe. All data were included up until reaching the study endpoint.

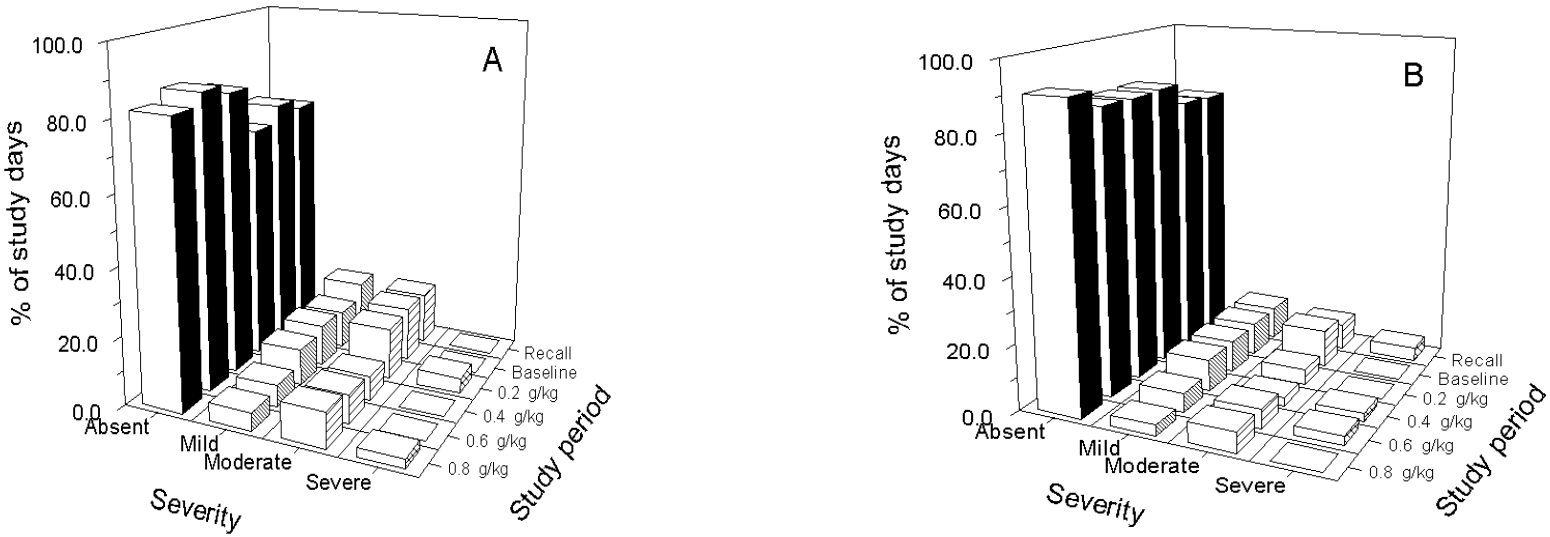


**Figure 6.** Percentage of study days where fussiness was noted in children given scFOS (A) or sucrose (B). The severity of fussiness was recorded daily by the parents and rated as: absent, mild, moderate, or severe. All data were included up until reaching the study endpoint.

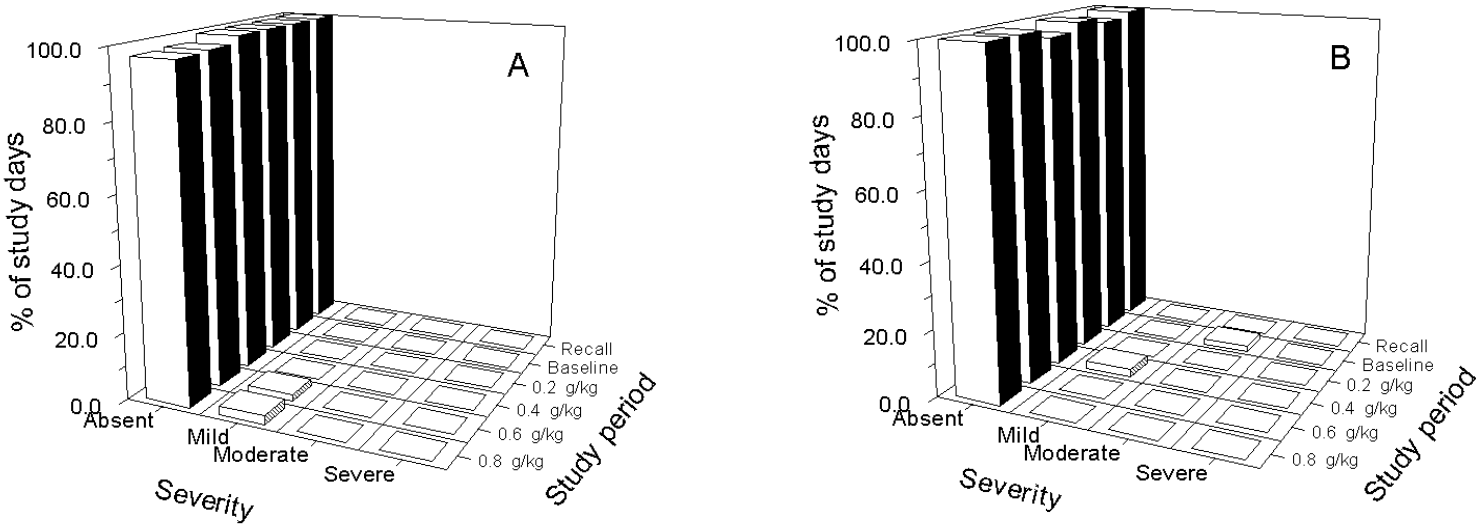


**Figure 7.** Percentage of study days where vomiting was noted in children given scFOS (A) or sucrose (B). The severity of vomiting was recorded daily by the parents and rated as: absent, mild, moderate, or severe. All data were included up until reaching the study endpoint.