Procter&Gamble

The Procter & Gamble Company
Winton Hill Technical Center
6071 Center Hill Avenue, Cincinnati, Ohio 45224-1703 2658 '00 MAR -6 A9:28

March 3, 2000

Docket Management Office
5630 Fisher's Lane
Rockville, MD 20852

Dear Madam:

We wish to submit the enclosed report and cover letter entitled "FP-148 Final Report - Stool Composition and Consistency in Humans Consuming Olestra" to the olestra docket #00F-0792 so that it is publicly available in order to resolve any questions regarding the report or its recommendations. This report was previously submitted to Mary Ditto of FDA's Office of Pre-market Approval on February 10, 1998.

In addition, this information was presented at the 1998 Summer Toxicity Forum and the proceedings were previously submitted to the olestra docket. The Toxicology Forum proceedings were published as listed below. We attached a copy for your convenience.

> McRorie, J., Stool Composition Study, Proceedings of the Toxicology Forum, July 12-17, 1998; pp. 111-121

Please let me know if you have any questions (513-634-6808).

Thank you.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Greg Allgood/rd

Greg Allgood, Ph.D.
Associate Director
Regulatory & Clinical Development

00F-0792

RPT6

STOOL COMPOSITION STUDY

John McRorie
Procter & Gamble, OH

2659 '00 MAR -6 A9:29

DR. HALL: Our first speaker is Dr. John McRorie of Procter & Gamble. John has had a colorful career, including stints as a US Army Airborne Ranger and a rodeo clown. What is relevant to our meeting today, however, is that he has a dual PhD in neuroscience and physiology from Michigan State and he has had a background with P&G in health care, and GI physiology. He is at present the GI physiologist on the olestra project.

John?

DR. MC RORIE: (Microphone turned off at beginning of speech.) So, we know olestra has no effect on the microflora. Olestra is not fermented in the bowel. We know from numerous human studies that there is no significant change in GI transit and, also, in animal studies, and we know that olestra doesn't affect micronutrient absorption. So, the question is we know the effects of olestra on the bowel itself, what does olestra do to stool?

The reason we undertook this study was to better understand what olestra actually does to the content and consistency of stool. To accomplish this we examined a number of objective parameters; the number of bowel movements per day as the subjects reported and recorded the time and day of the bowel movements, the total stool output per day in grams per day, stool water and stool electrolyte output which is the major parameter that you watch in clinical diarrhea and lastly stool viscosity.

The study was a randomized double-blind, parallel designed study. We had both positive and negative placebos. For the negative placebo we simply fed the subjects regular chips, (full-fat chips) and sugar candies throughout the study.

For our positive control we used sorbitol. Sorbitol is a sugar alcohol that is poorly absorbed in the bowel and has very well-documented osmotic effects that, with sufficient dosing, can lead to an osmotic diarrhea. Subjects were housed on a metabolic ward for 12 days. Access to the bathrooms was controlled. Subjects had to see one of the study monitors and obtain a stool specimen container to gain access to the bathroom. Over 1000 stool samples were collected and assessed.

Sixty-six subjects ranging in age from 18 years to 74 years, 60 percent female, participated in the study. Our clinical consultant on this study, Dr. Ralph Gianella, is a professor and head of gastroenterology at the University of Cincinnati. He is also the President-Elect of the American Gastroenterological Association and in May presented the results of this study at Digestive Disease Week, the largest gastroenterological meeting annually in the US.

This study had a 6-day baseline and a 6-day treatment period. During the 6-day baseline, all 66 subjects consumed placebo candy and placebo chips and for your reference I brought some along.

The placebo candy consisted of regular Smarties, 1.5 ounces and the chips consisted of 5 ounces of regular triglyceride chips.

During the 6-day treatment period the placebo subjects continued to eat the regular candy (full-sugar candy) and the full-fat chips. The olestra 20-gram/day group had placebo candy in the morning and in the afternoon chips. Because of the volume, chips were divided into two sessions of eating, about an hour and one-half apart. During the first session they had all olestra chips (2.5 ounces of olestra chips) and during the second session they would have all placebo chips.

The olestra 40-grams-per-day group had placebo candy and then both sessions in the afternoon were olestra chips. The sorbitol group had sorbitol candy in the morning and placebo chips in the afternoon.

Now, one further note about sorbitol. Sorbitol, because of its laxative and potential diarrhea effects, requires an FDA-mandated information label, but not until you reach a predicted consumption level of 50 grams per day. In this study we were only giving 40 grams per day, which is 80 percent of the dose requiring a label.

Our first data slide is total stool output. It is the sum of all the stool the subjects produced per day, and this is averaged data. The baselines for each of the individual treatment groups are in the hashed columns and then the treatment groups are in the open columns.

You can see that placebo actually went down slightly from its baseline. Compared to placebo the two olestra groups were significantly greater but compared to their own baselines Olestra only increased stool output slightly. For your convenience I have drawn a bar at 20 grams and at 40 grams so that you can see the actual change from their own baseline which is slightly more than the actual amount of olestra ingested.

In contrast, 40 grams of sorbitol per day resulted in about 9 grams per gram, 9 grams of stool produced for every gram of sorbitol ingested, so, you see a rather large increase in daily stool output.

This slide shows bowel movement frequency, the recorded number of bowel movements per day per subject. Baselines are again in the hashed bars. Here you can see the baselines are relatively constant. On average these subjects, consuming an American Heart Association step one diet, had about one and one-half bowel movements per day. The placebo group again went down slightly compared to baseline. This group was getting approximately 1000 calories a day from their placebo snacks, and I suspect that they had such a calorie load they stopped eating as much of their diet and were gradually easing toward constipation.

You can see there was no change in bowel movement frequency in the olestra 20 g/day group, a slight increase from one and one-half to two bowel movements per day in the olestra 40 g/day group and approximately three bowel movements per day in the sorbitol 40 g/day group.

Stool water output, is one of the watchdogs for a clinical diagnosis of diarrhea. You actually want to watch both stool water and electrolytes. The baselines are in the hashed bars, and once again, you can see the slight decrease from baseline in the placebo group.

Compared to placebo there was a statistically significant increase in stool water output in the two olestra treatment groups, but when you compare them to their own baselines the increases were equal to two teaspoons and two and one-half tablespoons difference per day, clearly not a clinical concern.

In contrast when you look at the change from sorbitol from its baseline, that is the equivalent of 11 ounces of water, a good-sized drinking glass of water difference in stool water output.

Stool sodium output, (we averaged all the baselines for this particular slide), was similar to stool water. There is a slight decrease for placebo and a slight increase for each of the two olestra groups, and as you saw in the water output slide, a rather large jump in the sorbitol treatment group.

Now that we have seen some of the objective measures that are commonly used in clinical practice, let us take a look at what we would predict would happen with olestra consumption and stool viscosity, because viscosity has not been previously measured.

As you consume olestra and your daily consumption goes up, it is not a linear relationship. If you consume 40 grams of olestra, (assuming the national average of 100 grams of stool per day), the US is actually far below the rest of the world in stool output because of our calorie rich, fat rich diet. If you go to some African countries they produce up to four and five hundred grams of stool per day. The US

is down around 100 g/day. So, as you increase the olestra dose per day you would increase the percentage of the olestra content in the stool, and you will predict because olestra is softer than stool; it is a semi-solid, but it is softer than formed stool, you would predict a stool-softening effect, and that is exactly what you see.

Let me take a minute and walk you through the slide. Recall that the first 6 days of the study were a baseline period. The first 2 days we allowed subjects to acclimate to the unit, acclimate to the meals, and we did not collect stool samples. So, your baseline period here is days 3, 4, 5 and 6.

Here stool viscosity is measured as a log of peak force. Stool samples were loaded into a cylinder. A probe was driven into the cylinder. The sample had to back extrude around the equatorial region of the probe and the greater the peak force, the higher the viscosity of the stool, the greater force it took to drive the probe into the stool.

You can see during the baseline period stool viscosity was relatively constant. It is a peak force of about 1000 grams, and that is formed stool. On the first day of treatment you can see the sorbitol treatment group immediately fell down into the loose / liquid range of stool viscosity. The effect actually occurred within about an hour and one-half of consumption. So, within 1 to 3 hours stool viscosity dramatically decreased down to the loose / liquid range. There were 140 liquid bowel movements in the sorbitol treatment group during this treatment period.

Now, in contrast let us take a look at placebo first. You can see that placebo remained similar to baseline and toward the end, as I noted before, stool viscosity started slightly edging up as these subjects were gradually heading toward constipation.

With olestra 20 grams per day, the first 3 days of treatment, is similar to baseline and placebo. It wasn't until the fourth day of treatment that you actually started to see a stool-softening effect, and that is partially highlighted by the fact that placebo was going the other way. So, you can see a very gradual stool softening effect after about 4 days of treatment.

With olestra 40 grams per day there is no effect on the first day of treatment. There was a gradual softening effect on the second and third days. The fourth day you saw a peak stool softening that plateaued, and this is exactly what you would expect to see with a high fiber diet, if you suddenly changed your fiber intake. You would see a gradual stool softening over several days that would plateau.

Now, we can see what happened with stool viscosity and olestra consumption in man. Let us switch gears for just a moment and take a look at a comparison of stool viscosity effects between olestra and dietary fiber.

This study was conducted at Mississippi State University in pigs, and they fed these farm pigs either olestra 80 grams a day, wheat fiber 80 grams a day or just the regular pig chow diet for control. The large bowel was removed. The contents were removed from the bowel in 13 anatomically defined regions of the bowel. The 14th sample was the stool sample collected just before sacrifice. You can see by viscosity in the cecum all the contents are liquid.

Viscosity rises gradually throughout the bowel in the control pig to a stool viscosity of about 4000 grams of peak force. Recall the last study that human stool is approximately 1 to 2 thousand. So, pigs can create a little firmer stool than man.

When you fed pigs olestra or wheat bran 80 grams a day, the viscosities were virtually identical. There is no difference in the slopes. Both slopes were different from the control, but they were no different from each other, and what is causing this change in viscosity? In a recent study that I published in a similar method done with other fiber compounds we found that four, well, let us start at the beginning. You have got the bowel segments again. The pig has been sacrificed. You have got bowel segments 1 to 13, 1 being cecum, 12 being rectum, 14 being stool sample, and what you see is a rather rapid decline

in digest of water content in just the first few segments, that the cecum is liquid. It goes to a semisolid within about two segments and then you see a more gradual dropoff in percent water content down to a formed stool.

With wheat fiber, in this case bran buds, you see that throughout the length of the bowel the percent water content is actually higher. Wheat fibers softens stool by increasing the water content. With olestra virtually no change until you get to this point. As the contents continue to be dehydrated olestra is adding to the solid component but is not adding water. So, the percent water content is actually lower than placebo through the latter three-fifths of the bowel.

So, the mechanism of wheat fiber seems to be that it softens stool by increasing water content whereas the mechanism of olestra is just the presence of a softer semi-solid olestra.

In the second pig study conducted at the Oklahoma Foundation for Digestive Research we looked at four different parameters. This study was done in Yucatan minipigs that had a chronic cecal fistula giving us direct access to the cecum where we could either introduce markers, sample cecal contents or introduce a colonic motility probe.

Pigs were fed 80 grams of olestra or 80 grams of wheat fiber for 3 days and then monitored for those 3 days plus an additional 6 days, and what you find is in viscosity, I am sorry I started off with transit time going from cecum to anus. There was no difference between wheat bran control, olestra control or olestra and wheat bran.

Viscosity, they both softened stool equally. You saw stool viscosity cut approximately in half. Now, recall in the human study you had 1 to 2 thousand grams of peak force. These pigs can put out little bricks, but wheat and olestra made them softer bricks.

Stool output, the CRC Handbook of Dietary Fiber in Human Nutrition predicts that after reviewing all of the stool output data available the dietary fiber, you get about 5 grams of stool for each gram of fiber ingested. Most of that is due to or a lot of that is due to fermentation and increase in the biomass.

You can see that stool output was actually higher with the wheat bran than it was with the olestra. Just like predicted back in the last data for the stool composition study you got about 1 gram per gram. Every gram of olestra you ingest, stool output goes up about 1 gram.

We looked a propagating contractions. I won't go into detail about what all these different designations mean, but we divided propagating contractions in the large bowel into four different categories, and there was no statistical difference between any of the propagating contractions. So, the stool-softening effect is due to the wheat fiber increases the water content; the olestra increases the olestra content. There is no effect on motility at all.

So, in conclusion consumption of olestra does <u>not</u> cause diarrhea, and consumption of olestra does result in a predictable dose response stool softening effect that is very similar to the effects of dietary fiber.

Questions?

DR. HALL: We have time for one question.

John, thank you very, very much.

Background

- No effect on bowel mucosa
- No microflora changes or fermentation
- No significant changes in transit
- No macronutrient malabsorption

Figure 1

Objective: Better Understand the Effects of Olestra on Stool Content and Consistency

- Examine objective measures of stool
  - –number of bowel movements per day
  - –total stool output per day
  - –stool water and electrolyte output
  - –stool viscosity

Figure 2

Methods in Stool Consistency Study

- Randomized, double-blind, parallel
- Placebo- and positive-controls (sorbitol)
- Subjects housed for 12 days
- All stools collected and analyzed
- 66 subjects (18 to 74 yrs), 60% female
- Clinical Consultant : Ralph Giannella, MD Director of Digestive Diseases, University of Cincinnati

Figure 3

Study Design

- 6-day baseline eating placebo candy (1.5oz) and chips (5oz)
- 6-day treatment period with subjects eating:
  - placebo candy and placebo chips
  - placebo candy and olestra (20g/d) in chips
  - placebo candy and olestra (40g/d) in chips
  - sorbitol (40g/d) candy and placebo chips

Figure 4

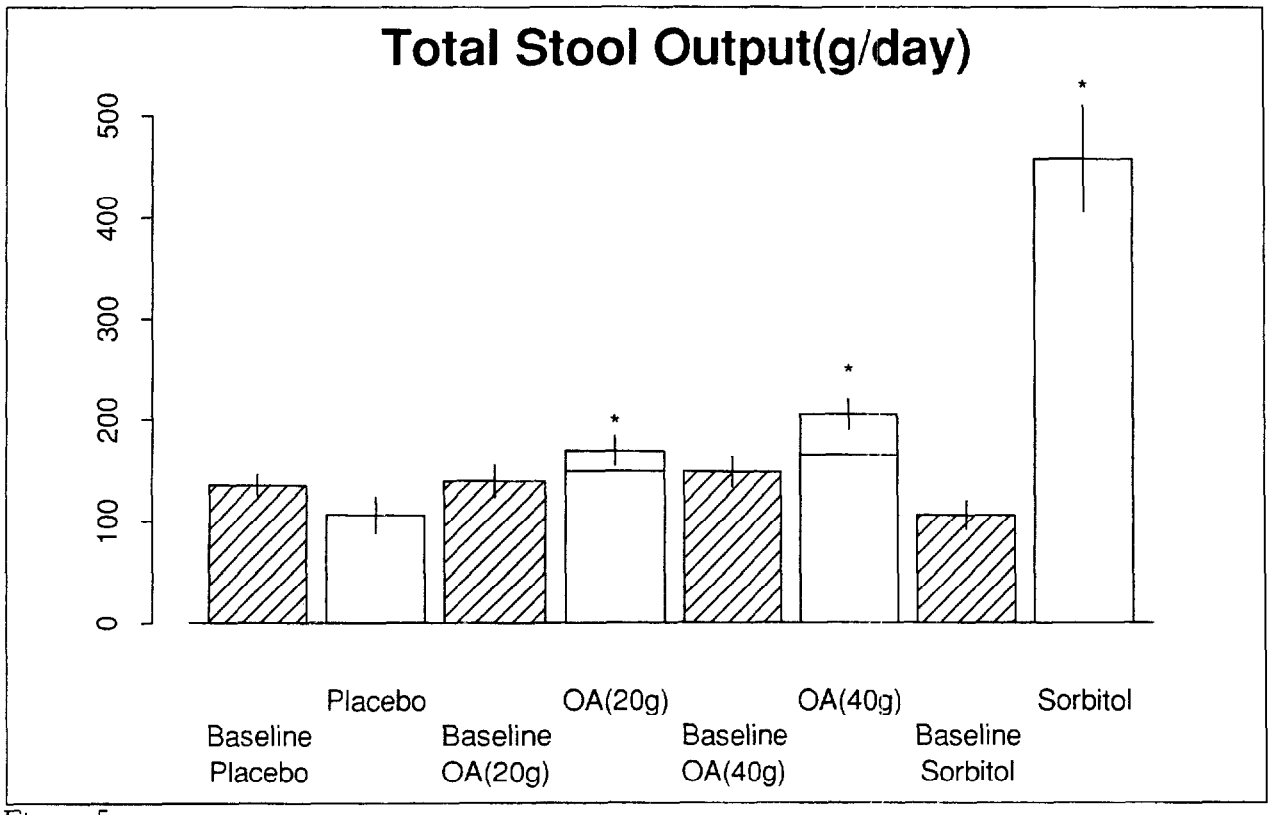


Figure 5

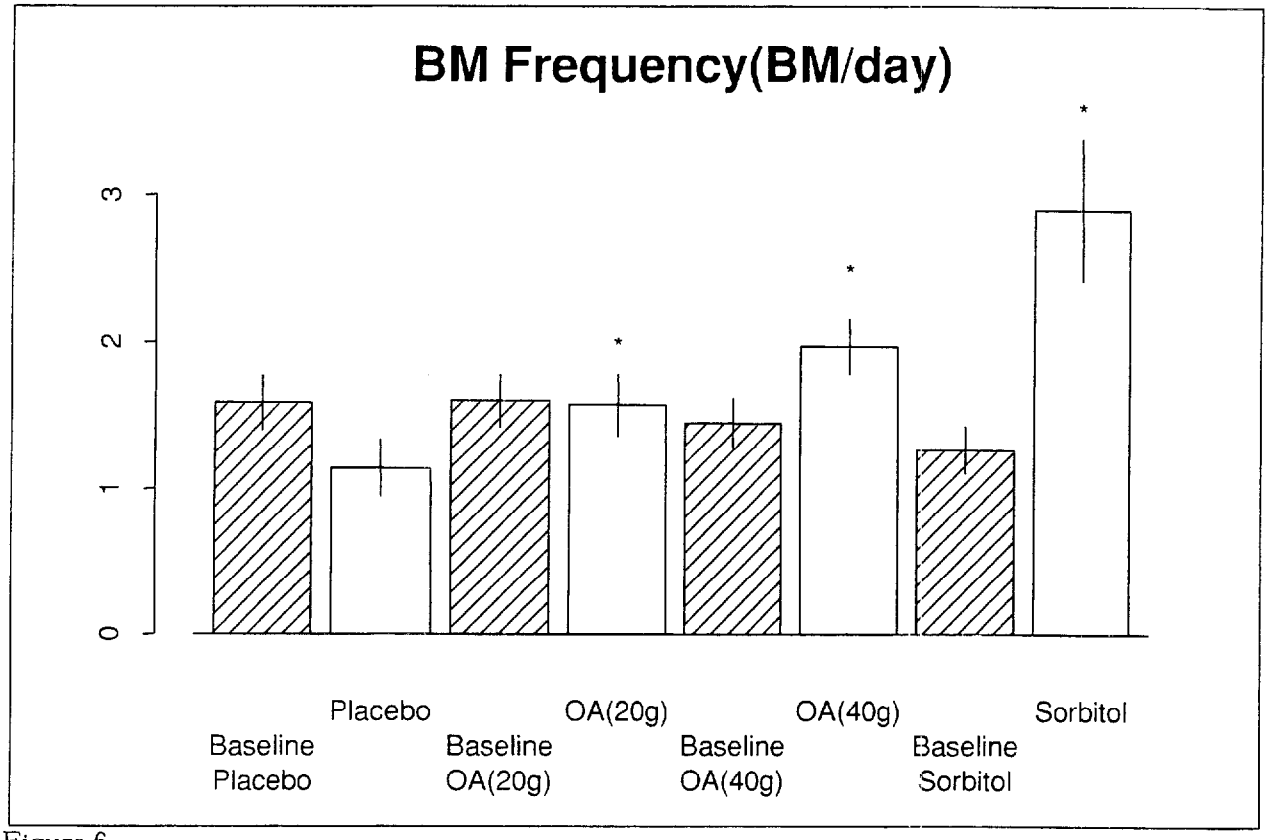


Figure 6

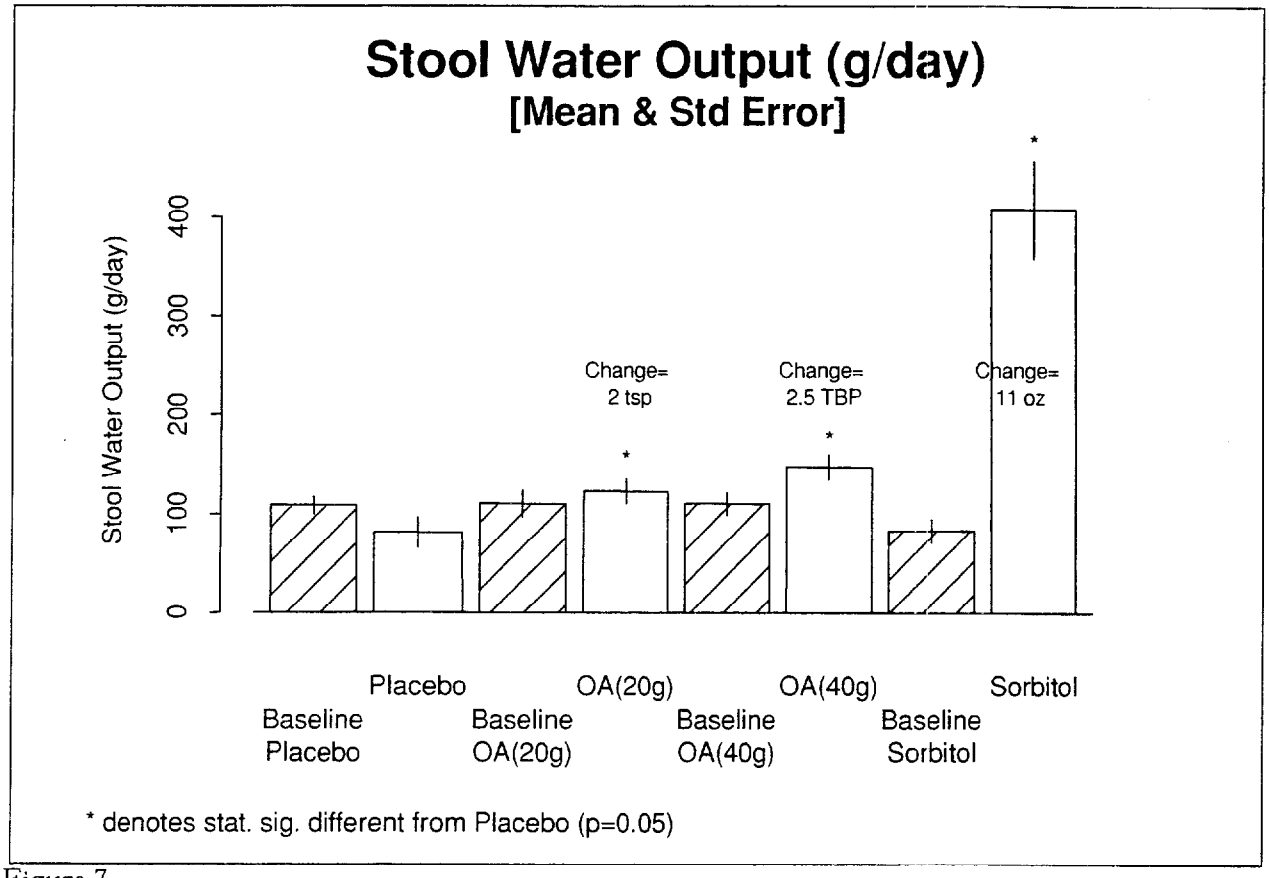


Figure 7

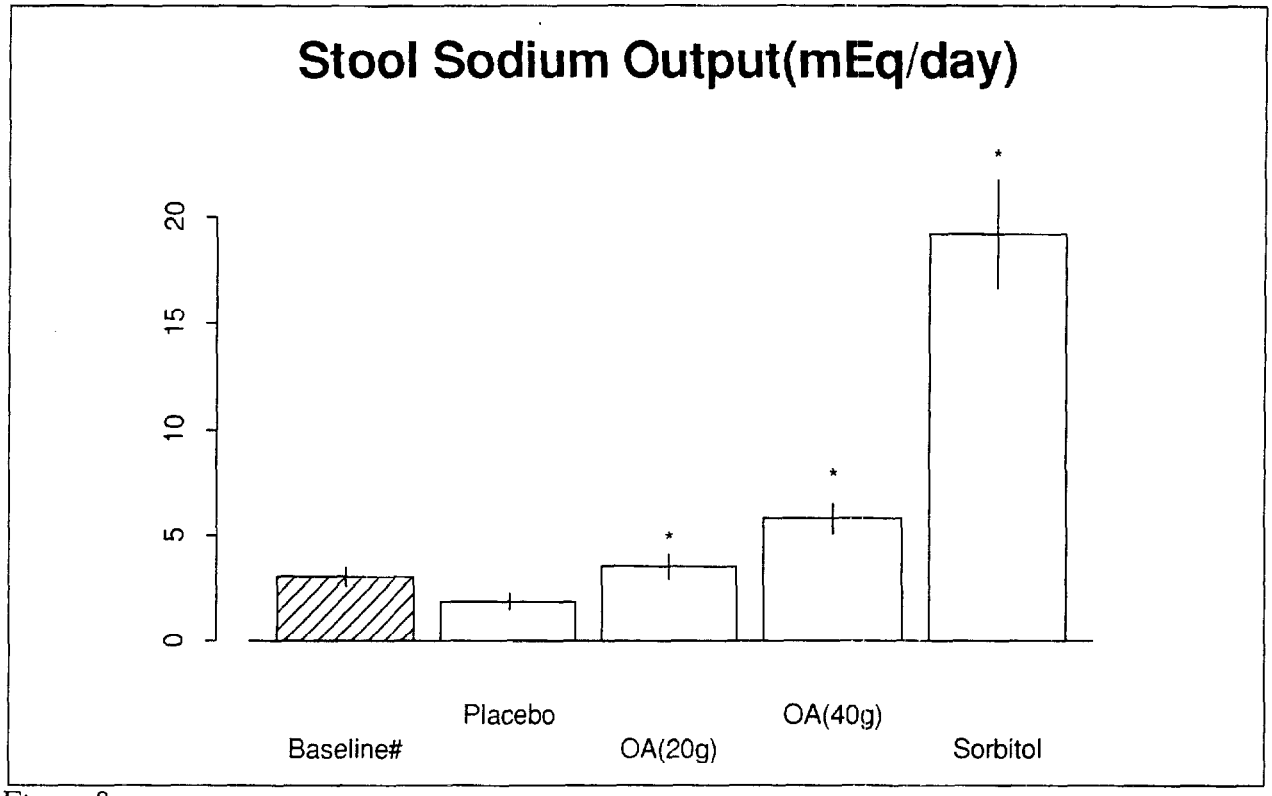


Figure 8

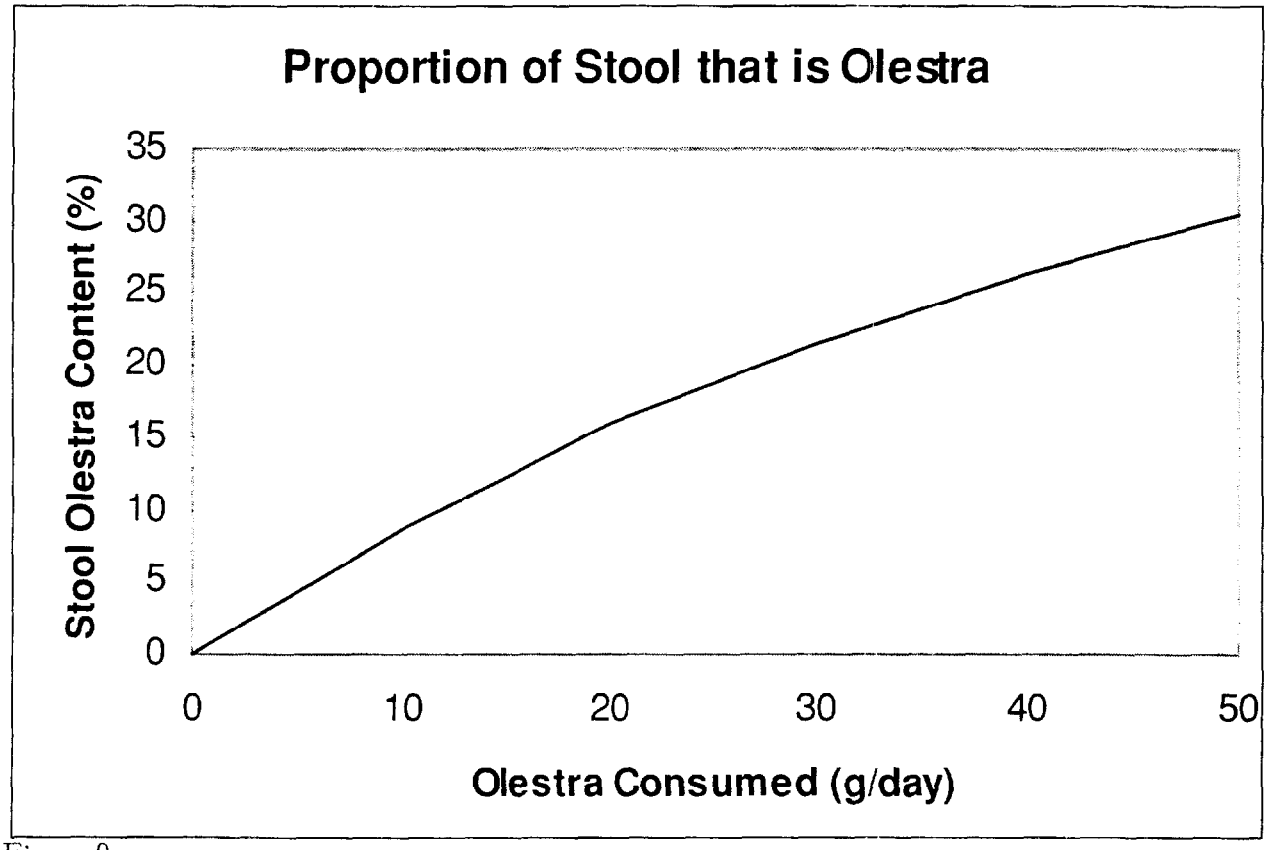


Figure 9

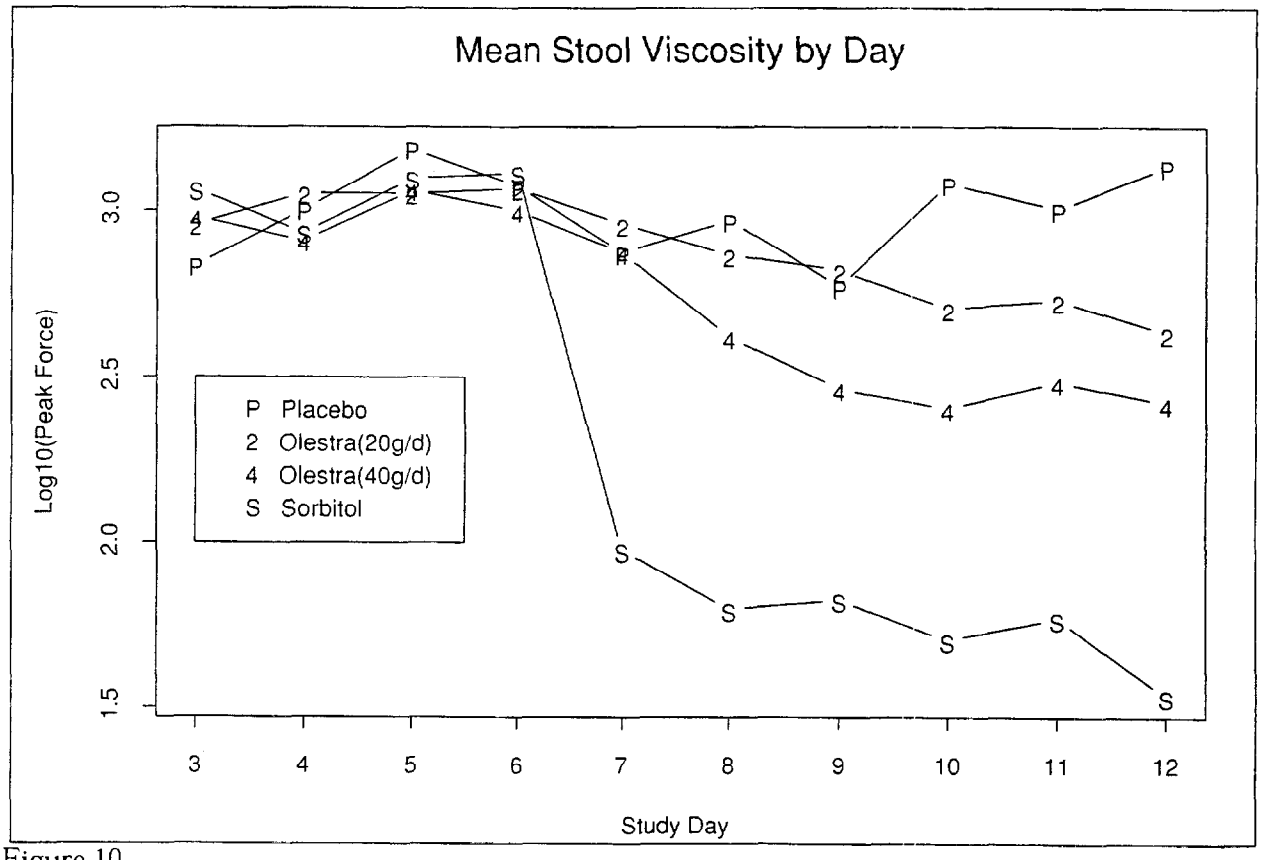


Figure 10

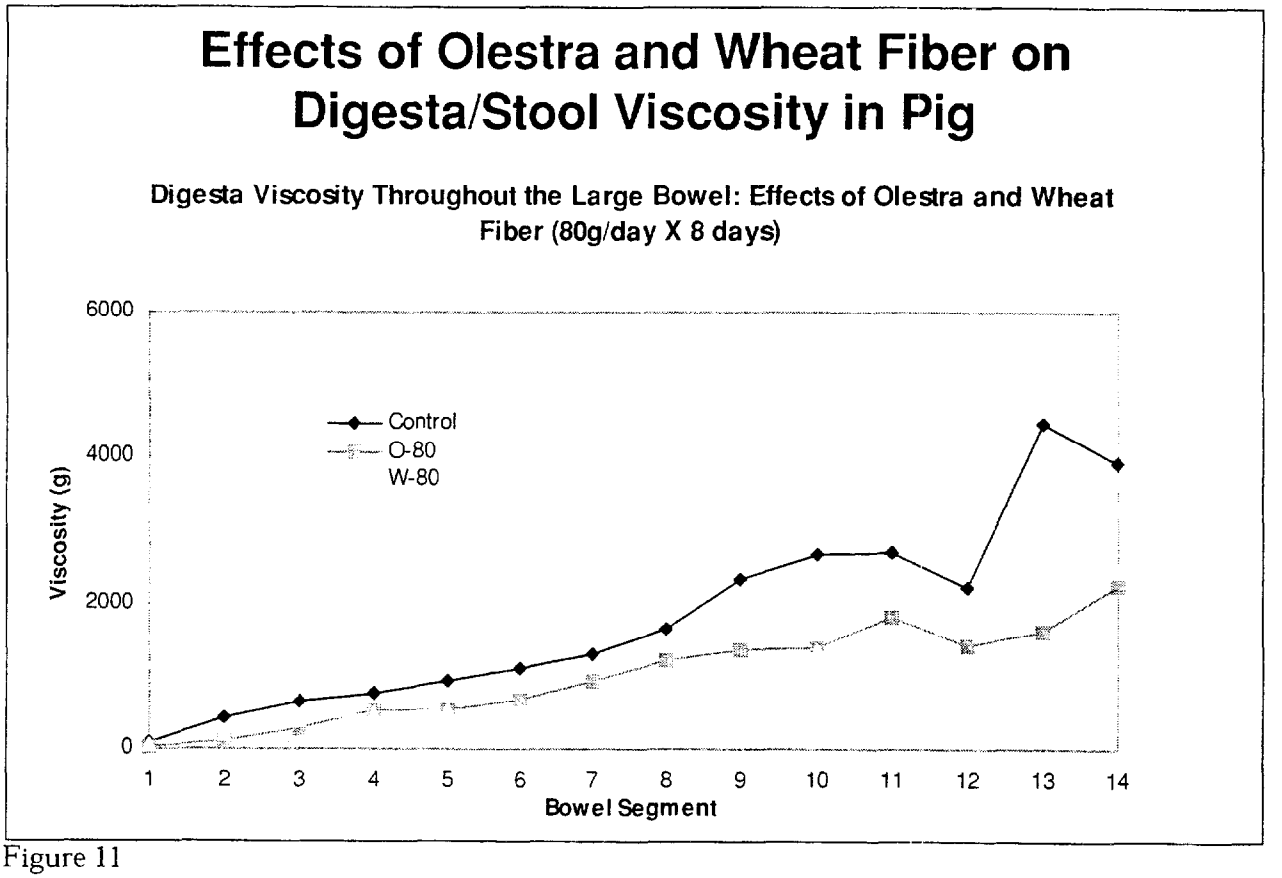


Figure 11

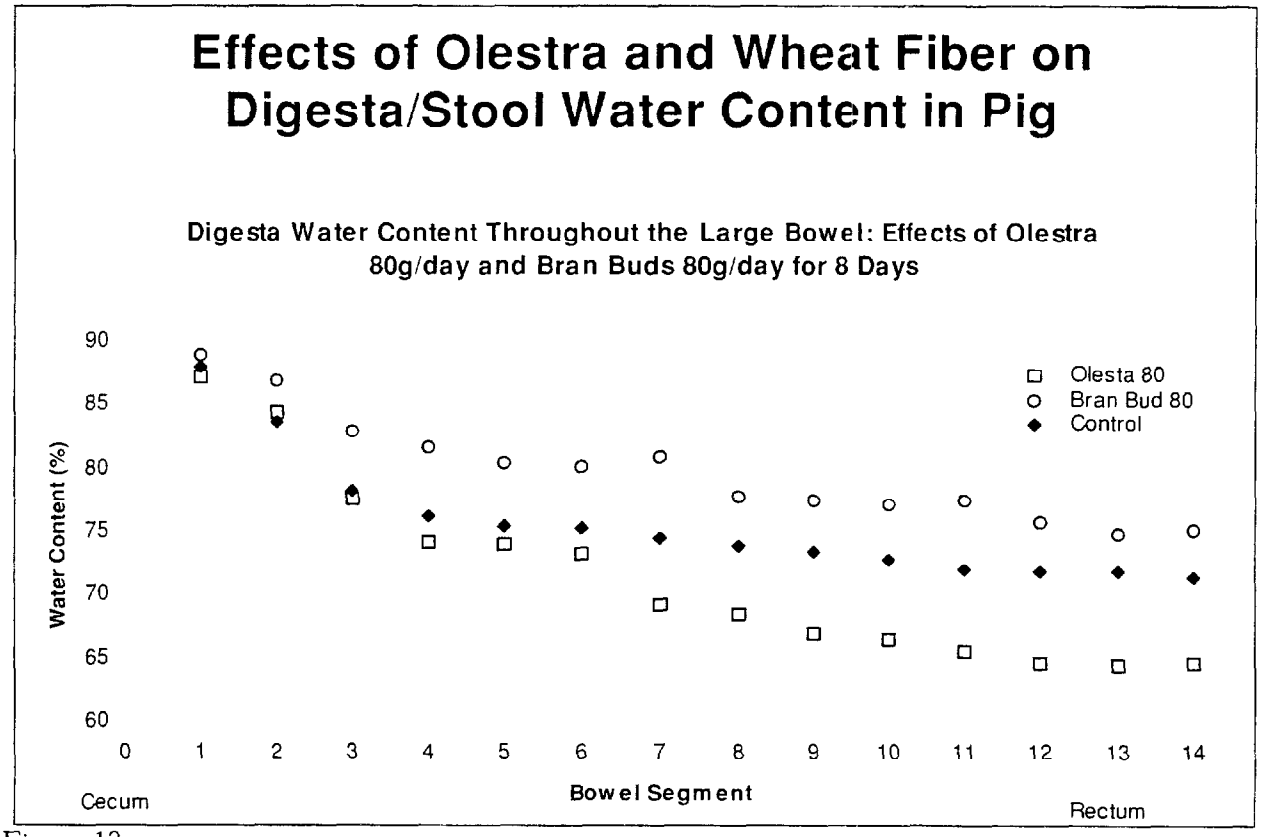


Figure 12

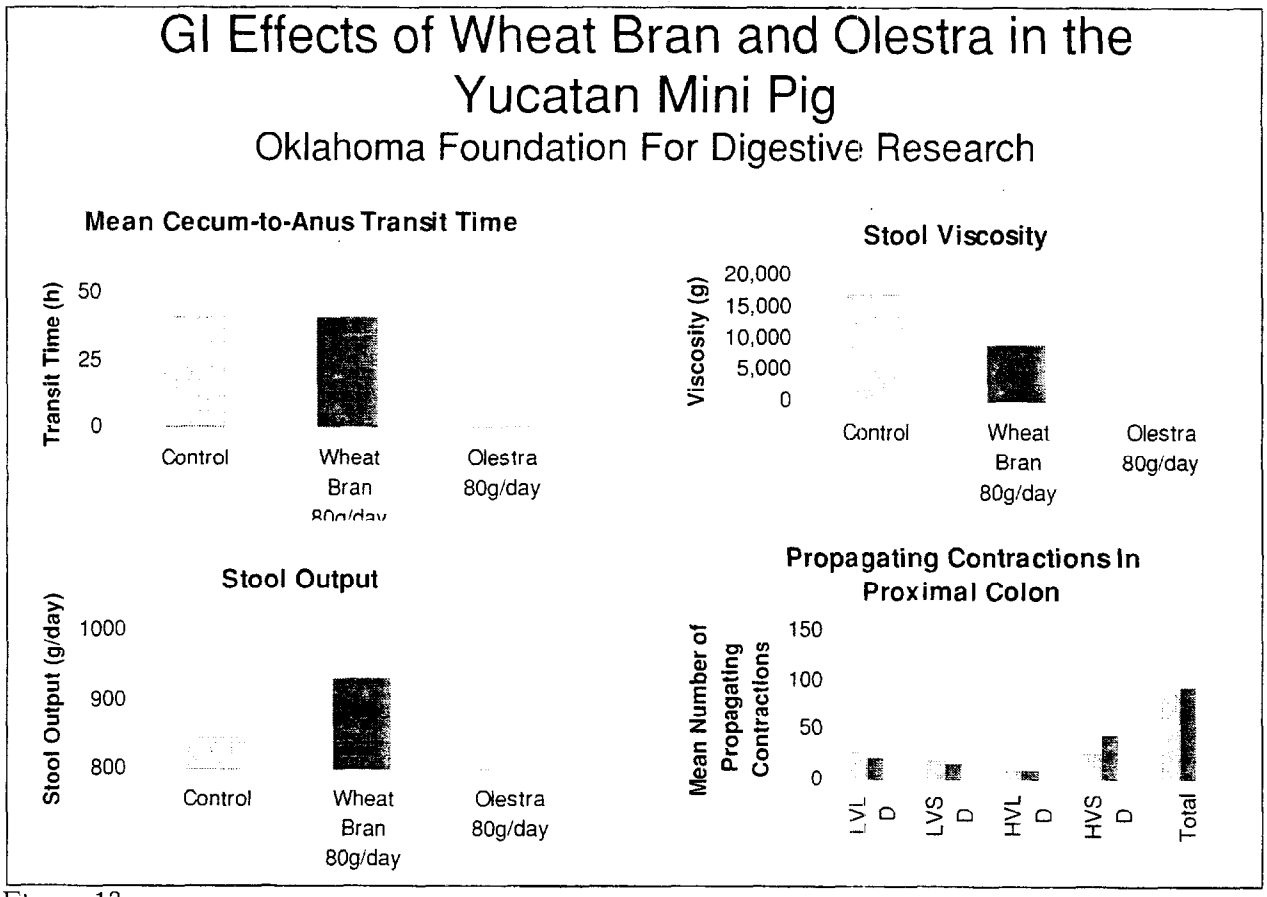


Figure 13

Conclusions

- Consumption of olestra:
  - does not cause diarrhea
  - results in predictable, dose-responsive stool softening similar to the effects of dietary fiber

Figure 14

Final Report: Stool Composition and Consistency in Humans Consuming Olestra

Sponsor	The Procter & Gamble Company Winton Hill Technical Center 6071 Center Hill Avenue Cincinnati, Ohio 45224
Gastrointestinal Consultant	Ralph A. Giannella, M.D. Mark Brown Professor of Medicine Director, Division of Digestive Diseases College of Medicine University of Cincinnati Cincinnati, Ohio
Contract Research Organization	Phoenix International Life Sciences, Inc. 5642 Hamilton Avenue Cincinnati, Ohio
Principal Investigator	Suman Wason, M.D Medical Director
Laboratories	Hill Top Research, Ltd. 900 Osceola Drive West Palm Beach, Florida Mayo Medical Laboratories 200 First Street, S.W. Rochester, Minnesota Health Alliance Laboratories 3200 Burnet Avenue Cincinnati, Ohio
Study Number	Procter & Gamble Study Number FP148
Sponsor's Study Personnel	Project Manager: John W. McRorie, Ph.D. Project Physician: Nora L. Zorich, M.D., Ph.D. Clinical Monitor: Karen A. Riccardi, B.S. Project Statistician: Thomas G. Filloon, Ph.D.
Study Dates	April 29, 1997 to June 22, 1997

Final Report - Stool Composition and Consistency in Humans Consuming Olestra

Table of Contents

	Page
Summary	7
Introduction	12
Study Objectives	14
Regulatory Compliance	15
Study Design	16
Overall Design of the Study	16
Treatment Assignment and Blind	17
Study Site and Investigator	17
Subject Selection	18
Inclusion/Exclusion Criteria	18
Subject Assignment and Identification	18
Rationale for Study Design	18
Materials and Methods	19
Test Products	19
Administration of Test Products	19
Measurement of Test Product Consumption	19
Measurement of Stool Content and Consistency	20
Measurement of Gastrointestinal Symptoms	20
Adverse Experience Reporting Procedures	20
Statistical Methods	21
Results	22
Subject Demographics	22
Subject Compliance	23
Protocol Deviations	23
Adverse Events	24
Objective Measures	24
Individual Stool Weight, Stool Water Content	24
Daily Total Stool Output	25
Daily Stool Water Output	25
Daily Stool Electrolyte Output	25
Stool Consistency	25
Bowel Movement Frequency	26
Subjective Ratings	26
Reports of Diarrhea	26
Gastrointestinal Symptoms	27
Concomitant Medications	28

Table of Contents - (cont'd)

	Page
Discussion	29
Conclusions	33
Signatures	34
References	35

Table of Contents - (cont'd)

Exhibits

		Page
Exhibits		147
Exhibit 1	Mean Stool Weight (g/BM)	148
Exhibit 2	Percent Water Content (%/BM)	149
Exhibit 3	Total Stool Output (g/d)	150
Exhibit 4	Mean Stool Responses	151
Exhibit 5	Total Stool Water Output (g/d)	152
Exhibit 6	Stool Water Output (g/d)	153
Exhibit 7	24-Hour Stool Water Output and BM Rating for All Subjects by Treatment	154
Exhibit 8	Stool Electrolytes	155
Exhibit 9	Mean Stool Consistency (Peak force, g)	156
Exhibit 10	Mean Stool Consistency over Time	157
Exhibit 11	Mean Stool Responses (BM Frequency/Day)	158
Exhibit 12	24-Hour Frequency of BMs During Treatment Phase	159
Exhibit 13	Distribution of Subjective BM Rating During Treatment Phase	160
Exhibit 14	Distribution of Stool Viscosity Values by Subjective BM Rating	161
Exhibit 15	GI Symptom Frequency	162
Exhibit 16	GI Symptom Severity	163

Table of Contents - (cont'd)

Exhibits

		Page
Exhibit 17	Percentage of Subjects Reporting Abdominal Cramping by Study Day	164
Exhibit 18	Mean Severity of Subjects Reporting Abdominal Cramping by Study Day	165
Exhibit 19	Percentage of Subjects Reporting Urgency by Study Day	166
Exhibit 20	Mean Severity of Subjects Reporting Urgency by Study Day	167

Table of Contents - (cont'd)

Appendices*

		Page
Appendices		168
Appendix 1	Study Protocol, Informed Consent, and Institutional Review Board Approval Letter	169
Appendix 2	Peak Force for Extrusion Correlated with Viscosity	206
Appendix 3	Case Report Forms	208
Appendix 4	Adverse Events	231
Appendix 5	Concomitant Medications	249
Appendix 6	Abstracts	252
Appendix 7	Curriculum Vitae	255
Appendix 8	Investigator's Clinical Report	305
Appendix 9	References for Stool Viscosity Measurement Techniques	322
Appendix 10	Electronic Data and Disk	368

* Appendices were submitted directly to the FDA's Office of Premarket Approval and portions may be requested by way of the Freedom of Information Act.

Stool Composition and Consistency in Humans Consuming Olestra

Summary

The most commonly used determinants of clinical diarrhea are: an increase in stool output and stool water output/electrolyte output, a significant decrease in stool viscosity, and an increase in bowel movement (BM) frequency. While no universally accepted values defining diarrhea exist, standard medical textbooks offer accepted measurements as guidelines: 1) increased stool output (>200-250g/d, varying greatly with dietary fiber intake); 2) watery, difficult to control bowel movements (qualitative assessment only); and 3) bowel movement frequency exceeding 3 BMs/d. All three of these measures directly or indirectly are intended to gauge the magnitude of stool water and stool electrolyte output, which is the primary concern of clinical diarrhea. The aim of this study was to determine the effects of olestra consumption on all three measures of diarrhea, with an emphasis on the measures indicative of clinical diarrhea: stool water and stool electrolyte output.

The effects of olestra 20g/d and olestra 40g/d on stool composition and consistency were assessed in a double-blind, placebo-controlled clinical trial. The study was designed to determine the relationship between three objective measures, (stool water and electrolyte content, stool consistency, and total daily stool output) and subjective reporting of 'diarrhea' by comparing and contrasting the effects of olestra, a non-absorbed oil, to placebo and sorbitol, a poorly absorbed sugar-alcohol (with known osmotic laxative effects) marketed as a 'sugar-free' sweetener. This study also compared objective measures of stool viscosity and stool composition (e.g. water, electrolytes) with subjective gastrointestinal (GI) experiences (e.g. complaints of cramping, passing gas, bloating).

Methods Sixty-six subjects were housed on a metabolic ward for 12 days and consumed meals *ad libitum* which conformed to AHA Step I diet guidelines (no more than 30% of calories from fat). Beverages were available *ad libitum*. Subjects were required to consume all test products each day. Subjects were fed test snacks as given in the study design (Summary Table 1).

Summary Table 1

Study Design

	2-day lead-in	4-day baseline	6-day treatment
	Days 1, 2	Days 3, 4, 5, 6	Days 7, 8, 9, 10, 11, 12
	Adapt to diet and housing	All stools and symptoms collected	All stools and symptoms collected
Placebo n = 12	*conventional candy & chips*	*conventional candy & chips*	*conventional candy & chips*
Olestra 20g/d n = 18	*conventional candy & chips*	*conventional candy & chips*	*conventional candy* ½ olestra chips + ½ *conventional chips*
Olestra 40g/d n = 18	*conventional candy & chips*	*conventional candy & chips*	*conventional candy* olestra chips
Sorbitol 40g/d n = 18	*conventional candy & chips*	*conventional candy & chips*	sorbitol candy *conventional chips*

Conventional candy and potato chips were selected to closely match appearance and taste of treatment products. All snacks and candies were sealed in plain white foil packets for blinding and freshness. Access to the bathroom was controlled and stool samples were collected in pre-weighed air-tight containers. All stools (1098 samples) were assessed objectively by monitoring rheology (peak force for extrusion), weight and water content. For each subject, stools were pooled across 24 hours for electrolyte measurements. In addition, the consistency of each stool was visually rated by a technician (Johns Hopkins Stool Description Visual Scale) and each BM was rated by the subject using a 7-point scale. Gastrointestinal (GI) experiences were captured by daily diary. Stool electrolyte measurements were conducted at the Mayo Medical Laboratories, Rochester, MN, while stool water was measured at Hilltop Research, Ltd., West Palm Beach, FL.

Results

Demographics. The 66 subjects in the study ranged in age from 18 to 74 years, with a mean age of 39. There were 31 males and 35 females. Fifty of the subjects were Caucasian, 15 African-American and one Asian. Five subjects did not complete the study.

In the sorbitol 40g/d treatment group, subject 112 was dropped on day 8 due to non-compliance (did not consume candy) following diarrhea symptoms (10 BMs/d after first dose of sorbitol). Subject 305 withdrew on day 10 following complaints of passing gas, heartburn, abdominal pain and diarrhea beginning study day 8. Subject 406 withdrew on day 9 after reporting sore throat and vomiting on day 8.

In the olestra 20g/d treatment group, subject 215 withdrew on day 7, prior to the first dose of olestra, due to symptoms of dizziness on day 3, abdominal cramps beginning day 4 (continuing for approximately two weeks), and vomiting on day 4.

In the olestra 40g/d treatment group, subject 217 withdrew on day 11 due to menorrhagia.

Stool Water and Electrolytes. Stool samples from each subject for each 24-hour period were assessed for stool water content. Stool water output (g/d) results are summarized in Summary Table 2. Compared to baseline, mean stool water output increased 8.8g/d with olestra 20g/d, 37.4g/d with olestra 40g/d, and 345.9g/d with sorbitol 40g/d. Stool water output decreased 27.5g/d for placebo. Subjects occasionally exceeded 250g stool water output in 24 hours during baseline, and during placebo and olestra treatment periods. A majority of subjects consuming sorbitol 40 g/d exceeded 250g stool water output in 24 hours. Stool electrolyte output was consistent with stool water output.

Summary Table 2

Total Stool Water Output (g/d)

		Placebo	Olestra 20 g/d	Olestra 40 g/d	Sorbitol 40 g/d
		(*n*=12)	(*n*=18)	(*n*=18)	(*n*=18)
Baseline Phase	Mean	109.0	110.4	110.2	82.8
	Std Error	9.0	13.8	11.4	11.6
Change from Baseline	Mean	-27.5	8.8	37.4	345.9
	Std Error	10.3	8.9	11.1	47.0
Treatment Phase	Mean*	81.5	129.6	147.6	407.7
	Std Error	15.3	14.7	12.3	48.8

(*mean values in the treatment phase may differ from the sum of mean baseline values plus mean change from baseline because some subjects included in baseline calculations did not complete the entire treatment phase)

Stool Consistency. The consistency of each stool sample was measured as 'peak force for extrusion' employing a Steven's QTS 25 Texture Analyzer and was evaluated subjectively by a technician using the Johns Hopkins Stool Description Visual Rating Scale. Johns Hopkins visual

ratings correlated well with mechanical measures of stool viscosity (g of peak force) (i.e., peak force between 2651-1131g = firm/formed stool, 1047-425g = soft/less formed stool, 315-68g = runny/loose stool, and <68g = liquid/rice-water stool). Mean stool consistency was comparable and constant for all treatment groups during baseline. Mean peak force for extrusion for the placebo group was 1363g (firm, formed stool). Olestra exhibited a gradual dose-responsive, stool-softening effect after 2-4 days of consumption. Mean peak force across the 6-day treatment period for olestra 20g/d and olestra 40g/d decreased to 'soft/less formed' stool (mean = 743.3g and 563.3g peak force, respectively). There were no liquid/rice-water BMs (<68g peak force) in the olestra 20g/d treatment group, and the placebo and olestra 40g/d group had only one liquid BM each. In contrast, subjects in the sorbitol 40g/d treatment group experienced a total of 145 liquid/rice-water BMs over the 6-day treatment period, 140 of which were of sufficient sample size to be evaluable. Mean stool consistency decreased to 'runny, loose' the first day of treatment and all subsequent days for the sorbitol 40g/d treatment group (mean = 249g peak force).

BM Frequency. Mean bowel movement frequency throughout the study was ≤ 3 BMs/d for all treatment groups. During the baseline period and treatment days, individual subjects in all groups experienced occasional days when BM frequency exceeded 3 BMs/d (maximum = 10 BMs/d; sorbitol).

Reports of Diarrhea. Each BM was rated by the subject on a 7-point scale (1 = watery, difficult to control diarrhea; 7 = hard, difficult to pass constipation). Mean BM ratings were: 3.9 for placebo, 3.1 for olestra 20g/d, 2.4 for olestra 40g/d, and 1.5 for sorbitol 40g/d. Stool water output for subjects consuming olestra did not increase above levels observed in baseline and placebo treatment phases, even though subjects reported some of these BMs as 'diarrhea'.

Gastrointestinal Symptoms. Self-assessed gastrointestinal experiences were collected by means of a diary. There were no obvious differences noted among the groups for bloating, passing gas, or heartburn. Sorbitol, but not olestra, significantly increased the frequency and severity of nausea compared to placebo. The frequency and severity of reports of abdominal cramping and urgency increased proportional to decreases in stool viscosity.

Olestra 20g/d, which exhibited a slight stool softening effect, did not increase the frequency or severity of reports of abdominal cramping compared to placebo, suggesting that there is a threshold for inducing GI symptoms associated with decreases in stool viscosity. For olestra 40g/d, the frequency of reports of mild to moderate abdominal cramping showed an increase on days 9 and 10 (50.0% and 55.6% of subjects, respectively), returning to baseline levels for the final two days of study, which was consistent with gradual stool softening after several days of consumption. There were no reports of severe abdominal cramping with the olestra 40g/d treatment group.

For sorbitol 40g/d, reports of abdominal cramping increased to 66.7% of subjects and severity increased to 'moderate' the first day of dosing and remained higher than placebo each subsequent day, which was consistent with the rapid-onset decrease in stool consistency. Baseline rates for abdominal cramping were as high as 33% of subjects, supporting the concept that a significant portion of the general population normally experiences GI symptoms.

Conclusions

- Subject reports of 'diarrhea' associated with olestra consumption were not associated with any meaningful or clinically significant increases in fecal water or electrolyte output.

- Consumption of sorbitol 40g/d resulted in rapid-onset liquid/rice-water stools and an increase in mean stool water output of 345.9g /d (approximately 10 ounces/day).

- Consumption of olestra resulted in a dose-responsive, gradual stool softening effect after several days of consumption.

- The transient increase in incidence of reports of mild to moderate abdominal cramping noted on some of the treatment days in subjects consuming 5 ounces of chips (40g/d olestra) for 6 consecutive days was associated with decreases in fecal consistency. These effects were not severe, pose no risk to health and were not unique to olestra as similar effects were noted in all treatment groups and during baseline.

Final Report - Stool Composition and Consistency in Humans Consuming Olestra

Introduction

The effects of olestra 20g/d and olestra 40g/d on stool composition and consistency were assessed in a double-blind, placebo-controlled clinical trial. The study was designed to determine the relationship between three objective measures (stool water content, stool consistency, and total daily stool output), and subjective reporting of 'diarrhea' by comparing and contrasting the effects of olestra, a non-absorbed oil, to placebo and sorbitol. This study also compared objective measures of stool viscosity and stool composition (e.g. water, electrolytes) with subjective GI experiences (e.g. complaints of cramping, passing gas, bloating).

Olestra, a mixture of hexa, hepta and octa sucrose polyesters, is a lipid that possesses physical and organoleptic properties of conventional fats and oils, but is neither digested nor absorbed. Olestra was approved by the US Food and Drug Administration in January, 1996, for use in savory snacks such as potato chips, tortilla chips and crackers. Studies in humans have demonstrated that after single eating occasions and typical snack eating simulations, there is little to no difference between the frequency of reporting of meaningful gastrointestinal symptoms or effects when consuming chips made with olestra or conventional fat. In a large, well-controlled study where subjects consumed 34 g/d of olestra for five consecutive days, there were no statistical differences in reporting rates of diarrhea, loose stools or abdominal cramping (1). In a recent double-blind, randomized study, 1136 participants, ranging in age from 13 to 88 years, ate as much as they wanted of a 13 ounce bag of chips made with olestra or conventional fat. Gastrointestinal symptoms were monitored three to five days later. There was no difference in the incidence of reporting of gastrointestinal symptoms overall, or any individual gastrointestinal symptom (2).

In placebo-controlled studies where olestra was consumed in various foods at daily consumption levels of about 20 g/d for 16 weeks in normal healthy subjects (3), and for four weeks in persons with inflammatory bowel disease (4), there were no differences in reporting rates between the groups of any gastrointestinal symptoms including diarrhea or abdominal cramping, except for more reports of minor changes in stool frequency or stool character by subjects with inflammatory bowel disease when they ate foods made with olestra. Importantly, these changes were not characterized as diarrhea by these inflammatory bowel disease patients (4). In an extended-use, market simulation study where participants had chips available in the home for up to five months, there were no differences in rates of reports of diarrhea or abdominal cramping (5).

In two eight-week chronic dosing studies, subjects were required to consume foods made with olestra at each meal for 56 consecutive days (168 consecutive meals) at daily doses of 8, 20 and 32 g/d (6,7). In these studies there were increases in abdominal cramping and diarrhea/loose stools reported by some individuals consuming 20 and 32 g/d. Symptom onset, when it was noted, was generally observed after several days of olestra consumption.

Symptoms were usually intermittent with the exception of a few individuals who reported mild to moderate symptoms during most of the study. All persons describing chronic symptoms were evaluated by the physician at the study site and found to have normal physical examinations and normal laboratory findings (i.e., no evidence of dehydration or electrolyte disturbance). It is noteworthy that no one elected to drop from these studies because of loose stools, diarrhea, abdominal pain or cramping. Although these symptoms were increased in the 8-week studies at the 20 and 32 g/d consumption level, in a 14-day study conducted concurrently with the same doses of olestra fed at every meal, there was no dose-related increase in abdominal cramping or diarrhea (8).

Sorbitol, a hexahydric alcohol with known osmotic laxative effects, was used as a positive control in this study to verify the sensitivity of the methods used to detect stool water output (9). Sorbitol is a normal constituent of many fruits, such as cherries, plums (prunes), pears and apples, and, in the food industry, sorbitol is used as a sweetener and to improve the quality, texture and shelf-life of foods. Sorbitol is present in foods such as hard and soft candy, chewing gum, baked goods, dairy products, and poultry, fish and meat products. Sorbitol is Generally Recognized As Safe (GRAS) by the Food and Drug Administration (FDA). Foods that contain sorbitol in amounts that are likely to be consumed in excess of 50 g of sorbitol per day are required to have a label stating "Excess consumption may have a laxative effect". The dose used in this study was less than the dose requiring that label.

As with any substance that exhibits limited or no absorption by the small bowel, olestra and sorbitol, delivered to the large bowel in sufficient quantities, have the potential to affect stool quantity and consistency. Sorbitol exerts a laxative effect by generating an osmotic gradient that overcomes the large bowel's ability to reabsorb water from the digesta. Ingestion of sorbitol leads to an osmotic diarrhea at higher doses. The mechanism for reports of 'diarrhea' observed with ingestion of chronic high doses of olestra is believed to result from a non-osmotic alteration in stool consistency that does not result in clinically significant stool water output. This study was designed to determine the relationship between subjective reports of 'diarrhea' and objective measures of stool consistency and water/electrolyte content of stools with 20g/d and 40g/d olestra ingestion, and to compare these objective measures to the osmotic watery-diarrheal stools observed with moderate sorbitol ingestion.

Study Objectives

This study examined the dose response of olestra consumption at 20g/d and 40g/d on objective measures of stool water content, stool consistency, as well as total daily stool output, and compared these measures with reports of "diarrhea". This was accomplished by comparing and contrasting the effects observed with olestra ingestion to the osmotic (water and electrolyte) effects observed with moderate doses of sorbitol.

This study also examined the relationship between objective measures of stool content (water, electrolytes) and consistency and subjective gastrointestinal experiences (e.g. reports of gas, bloating, abdominal cramping) between treatment groups.

Regulatory Compliance

This study was conducted in compliance with the United States Code of Federal Regulations, Title 21, Part 50 (Informed Consent of Human Subjects), Part 56 (Institutional Review Boards), and Part 312 (Good Clinical Practice [GCP] Regulations).

Study Design

Overall Design of the Study

This was a single-site, double-blind, placebo-controlled parallel clinical trial. Sixty-six subjects, ages 18 to 74, were housed on a metabolic ward for 12 days and consumed meals *ad libitum* which conformed to AHA Step I diet guidelines (no more than 30% of calories from fat). Beverages were available *ad libitum*. Subjects were required to consume all test products each day. The study design is presented in Table 1. The first two days (study days 1-2) were a lead-in period during which subjects were acclimated to the living conditions and diet and consumed placebo snacks (triglyceride potato chips and sucrose candies). Stool samples were not collected during the lead-in period. The next four days (study days 3-6) comprised the baseline period, in which subjects continued to consume placebo snacks, and all stool samples, bowel movement (BM) ratings and gastrointestinal (GI) symptoms were collected. For the final 6 days (study days 7-12) subjects consumed snacks according to their randomly assigned treatment group, and all stool samples, BM ratings, and GI symptoms were collected. The study protocol, informed consent, and Institutional Review Board (IRB) are provided in Appendix 1.

Table 1

Study Design

	2-day lead-in	4-day baseline	6-day treatment
	Days 1, 2	Days 3, 4, 5, 6	Days 7, 8, 9, 10, 11, 12
	Adapt to diet and housing	All stools and symptoms collected	All stools and symptoms collected
Placebo n = 12	*conventional candy & chips*	*conventional candy & chips*	*conventional candy & chips*
Olestra 20g/d n = 18	*conventional candy & chips*	*conventional candy & chips*	*conventional candy* ½ olestra chips + ½ *conventional chips*
Olestra 40g/d n = 18	*conventional candy & chips*	*conventional candy & chips*	*conventional candy* olestra chips
Sorbitol 40g/d n = 18	*conventional candy & chips*	*conventional candy & chips*	sorbitol candy *conventional chips*

Treatment Assignment and Blind

Sixty-six adult subjects were enrolled and randomly assigned to one of four treatment groups, balanced with respect to age and sex (olestra and sorbitol treatment groups had 18 subjects each, the placebo treatment group had 12 subjects). All treatments were delivered in the form of snacks. Olestra snacks (potato chips) and sorbitol snacks (candy) had corresponding placebo snacks selected from marketed conventional products (triglyceride potato chips and sucrose candies) to match the appearance and characteristics of the olestra and sorbitol snacks to maintain the study blind. The study was double-blinded: snacks were delivered sealed in white foil packets with tear-off blinded labels, and all study personnel (investigator and sub-investigators, study staff, and subjects) associated with the collection, processing or analysis of the data were blinded to the treatment assignment. The sponsor's project manager, project physician, project monitor, project data manager and the project statistician were also blinded to the treatment assignment.

Study Site and Investigator

The study site was Phoenix International Life Sciences (US), Inc. (5642 Hamilton Avenue Cincinnati, Ohio). The Principal Investigator was Suman Wason, M.D., the Medical Director for Phoenix International. Dr. Wason was responsible for the overall conduct of the investigation, ensuring that the study was conducted in accordance with the protocol. The GI consultant, Ralph Giannella, M.D. (Director, Division of Digestive Diseases, College of Medicine, University of Cincinnati, Cincinnati, OH), is an expert in the field of gastroenterology and diarrhea, and worked closely with the project team on protocol design and the interpretation and publication of results. Dr. Giannella also met with Dr. Wason at the Phoenix International study site to confer on the execution of the study and observe laboratory procedures. The clinical study was reviewed and approved by an independent Institutional Review Board, Schulman Associates, Institutional Review Board, Inc. (Cincinnati, OH). Admission clinical laboratory studies (e.g. serum chemistry, hematology, urinalysis, etc.) were processed by Health Alliance Laboratories (3200 Burnet Avenue, Cincinnati, Ohio).

Subject Selection

Inclusion/Exclusion Criteria

The study was open to all subjects 18 or older who did not have conditions that might preclude participation in a controlled feeding/stool collection study (e.g. recent GI surgery, moderate/severe constipation: since constipated subjects would likely not produce sufficient quantities of stool for analysis, special dietary requirements not provided in protocol, or who were unwilling to follow the protocol.

Subject Assignment and Identification

Subjects were randomly assigned to one of four treatment groups which were balanced for gender and age. Treatment assignment was based upon a randomization scheme supplied by the project statistician. In order to insure appropriate rapid handling of stool samples, subjects were tested under the protocol in multiple cohorts of no more than 20 subjects each. Each subject was assigned a three digit number, which, when used in conjunction with the five characters of the protocol number and the four-digit investigator number, uniquely identified that subject. Within each cohort, subject numbers were assigned in consecutive order beginning with 101 for cohort 1, 201 for cohort 2, 301 for cohort 3, and 401 for cohort 4, to each subject who signed an informed consent statement for this study. This number remained with the subject throughout this study and was used in all references to the subject on the study.

Rationale for Study Design

The 20g/d olestra dose exceeds the chronic daily intake of the highest consuming age/gender population sub-group based on Market Research Corporation of America (MRCA) data (10), and represents the 'worst-case' chronic consumption value predicted by the Food and Drug Administration (11). The 40g/d olestra dose exceeds the chronic daily intake of the highest consuming subgroup by several fold based on MRCA data (10) and is twice the 'worst-case' chronic consumption value predicted by the Food and Drug Administration (11). The potato chips were delivered as two, closely spaced afternoon snacks due to the large volume (approximately 5 ounces of potato chips). Olestra 20g/d was delivered as a single dose in the first afternoon snack, followed by placebo chips in the second afternoon snack. Olestra 40g/d was delivered as two 20g doses. The positive control, sorbitol 40g/d, has known osmotic laxative effects and represents 80% of the ED50 (50kg individual) for sorbitol-induced diarrhea (ED50 for laxation is 1g/kg/d body weight)(9). The sorbitol dose represents the amount of sorbitol contained in approximately 1.7 ounces of Smarties® and was delivered in one serving each morning.

Materials and Methods

Test Products

The olestra test product was potato chips prepared with olestra. Potato chips were chosen because they are available in the marketplace and they elicit good compliance. The olestra potato chips were Frito-Lay Ruffles WOW® brand chips. The corresponding conventional potato chips were Frito-Lay Ruffles Reduced Fat® brand potato chips. The reduced fat chips were selected to minimize fat-induced GI symptoms and attenuate the appetite suppressing effects of the high fat and calorie load of placebo snacks, allowing subjects to consume a healthy AHA Step I diet. The sorbitol test product was Smarties® sugar-free candies and the placebo was the corresponding sucrose containing Smarties® candies. Both are produced by CeDe Candy, Inc., and are widely available in the marketplace.

Products were purchased and repackaged in plain, food grade bags made of white foil laminate. Each bag was labeled with a declaration of contents, subject identification number, and a statement that the contents were for research purposes only. A tear-off portion of the label contained the same information on the outside, with a sealed pouch that listed the unblinded contents of the bag. The olestra chips were analyzed for olestra content and packaged by weight to deliver a minimum of 20 g of olestra per single serving bag. The conventional potato chips were packaged to the same weight. The sorbitol candies were analyzed for sorbitol content (mean 86% sorbitol by weight) and packaged to deliver a minimum of 40 g of sorbitol per single serving of candy. The sucrose containing candies were packaged to the same weight.

Administration of Test Products

During the 2-day lead-in and 4-day baseline phases, all subjects received placebo candy for the morning snack (10:00AM) and placebo potato chips for the two afternoon snacks (2:30PM and 5:00PM). During the treatment phase, the placebo treatment group received placebo potato chips and candy; the olestra 20g/d treatment group received placebo candy for the morning snack, olestra chips for the first afternoon snack and placebo chips for the second afternoon snack; the olestra 40g/d treatment group received placebo candy for the morning snack and olestra chips for both afternoon snacks; and the sorbitol 40g/d treatment group received sorbitol candy for the morning snack and placebo chips for both afternoon snacks.

Measurement of Test Product Consumption

All potato chips were weighed before, and any residual chips were weighed after, the snack period and the actual olestra or conventional fat intake was calculated for each subject. All candy was weighed before, and any residual candy was weighed after, the snack period and the actual sorbitol or conventional sugar intake was calculated for each subject. Subjects were considered to be 'evaluable' if they consumed at least 90% of the assigned active treatment material.

Measurement of Stool Content and Consistency

All stool was collected with each bowel movement by each subject in pre-weighed/labeled stool collection containers. Subjects were instructed to keep the stool sample free of urine and toilet paper. Each stool specimen was returned to study personnel, weighed, and graded for stool consistency using a subjective score (Johns Hopkins Stool Description Visual Rating Scale) (12), and an objective measure of viscosity (Stevens Texture Analyzer) (13). The Johns Hopkins Stool Description Visual Rating Scale was developed at Johns Hopkins University to visually grade stools in diarrhea studies (12). The Stevens QTS25 Texture Analyzer is a rheometer that was used to determine peak force for extrusion (proportional to viscosity, Appendix 2) of stool samples. The Stevens QTS-25 Texture Analyzer was selected for this study because it is capable of analyzing all stool consistencies, from liquid to solid (13), and it requires minimal training/expertise to operate. After determination of stool consistency, each BM was returned to its' zip-lock bag and homogenized by kneading the sealed zip-lock bag. An aliquot of stool was collected from the homogenized sample, frozen and shipped on dry ice to Hill Top Research, Ltd., West Palm Beach, Florida, for determination of stool water content for each BM. A second aliquot of stool was frozen and shipped on dry ice to Mayo Clinical Laboratories, Rochester, Minnesota, where it was pooled as a 24-hour sample for each subject and stool electrolytes (sodium, potassium and chloride) were determined.

Measurement of Gastrointestinal Symptoms

With each bowel movement, subjects completed a bowel movement description card, on which they could rate their bowel movement on a 7-point scale (1 = watery, difficult to control diarrhea, 4 = normal, 7 = hard, difficult to pass constipation) (Appendix 3). These data facilitated comparisons of the subject's perception of the BM with objective measures of stool consistency and stool water content. Subjects also recorded gastrointestinal symptoms on a daily basis in a self-administered diary (completed each morning for the previous 24-hours) (Appendix 3), facilitating comparisons of GI symptom frequency and severity with objective stool measures.

Adverse Experience Reporting Procedures

Adverse experiences were assessed from the time the subject signed the informed consent on day 0 until exit from the study. At the same time every day, subjects were asked a standard question to elicit any medically related (i.e., pain, discomfort, etc.) changes in their well-being. Subjects were instructed to report any medically related changes in their well-being to study personnel. Gastrointestinal symptoms reported by the subject on the GI diary or BM Description Card were not also recorded as adverse experiences unless they were voluntarily reported to study personnel. Any adverse experiences reported by the subjects or noted by study personnel were recorded on an Adverse Experience form (Appendix 3). This form described the event or condition, date of onset, severity, duration, and the physician's assessment as to whether the event was related to the

consumption of the test products. If a diagnosis was made by a medical professional, then that diagnosis was entered as the adverse event. If a subject experienced multiple symptoms, then a separate Adverse Experience form was completed for each symptom. A summary of all adverse experiences was provided to the IRB at the completion of the study.

Statistical Methods

Data from all subjects were included in the analysis. Objective and subjective measures were averaged over the baseline and treatment periods, respectively, with a change from baseline being determined from each subject's average treatment and baseline values. As the change from baseline approach did not provide a more precise analysis, primary analysis came from the (unadjusted) treatment period responses. From analysis of the objective and subjective responses, it was found that many responses were not normally distributed and that group variances were not constant across treatments. Also, given the sample size (12 - 18/group), a 'means' analysis can be highly influenced by a few extreme observations and validity of 'normal' p-values could be questioned. In order to provide a robust, valid analysis that could be applied consistently across all of the subjective and objective responses, a Wilcoxon rank sum approach was performed for pair-wise treatment comparisons of the treatment phase data for all response variables.

Results

Subject Demographics

Treatment groups were balanced, as closely as possible, for gender, age and race as shown in Tables 2 through 4.

Table 2

Subject Gender by Treatment Group

	Male	Female	Total
Placebo	6	6	12
Olestra 20 g/d	7	11	18
Olestra 40 g/d	8	10	18
Sorbitol 40 g/d	10	8	18

Table 3

Subject Age by Treatment Group

	Mean	Minimum	Maximum
Placebo	42	19	67
Olestra 20 g/d	40	18	74
Olestra 40 g/d	37	18	62
Sorbitol 40 g/d	40	18	72

Table 4

Subject Race by Treatment Group

	Caucasian	Black	Asian
Placebo	9	3	0
Olestra 20 g/d	16	2	0
Olestra 40 g/d	14	4	0
Sorbitol 40 g/d	11	6	1

Subject Compliance

All test products were weighed before consumption and any residual test product was re-weighed after the dosing period to determine compliance. Subjects were considered to be 'evaluable' if they consumed at least 90% of their treatment dose. All subjects met the ≥90% compliance criteria for consuming test product for the study days completed. Table 5 shows the compliance of subjects by treatment group.

Table 5

Test Product Consumption Compliance Throughout Entire Study

Compliance	Placebo	Olestra 20 g/d	Olestra 40 g/d	Sorbitol 40 g/d
94%	0	0	0	1
96%	0	0	1	2
97%	0	0	1	0
98%	0	0	0	1
99%	2	2	0	3
100%	10	16	16	11

Five subjects did not complete the study
For the sorbitol 40g/d treatment group, subject 112 was dropped on study day 8 due to non-compliance (did not consume candy) following diarrhea symptoms (10 BMs/d after first dose of sorbitol), subject 305 withdrew on study day 10 following complaints of passing gas, heartburn, abdominal pain and diarrhea beginning study day 8, and subject 406 withdrew on study day 9 after reporting sore throat and vomiting on study day 8.

For the olestra 20g/d treatment group, subject 215 withdrew on study day 7 prior to the first dose of olestra due to dizziness on day 3, abdominal cramps beginning study day 4 (continuing for approximately two weeks), and vomiting on study day 4.

For the olestra 40g/d treatment group, subject 217 withdrew on study day 11 due to menorrhagia.

Protocol Deviations

All subjects received meals that conformed to the American Heart Association Step I diet with the following exceptions: day 2, cohort 1 inadvertently received 2% milk with breakfast instead of skim milk; and day 6, cohort 1 received 1 serving of tapioca pudding that was not in the pre-planned menu and not served to the other cohorts.

All stool for each subject was collected, weighed, aliquoted and processed according to the protocol with the following exceptions: a freezer malfunction on May 24, 1997, causing stool

aliquots from cohorts 1 and 2 to thaw briefly before being transferred to a working freezer. The specimens were sealed in airtight containers, and there was no apparent impact on stool water content measures. For cohort 3, the load cell on the Stevens Texture Analyzer was damaged. The load cell was replaced and re-calibrated within 4 hours. Stool samples were collected and refrigerated during load cell repairs, then rewarmed and analyzed per protocol.

For cohort 1, sugar-containing beverages were inadvertently served on study day 1. For cohort 3: the post-consumption weight of snack 2 on study day 10 was not recorded; the beverage refrigerator was inadvertently stocked with apple and grape juice on study day 1. The drinks were removed on study day 2. Subjects 303, 304, 307, 311, 312, 314, 316 and 319 found it difficult to chew the candy (cohort 3 was comprised primarily of older subjects with dentures, bridge-work, etc.). An alternative was offered to all subjects starting study day 9 and continuing to the end of the study: in these cases the candy was dissolved in warm water and served as a drink.

Adverse Events

No serious adverse events occurred in this study. Gastrointestinal symptoms were recorded on a daily basis using a diary. All non-gastrointestinal complaints and any additional gastrointestinal complaints which were volunteered by study subjects were recorded on adverse event forms. The most commonly reported non-GI adverse events during the treatment phase were headache and sore throat. Voluntary comments regarding GI symptoms during the treatment phase were exclusively reported by subjects in the sorbitol treatment group, with the exception of 1 report of bloating (olestra 40g/d treatment group), 2 subjects reporting heartburn (olestra 40g/d and placebo treatment groups), and 1 report of oily stool (olestra 40g/d treatment group). All adverse events are listed by treatment group in Appendix 4.

Objective Measures

Individual Stool Weight, Stool Water Content

All bowel movements (1098 stool samples) were collected and measured for stool wet weight (g/BM) and stool water content (%). All stool weights per subject per day were summed for stool output (g/d). Stool weights ranged from 2g/BM (olestra 20g/d) to 730g/BM (sorbitol 40g/d). Mean treatment phase stool wet weight (Exhibit 1) significantly ($p<0.05$) increased for the sorbitol 40g/d treatment group (186.0g/BM) compared to placebo (111.8g/BM). Olestra 20g/d (119.1g/BM) and olestra 40g/d (121.1g/BM) were not statistically different from placebo. Stool water content (Exhibit 2) ranged from 45% (placebo, very firm stool) to 98% (sorbitol, rice-water stool). Compared to placebo (77.1%), mean stool water content significantly ($p<0.05$) decreased for olestra 20g/d (72.5%) and olestra 40g/d (72.1%), and significantly increased for sorbitol 40g/d (89.7%).

Daily Total Stool Output

Total daily stool output ranged from 0g/d (no BM that day) to 1,102g/d (sorbitol 40g/d). Compared to the respective baseline, stool output increased 24.7g/d for olestra 20g/d, 56.7g/d for olestra 40g/d and 375.7g/d for sorbitol 40g/d (Exhibit 3). These values are remarkably close to the additional weight of the olestra added to the diet, i.e, 20 and 40 g/d. Stool output for the placebo group decreased 29.1g/d compared to baseline (Exhibit 4).

Daily Stool Water Output

Compared to the respective baseline, mean daily stool water output decreased 27.5g/d for placebo, and increased 8.8g/d with olestra 20g/d, 37.4g/d with olestra 40g/d, and 345.9g/d with sorbitol 40g/d (Exhibit 5). Although the increases in stool water noted in the olestra treatment groups were minor, daily stool water output was significantly ($p<0.05$) different than the placebo group because of the decrease in stool water in that group (Exhibit 6). Individual responses were variable, as exhibited by the range of daily stool water output: baseline, 6g/d to 234g/d; placebo, 21g/d to 205g/d; olestra 20g/d, 62g/d to 251g/d; olestra 40g/d, 64g/d to 249g/d; and sorbitol, 56g/d to 688g/d.

When bowel movements rated by subjects as 'diarrhea' (BM rating = 1 or 2 using subjective rating scale) are considered separately, mean daily stool water output for 'diarrhea' stools was 110g/d for baseline, and during the treatment phase, 143g/d for placebo, 127g/d for olestra 20g/d, 159g/d for olestra 40g/d, and 434g/d for sorbitol 40g/d. Stool water output exceeded 500g/d in some cases (for sorbitol 40.8% of treatment days and during baseline 0.4% of treatment days), but did not result in clinical dehydration or require medical intervention. Subjects consuming olestra 20g/d or olestra 40g/d and subjects in the placebo group did not exceed 500g/d stool water output (Exhibit 7).

Daily Stool Electrolyte Output

Stool electrolyte output (Exhibit 8) was consistent with stool water output (Exhibit 6). Compared to the respective baseline, mean sodium output decreased 0.6 mEq/d with placebo and 0.4mEq/d with olestra 20g/d, and increased 3.4mEq/d with olestra 40g/d and 15.9mEq/d with sorbitol 40g/d. Stool chloride output was consistent with stool sodium output. Stool potassium output was greater than sodium or chloride output for all treatment groups, including baseline. Stool sodium output exceeded 15mEq/d in some cases (sorbitol 58.2%, baseline 3.0%, olestra 20g/d 2.9%, and olestra 40g/d 5.6% of treatment days), but did not require medical intervention.

Stool Consistency

The consistency of human stool was evaluated using two measures. The 'Johns Hopkins Stool Description Visual Rating Scale' grades stool by appearance. The Stevens Texture Analyzer measures stool viscosity. The correlation between these measures for all stool samples collected in this study is shown in Table 6 without regard to treatment group.

Table 6

Distribution of Peak Force for Extrusion Measure Across
Johns Hopkins Stool Description Visual Rating Scale

Johns Hopkins Stool Descriptors	Peak Force for Extrusion (g) 75th - 25th Percentile
Firm *(Normal, formed)*	2651 - 1131
Soft *(Less form)*	1047 - 425
Runny *(Loose)*	315 - 68
Liquid *(Little solid material)*	55 - 13
Rice Water *(Clear liquid with flecks of solid material)*	46 - 15

The 75th to 25th percentile peak force values can be used to define the range of mechanical force that corresponds to the stool descriptors for the Johns Hopkins Visual Scale. Firm/formed stools ranged between 1131 and 2651g, soft/less formed stools ranged from 425 to 1047g, runny/loose stools ranged from 68 to 315g, and liquid/rice-water stools could not be separated by this measure but would, from this comparison, generate a peak force for extrusion of less than 68g. Across treatment groups, stool consistency ranged from rice-water (2.5g peak force, sorbitol 40g/d) to very firm (9,148g peak force, baseline). Mean stool consistency data, with comparisons to the respective baseline, is presented in Exhibit 9. Mean stool consistency was comparable equal and constant over time for all treatment groups during the baseline phase (Exhibit 10, days 3-6). For the olestra 20g/d and olestra 40g/d treatment groups, a gradual, dose-responsive decrease in stool consistency was observed beginning 2 to 4 days after initiation of dosing (Exhibit 10, days 7-12). For the sorbitol treatment group, mean daily stool consistency decreased the first day of dosing and was consistently lower than all other treatment groups for the remainder of the treatment phase (Exhibit 10, days 7-12).

Bowel Movement Frequency

Mean bowel movement frequency throughout the study (Exhibit 11) was ≤ 3 BMs/d for all treatment groups. Individual responses were variable, as exhibited by the range of BM frequency: baseline, 0 to 6 BMs/d; placebo, 0 to 4 BMs/d; olestra 20g/d, 0 to 6 BMs/d; olestra 40g/d, 0 to 5 BMs/d; and sorbitol 40g/d, 0 to 10 BMs/d. When BM occurrence is plotted over 24 hours (Exhibit 12), an increase in BM frequency was observed between 11am and 2pm for the sorbitol treatment group, with the peak frequency of BMs occurring 1.5 to 2 hours post sorbitol consumption (10 - 10:30am). Slight increases in BM frequency are noted at 7pm to 9pm for olestra 40g/d and 6am to 8am (Exhibit 12), demonstrating that consumption of olestra does not lead to rapid onset (within a few hours) of bowel movements.

Subjective Ratings

Reports of Diarrhea

Immediately after each BM, subjects characterized their own perceptions of the bowel movement based on a 7-point scale (1 = watery, difficult to control diarrhea; 4 = normal; 7 = hard, difficult

to pass constipation). The distribution of BM ratings (Exhibit 13) are centered around a BM rating of 4 (mean 3.9) for the placebo group, 3 (mean 3.1) for the olestra 20g/d treatment group, 2-3 (mean 2.4) for the olestra 40g/d treatment group, and 1 (mean 1.5) for the sorbitol 40g/d treatment group. Exhibit 7 shows the relationship between total 24-hour stool water output and subject self-assessed BM ratings. Subjects who rated their BMs as category 1 or 2 (diarrhea) are indicated by a plus. All other BM ratings are indicated by a circle. These data demonstrate that reports of 'diarrhea' in the olestra treatment groups are not associated with an increase in total water output outside the normal range (i.e., the range observed during the baseline period and in the placebo group). Exhibit 14 correlates BM ratings and stool viscosity without regard to treatment. Note that mean BM rating decreases as mean stool viscosity decreases. Note also that there is a considerable amount of overlap in BM ratings for a wide middle range of stool consistencies: from approximately 300g (log 2.5) to 1,500g (log 3.2) peak force, similar stool consistencies were reported as all BM ratings, from watery, difficult to control diarrhea (rating = 1) to hard, difficult to pass constipation (rating = 7). Subjects also reported 'watery, difficult to control diarrhea' (rating = 1) for a wide range of stool viscosity, from firm (1,520g peak force) to rice-water (3g peak force).

Gastrointestinal Symptoms

Self-assessed gastrointestinal experiences were collected by means of a daily diary (Appendix 3). Exhibit 15 shows mean symptom frequency and Exhibit 16 shows mean symptoms severity by treatment group.

There were no differences between any groups in the incidence or severity of bloating, passing gas or heartburn. Sorbitol 40g/d, but not olestra 20g/d or olestra 40g/d, increased the frequency and severity of nausea compared to placebo (Exhibits 15,16).

Ingestion of sorbitol 40g/d resulted in marked increases in the number of reports of abdominal cramping and urgency, while smaller increases were observed for the olestra 40g/d treatment group (Exhibit 15). To better understand the correlation between reports of abdominal cramping and urgency versus stool viscosity, comparisons will be made between the daily incidence and severity of these GI symptoms and the daily mean stool viscosity of each treatment group. The frequency and severity of reports of abdominal cramping (Exhibits 17 and 18, respectively) and urgency (Exhibits 19 and 20, respectively) increased proportional to decreases in stool viscosity (Exhibit 10). For sorbitol 40g/d, reports of abdominal cramping increased to 66.7% of subjects (Exhibit 17) and average severity increased to 'moderate' the first day of dosing (day 7, Exhibit 18) and remained higher than placebo each subsequent study day, consistent with rapid-onset decrease in stool consistency (Exhibit 10). Olestra 20g/d, which showed a stool softening effect on the 4th day of dosing, did not increase the mean frequency (Exhibit 17) or severity (Exhibit 18) of reports of abdominal cramping compared to placebo. Overall, the proportion of subjects reporting cramping in the olestra 20g/d group decreased compared to baseline (Exhibit 15). There was one subject (#313) consuming olestra 20g/d who reported 'severe' abdominal cramping on the 4th day of olestra dosing (study day 10). For olestra 40g/d, the frequency (Exhibit 17) of reports of mild to moderate (Exhibit 18) abdominal cramping showed an increase only after 3-4 days of dosing (study days 9 and 10; 50.0% and 55.6% of subjects, respectively), consistent with gradual stool softening after several days of consumption (Exhibit 10). No subjects reported severe abdominal cramping while consuming olestra 40g/d.

Consumption of sorbitol 40g/d resulted in a marked increase in the frequency (Exhibit 19) and severity (Exhibit 20) of urgency on the first day of dosing, and remained above baseline throughout the remainder of the treatment phase. Olestra 20g/d, which showed a stool softening effect after the 4th day of dosing, did not increase the mean frequency (Exhibit 19) or severity (Exhibit 20) of reports of urgency compared to baseline. For olestra 40g/d, the frequency (Exhibit 19) of reports of mild (Exhibit 20) urgency showed a modest increase only after several days of dosing, consistent with gradual stool softening after several days of consumption (Exhibit 9). The placebo treatment group showed a decrease in the urge to defecate, consistent with the gradual hardening of stool noted in the last three days of the treatment period (Exhibit 10). These data show that the urge to defecate is inversely proportional to stool viscosity.

Concomitant Medications

Subjects were allowed to continue taking their routine medications during the study, under the supervision of the study personnel. A listing of all medications, including those administered for symptoms reported during the study (e.g. Tylenol for headaches) are included in Appendix 5.

Discussion

Concerns were raised that consumption of olestra would cause diarrhea and potentially place elderly subjects at risk of dehydration (14). In this study, we demonstrated that olestra consumption did not result in clinically meaningful increases in stool water output, even in those subjects reporting 'diarrhea'. The most commonly used determinants of clinically meaningful diarrhea are: an increase in stool output and stool water output/electrolyte output, a significant decrease in stool viscosity, and an increase in BM frequency (15,16). While no universally accepted values defining diarrhea exist, standard medical textbooks (15,16) offer accepted measurements as guidelines: 1) increased stool output [>200-250g/d, varying greatly with dietary fiber intake (17)]; 2) watery, difficult to control bowel movements (qualitative assessment only); and 3) bowel movement frequency exceeding 3 bowel movements per day. These measures directly or indirectly are intended to gauge the magnitude of stool water and electrolyte output, the primary focus of clinical diarrhea. The aim of this study was to determine the effects of olestra consumption on all three accepted measures of diarrhea, with an emphasis on the primary focus of clinical diarrhea: stool water and stool electrolyte output. Sorbitol, a poorly absorbed sugar-alcohol with known osmotic laxative effects (9), was used as a positive control.

Of the three accepted measures of diarrhea, mean daily stool output is the most dependent on dietary fiber intake. Mean daily stool output in the U.S. is estimated to be only 100g/d, presumably due to low dietary fiber intake (17). This is in contrast to mean stool output among healthy individuals in India (311g/d), Peru (325g/d), Malaysia (465g/d), and Uganda (470g/d) (17). A mean daily stool output of at least 150g/d is recommended to reduce the risk of bowel cancer (17). In this study, mean total stool output was within normal limits for olestra 20g/d and olestra 40g/d treatment groups (177.9g/d and 204.6g/d, respectively), and exceeded normal limits for the sorbitol 40g/d treatment group (457.2g/d). Consumption of olestra increased total stool output by 25.6g/d and 56.7g/d, close to what would be expected from the actual dose of olestra consumed (20g/d and 40g/d, respectively). For stool water output, consumption of olestra 20g/d and olestra 40g/d resulted in modest, clinically insignificant increases in stool water output (8.8g/d and 37.4g/d, respectively, which equals approximately 2 teaspoons and 2.5 tablespoons of water per day, respectively) compared to their respective baselines. In contrast, consumption of sorbitol at 40g/d resulted in 345.9g/d (approximately 10 ounces) of additional stool water output per day compared to the respective baseline.

Stool viscosity, the second determinant of clinical diarrhea, has been correlated with stool water content (13), and therefore has been considered qualitatively indicative of stool water output. With daily consumption of olestra, however, a dose-responsive modest decrease in stool consistency was observed without a concomitant increase in stool water content or a clinically significant increase in daily stool water output. Consumption of olestra at 20g/d (approximately 2.5 ounces of chips) resulted in a gradual, modest stool softening effect after 4 days of consumption, and consumption of olestra at 40g/d (approximately 5 ounces of chips) resulted in a gradual stool softening effect after 2 days of consumption. In contrast, consumption of sorbitol 40g/d resulted in liquid/rice-water diarrhea-like stools within 1-2 hours of consumption. There

were no liquid/watery stools in the olestra 20g/d treatment group, and both the placebo group and the olestra 40g/d treatment groups had one liquid/watery stool each. The sorbitol 40g/d treatment group had 145 liquid/watery stools, 140 of which were of sufficient sample size to be evaluable. Sugar-alcohols, such as sorbitol, osmotically compete with the bowels' ability to reabsorb water, and stool viscosity is highly sensitive to increases in stool water content (13). Formed stool, which had a mean peak force for extrusion of 2,217g and a percent water content of 76.7%, became liquid/rice-water (peak force <65g) with an increase in the water content to 93.1%, an absolute change in water content of only 16.4%. In contrast, a similar percent increase in estimated olestra stool content had a less dramatic effect on stool viscosity. After several days of olestra consumption (which would allow for colonic mixing and transit), olestra 20g/d and olestra 40g/d would represent an estimated stool olestra content (assuming olestra 20g/d and olestra 40g/d in stool, respectively) of approximately 11% (20g/d olestra / 178g/d stool) and 20% (40g/d olestra / 205 g/d stool), respectively, resulting in an overall stool softening effect. The observation that olestra exerts a stool softening effect without a concomitant increase in stool water content demonstrates that the decrease in stool viscosity is due to the viscosity of the oil itself and the potential of olestra to disrupt the stool matrix. This study has shown that the dose-responsive stool softening effects observed with daily consumption of olestra are not consistent with the 'watery, difficult to control bowel movements' described in medical texts.

Bowel movement frequency is often used as a benchmark in GI studies for the simplistic reason that it is easy to collect and does not involve the unpleasant task of collecting and handling feces. Caution should be exercised, however, when assessing 'diarrhea' in light of a single day with a BM frequency greater than three. A subject who produced four small, formed stools (4BMs/d) is not comparable to a subject who experienced four 200g watery, difficult to control bowel movements (also 4 BMs/d). Bowel movement frequency should be considered in light of the other measures associated with diarrhea. In this study, bowel movement frequency occasionally exceeded 3 BMs/d in baseline and all treatment groups, but mean BM frequency remained within normal limits ($\leq$ 3 BMs/d) for all treatment groups. When BM frequency is plotted over 24-hours, sorbitol exhibits an obvious increase in the frequency of BMs within 1-2 hours of dosing, while olestra does not exhibit a similar post-dose increase. These results show that chronic consumption of olestra leads to a dose-responsive, clinically insignificant increase in stool water output and BM frequency, and a gradual stool softening effect that is not consistent with clinical diarrhea. In contrast, consumption of sorbitol 40g/d lead to rapid-onset liquid stools and a marked increase in stool output and stool water output, but the effect was self-limiting (returned to higher viscosity stool once sorbitol was expelled) and did not result in dehydration or require medical intervention.

There were no liquid/rice-water BMs in the olestra 20g/d treatment group, and the placebo and olestra 40g/d had only one liquid BM each. Recently consumed food products normally undergo a considerable amount of mixing in the proximal large bowel, and at any given time the large bowel contains residue from meals consumed over several previous days (18). This gradual mixing and dilution of each meal in the large bowel is consistent with the gradual, dose-responsive stool softening effects observed with olestra consumption in this study. As olestra is

ingested and arrives in the large bowel, it would be admixed to and diluted by digesta already present in the proximal large bowel, attenuating the viscosity-reducing effects of olestra until a steady-state concentration is achieved after several days of chronic consumption. This gradual stool softening effect may actually offer a health benefit to constipated subjects. Constipation is the most common gastrointestinal complaint in the United States, resulting in 2.5 million physician visits each year, and hard stool is one of the primary complaints associated with constipation (19). Stool softening is a physician's first step in management of chronic constipation (20). In contrast to the stool softening effects observed with olestra consumption, subjects in the sorbitol 40g/d treatment group experienced a total of 140 evaluable liquid/rice-water BMs over the 6-day treatment period. Sorbitol exerts an osmotic effect that opposes the large bowels ability to absorb water, resulting in multiple, high water content, low viscosity stools.

The term 'diarrhea' is often used by the general population to describe a change in bowel habit, but the term may have limited application to assessing illness in such individuals without objective measures. A survey of 1,644 age- and gender-stratified adults (21) showed that clinical symptoms of diarrhea did not discriminate self-reported diarrhea from self-reported normal bowel habit. In the present study, mean values for stool viscosity were proportional to subjective BM ratings (i.e., the lower the stool viscosity, the lower the BM rating), but reports of 'watery, difficult to control diarrhea' occurred over a wide range of stool viscosity, from 1,520g (firm stool) to 3g ('rice-water' stool). This observation is exemplified by subject #102, who considered very firm stools (5,488g to 6,336g peak force) 'normal', and rated a softer formed stool (865g peak force) as 'diarrhea'. There is also a considerable amount of overlap in subject interpretation of similar stool viscosities. The data (Exhibit 13) show that a wide 'middle range' of stool viscosity, from approximately 300g to 1,500g peak force, received all 7 BM ratings (from 'watery, difficult to control diarrhea' to 'hard, difficult to pass constipation'). When reports of diarrhea are compared to stool water output, the data demonstrate that reports of 'diarrhea' in the olestra treatment groups are not associated with an increase in total water output outside the normal range. In contrast, BMs rated as 'diarrhea' in the sorbitol treatment group show a marked increase in stool water output.

Self-assessed gastrointestinal symptoms, collected by means of a diary, show that there were no significant differences between any groups for bloating, passing gas, or heartburn. Sorbitol, but not olestra, significantly increased the frequency and severity of nausea. Baseline frequency for abdominal cramping and urgency was as high as 33.3% of the subjects, supporting the concept that a significant percentage of the population normally experience abdominal cramping and urgency. Olestra 20g/d did not increase the frequency or severity of reports of any GI symptoms, including abdominal cramping and urgency, suggesting that there is a threshold for inducing GI symptoms associated with decreases in viscosity. Olestra 40g/d showed only a modest increase in the frequency of reports of mild abdominal cramping and urgency on two of six study days, while sorbitol 40g/d showed a more marked increase in the frequency and severity of reports of abdominal cramping and urgency the first day of dosing and each of the five subsequent days.

There were no reports of severe abdominal cramping in the olestra 40g/d treatment group. Stool viscosity increased for the placebo treatment group during the last three treatment days with a concomitant decrease in the urge to defecate for the same three treatment days. In total, these observations suggest that the probability of the occurrence of abdominal cramping and urgency is inversely proportional to stool viscosity.

Conclusions

Subject reports of 'diarrhea' associated with olestra, consumption are not associated with any meaningful or clinically significant increases in fecal water or electrolyte output. In contrast, consumption of sorbitol 40g/d resulted in rapid-onset liquid/rice-water stools and an increase in mean stool water output of 345.9g/d (approximately 10 ounces/d) and increased electrolyte output. Consumption of olestra resulted in a dose-responsive, gradual stool softening effect after several days of consumption. Reports of stool viscosity changes that were characterized by subjects as 'diarrhea' were associated with a decrease in fecal consistency but not an increase in stool water. Olestra consumption resulted in a dose-responsive modest increase in daily stool frequency with mean bowel movement frequency well within the normal ranges.

The transient increase in incidence of reports of mild to moderate abdominal cramping noted on some of the treatment days in subjects consuming 5 ounces of chips (40g/d olestra) for 6 consecutive days were associated with decreases in fecal consistency. These effects were not severe, posed no risk to health, and were not unique to olestra as similar effects were noted in all treatment groups and during baseline.

Signatures

J. W. McRorie, Ph.D., Project Manager — Date: 1-28-98

R. A. Giannella, M.D., GI Consultant — Date: 1/28/98

T. G. Filloon, Ph.D., Study Statistician — Date: 1/28/98

K. A. Riccardi, B.S., Clinical Monitor — Date: 1-28-98

References

1. Evaluation of oil loss in normal healthy subjects consuming olestra of various degrees of stiffness. In: Appendix EC - 59, FAP 7A 3997, Volume 206-207, April 29, 1993.

2. Cheskin, L.J., Miday, R., Zorich, N., Filloon, T. Gastrointestinal symptoms following consumption of olestra or regular triglyceride potato chips: a controlled comparison. JAMA 1998, 279:150-152. Submitted to FDA 7/97.

3. Koonsvitsky, B.P., Berry, D.A., Jones, M.B., Lin, P.Y.T., Cooper, D.A., Jones, D.Y., Jackson, J.E. Olestra affects serum concentrations of α-tocopherol and carotenoids but not vitamin D or vitamin K status in free-living subjects. J. Nutr. 1997, 127:1636S-1645S. In: Appendix EC-52, FAP 7A 3997, Volume 58-61, September 20, 1989.

4. Zorich, N.L., Jones, M.B., Kesler, J.M., Carter, S.B., Sutton, M.A., Bayless, T. A randomized, double-blind study of the effect of olestra on disease activity in patients with quiescent inflammatory bowel disease. Am. J. Med. 1997, 103:389-399. In: Appendix EC-57, FAP 7A, 3997, Volume 192-194, February, 10, 1993.

5. Consumer use and perception of olestra snack products. In: Appendix EC-65, FAP 7A 3997, Volume 281, December 11, 1995.

6. Schlagheck, T. G., Ricardi, K.A., Zorich, N.L., Torri, S.A., Dugan, L.D., Peters, J.C. Olestra dose response on fat-soluble and water-soluble nutrients in humans. J. Nutr. 1997, 127:1646S-1665S. In: Appendix EC-56, FAP 7A 3997, Volume 185-191, 240-245 January 29, 1993.

7. Schlagheck, T. G. Kesler, J.M., Jones, M.B., Zorich, N.L., Dugan, L.D., Davidson, M.H., Peters, J.C. Olestra's effect on vitamins D and E in humans can be offset by increasing the dietary levels of these vitamins. J. Nutr. 1997, 127:1666S-1685S. In: Appendix EC-60, FAP 7A, 3997, Volume 209-216 June 2, 1993.

8. Daher, G. C., Cooper, D.A., Zorich, N.L., King, D., Riccardi, K.A., Peters, J.C. Olestra ingestion and dietary fat absorption in humans. J. Nutr. 1997, 127:1694S-1698S. In: Appendix EC-61, FAP 7A 3997, Volume 217-221, July 9, 1993.

9. Evaluation of the Health Aspects of Sorbitol as a Food Ingredient, FDA Report #FDABF-GRAS-119, December, 1972, prepared by the Life Sciences Research Office, Federation of American Societies for Experimental Biology, Contract #FDA 72-85.

10. Webb, D.R., Harrison, G.G., Lee, M-J., Huang, M-H. Estimated consumption and eating frequency of olestra from savory snacks using menu census data. J. Nutr. 1997, 127:1547S-1554S.

11. Federal Register, Part III, Department of Health and Human Services, Food and Drug Administration, 21 CFR Part 172, January 30, 1996.

12. Sack, D., Tacket, C., Cohen, M., Sack, R., Losonsky, G., Shimko, J., Nataro, J., Edelman, R., Levine, N., Giannella, R., Schiff, G., Lng, D. Validation of a volunteer model of cholera using frozen bacteria as the challenge. Infection and Immunity. 1998, In Press.

13. McRorie, J., Pepple, S., Rudolph, C. Effects of fiber laxatives and calcium docusate on regional water content and viscosity of digesta in the large intestine of the pig. Digestive Dis. Sci. 1998, In Press.

14. Review of Study Entitled "Measurement of Selected Fecal Parameters in Subjects Consuming Increasing Levels of Olestra" (FAP 3997, Volume 280). Department of Health & Human Services Memorandum, December 26, 1995, From: Medical Officer, Epidemiology Branch, Division of Market Studies (HFS-728), To: Helen Thorsheim, Ph.D., Consumer Safety Officer, Office of Premarket Approval (HFS-216).

15. Spiro, H.M., Editor. Clinical Gastroenterology, 4th Edition, McGraw-Hill, Inc. New York, NY. 1993, p. 355.

16. Braunwald, E., Isselbacher, K.J., Petersdorf, R.G., Wilson, J.D., Martin, J.B., Fauci, A.S., Editors. Harrison's Principles of Internal Medicine, 11th Edition. McGraw-Hill Book Company, New York, N.Y. 1987, p.177.

17. Cummings, J.H., Bingham, S.A., Heaton, K.W., Eastwood, M.A. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). Am. J. Gastroenterol. 1992, 103:1783-1789.

18. Wiggins, H.S., Cummings, J.H. Evidence for the mixing of residue in the human gut. Gut, 1976, 17:1007-1011.

19. Goldfinger, S.E. Constipation, Part 1: the hard facts. Harvard Health Letter, 1991, 16(4):1-4.

20. McRorie, J.W., Daggy, B.P., Morel, J.G., Diersing, P.S., Miner, P.B., Robinson, M. Psyllium is superior to docusate sodium for treatment of chronic constipation. Alimentary Pharmacol. Ther., 1998, In Press.

21. Talley, N.J., Weaver, A.L., Zinmeister, A.R., Melton, L.J. Self-reported diarrhea: what does it mean? Am. J. Gastroenterol., 1994, 89:1160-1164.

REFERENCES

Brief Report

Gastrointestinal Symptoms Following Consumption of Olestra or Regular Triglyceride Potato Chips

A Controlled Comparison

Lawrence J. Cheskin, MD; Robert Miday, MD; Nora Zorich, MD, PhD; Thomas Filloon, PhD

Context.—Olestra, a nonabsorbable, energy-free fat substitute used in snack foods, has been anecdotally reported to cause gastrointestinal (GI) adverse events, although such effects were not expected based on results from randomized trials, in which it was consumed in typical snack patterns.

Objective.—To determine whether ad libitum consumption of potato chips made with the fat substitute olestra results in a different level of GI symptoms than regular chips made with triglyceride (TG).

Design.—Randomized, double-blind, parallel, placebo-controlled trial.

Setting.—A suburban Chicago, Ill, multiplex cinema.

Subjects.—A total of 1123 volunteers aged 13 to 88 years.

Intervention.—Subjects were given a beverage and an unlabeled, white 369-g (13-oz) bag of potato chips made with olestra or TG during a free movie screening.

Main Outcome Measures.—Total and specific GI symptoms reported during a telephone interview conducted from 40 hours to 10 days after ingestion; level of potato chip consumption; and satiety level.

Results.—Of 563 evaluable subjects in the olestra chip group, 89 (15.8%) reported 1 or more GI symptoms, while 93 (17.6%) of the 529 evaluable subjects in the regular TG chip group did so (difference in symptom frequency between olestra and TG, −1.8; 95% confidence interval, −6.2 to 2.7; $P=.47$). For specific GI symptoms (eg, gas, diarrhea, abdominal cramping), there were no significant differences between olestra and TG chips. Fewer olestra chips were consumed than TG chips (60 vs 77 g [2.1 vs 2.7 oz]; $P<.001$), with olestra chips receiving lower taste scores (5.6 vs 6.4 on a 9-point scale; $P<.001$). Consumption levels did not correlate with the rate of symptom reporting in either the olestra or TG group. There was no difference in satiety scores between olestra and TG chips (5.7 vs 5.9 on a 9-point scale; $P=.07$).

Conclusions.—This study demonstrates that ad libitum consumption of olestra potato chips during 1 sitting is not associated with increased incidence or severity of GI symptoms, nor does the amount consumed predict who will report GI effects after short-term consumption of either olestra or TG potato chips.

JAMA. 1998;279:150-152

From the Division of Gastroenterology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Md (Dr Cheskin), and the Regulatory and Clinical Development Division, Procter & Gamble Company, Cincinnati, Ohio (Drs Miday, Zorich, and Filloon).

Dr Cheskin is a consultant to Procter & Gamble. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict of interest policies.

Reprints: Lawrence J. Cheskin, MD, The Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, 4940 Eastern Ave, Baltimore, MD 21224 (e-mail: cheskin@welchlink.welch.jhu.edu).

A DIET HIGH IN FAT is now well known to be associated with obesity and heart disease. The American Heart Association recommends a diet in which fat contributes 30% or less of total energy. One factor making it difficult for individuals to lower their fat intake is the lack of availability of low-fat foods with taste and aesthetics comparable to the full-fat varieties.

Olestra is a nonabsorbable, energy-free fat substitute approved by the US Food and Drug Administration (FDA) for use in the preparation of snack foods, including potato chips, corn chips, and crackers.[1] Olestra is a mixture of hexa-, hepta-, and octa-esters of sucrose formed from long-chain fatty acids prepared from any edible oil. Because olestra is not hydrolyzed by pancreatic enzymes,[2] it is not absorbed[3] and provides no dietary energy or fat. Extensive studies in laboratory animals and humans were reviewed by the FDA in its determination of the safe use of olestra in foods.[1,4]

There has been considerable publicity around anecdotal reports of consumers experiencing gastrointestinal (GI) adverse events from olestra.[5] We were interested in conducting a carefully controlled, blinded study that would allow a large number of participants unlimited access to chips in a single sitting (about a 2-hour period).

Participants and Methods

We studied 1123 adult and teenaged individuals who responded to recruitment flyers distributed at a suburban Chicago, Ill, multiplex cinema soliciting participants for a potato chip test at the movies. Potential subjects completed a telephone screening. The only exclusionary criteria were employment at a food or market research firm or participation of more than 2 individuals per household. Participants were scheduled for their choice of 4 first-run movies being shown on the study evenings and were instructed to eat their evening meal 1 to 2 hours prior to arriving at the theater. The theaters were closed to the public during the study.

The study protocol was approved by the local institutional review board. Written informed consent was obtained from all participants, as well as from a parent or guardian for minors. Two free

works of individual providers and are contracting with medical groups that can better coordinate physicians.

Two forms of organization are competing to develop health care delivery systems in this challenging environment: PHOs and PPM firms. The most successful PHOs have a strong local presence and reputation, capital resources from hospital profits and tax-exempt bonds, and existing ties with physicians through hospital medical staffs.[43,44] The most successful PPMs have competencies in capitation and utilization management built by leading medical groups, maintain access to financial capital through public equity markets, and are not burdened by responsibility for excess hospital capacity. Physician-hospital organizations tend to be nonprofit in ownership, built on a tradition of community service, and dominated by specialist physicians and hospital management. Physician practice management organizations tend to be for profit in ownership, built on a tradition of physician entrepreneurship, and dominated by primary care physicians and corporate management.

Physician practice management organizations face 3 major challenges in the increasingly competitive health care environment. First, they must continue their growth in physician affiliations, patient enrollment, and capitation revenues to sustain the confidence of investors and the value of their equity. This growth is achieved through new medical group acquisitions, new health plan contracts, and the attraction of new patients to already affiliated groups. "Same store growth" is a significant factor in evaluations by investment analysts, which influence the value of publicly traded PPM stock. This stock supplies the currency with which major mergers and acquisitions are financed and its price determines whether rapid growth is affordable.

The second challenge facing regional and national physician systems is to improve the economic efficiency, customer service, and clinical quality of the care offered through their affiliated medical groups and IPAs. Much of PPM growth is premised on the potential for a transfer of best business practices and clinical innovations from well-established medical groups to newer entities in communities only recently exposed to cost control pressures. These improvements are difficult to implement in a context of rapid organizational growth yet are essential for long-run profitability.

The third and greatest challenge facing PPMs is to make the needed changes in organization, financing, and practice patterns without undermining the confidence and commitment of the individual physicians affiliated with their medical groups and IPAs. The large organizational scale that brings better health plan contracts and more advantageous capital financing may threaten the sense of participation and control at the grass roots level. Insurance entities and hospitals that sought to create integrated delivery systems through practice acquisitions often have been plagued by low physician productivity. As they grow and consolidate, medical groups face the imperative to forge a culture that combines managerial efficiency and professional dedication.

This research was supported by the Robert Wood Johnson Foundation through its Investigators in Health Policy Research program.

References

1. Kletke PR, Emmons DW, Gillis KD. Current trends in physicians' practice arrangements: from owners to employees. *JAMA.* 1996;276:555-560.
2. Burns LR, Thorpe DP. Trends and models in physician-hospital organization. *Health Care Manage Rev.* 1993;18:7-20.
3. Shortell SM, Gillies RR, Anderson DA. New world of managed care: creating organized delivery systems. *Health Aff (Millwood).* 1994;13:46-64.
4. Morrisey MA, Alexander J, Burns LB, Johnson V. Managed care and physician/hospital integration. *Health Aff (Millwood).* 1996;15:62-73.
5. Rosenbluth JM. *Group Practice Management.* San Francisco, Calif: Volpe, Welty, and Co Equity Research; October 1993.
6. O'Neil BG, Manderfeld TB. *Physician Practice Management: Just What* the *Doctor Ordered.* Minneapolis, Minn: Piper Jaffray; August 1995.
7. Marsch LC, Weber MJ. *1995 Physician Medical Management and Services Report.* Philadelphia, Pa: Wheat First Butcher Singer, Investment Research Department; August 1995.
8. Kerms EH, Ockers NT. *Physician Practice Management Industry.* Baltimore, Md: Alex Brown Health Care; January 1996.
9. Hewitt CL, Abramowitz KS. *Physician Practice Management: Consolidating Physicians to Manage Care.* New York, NY: Berstein Research; December 1996.
10. Cain JE, Beith C, Deskin RB, Hollis SR. *The Best of the Breeds: A Comparison of Alternative Physician Practice Models.* New York, NY: Cain Brothers & Co; May 1996.
11. Laudan KR, Miller K, Johnson J. *The Physician Practice Management Industry and Company Update: Physicians Regroup and Take Stock.* San Francisco, Calif: Hambrecht & Quist; February 1996.
12. Moerschel G, McGuinnis P. *MedPartners, Inc.* Chicago, Ill: The Chicago Dearborn Co; December 1996.
13. MedPartners. *Prospectus for 7 and 3/4% Senior Notes Due 2006.* Birmingham, Ala: MedPartners; October 1996. Public securities offering sponsored by Smith Barney, Merrill Lynch, J.P. Morgan, Morgan Stanley, NationsBank Capital Markets.
14. MedPartners. *Prospectus for Common Stock.* Birmingham, Ala: MedPartners; October 1996. Public equity offering, New York Stock Exchange.
15. MedPartners/Mullikin. *1995 Annual Report.* Birmingham, Ala: MedPartners; 1996.
16. Kroll EE, Murphy KB. *FPA Medical Management, Inc.* New York, NY: Furman Selz; November 1996.
17. Wilson GL, Russ CS. *FPA Medical Management, Inc.* New York, NY: Lehman Brothers; November 1996.
18. Wiberg E, Ameer S. *FPA Medical Management, Inc.* New York, NY: UBS Securities; July 1996.
19. FPA Medical Management. *Value in Healthcare, 1995 Annual Report.* San Diego, Calif: FPA Medical Management; 1996.
20. FPA Medical Management. *Offering Memorandum, 6 and 1/2% Convertible Subordinated Debentures Due 2001.* San Diego, Calif: FPA Medical Management; December 1996. Public securities offering sponsored by Smith Barney, Bear Stearns, Lehman Brothers, Oppenheimer and Company, Neeham and Company.
21. FPA Medical Management. *Prospectus, Common Stock.* San Diego, Calif: FPA Medical Management; November 1995. Public equity offering sponsored by Bear, Stearns, Oppenheimer and Company, Hambrecht and Quist.
22. UniHealth. *Report to the Community, 1995.* Burbank, Calif: UniHealth; 1996.
23. Robinson JC, Casalino LP. Vertical integration and organizational networks in health care. *Health Aff (Millwood).* 1996;15:7-22.
24. Robinson JC, Casalino LP. The growth of medical groups paid through capitation in California. *N Engl J Med.* 1995;333:1684-1687.
25. Robinson JC. The dynamics and limits of corporate growth in health care. *Health Aff (Millwood).* 1996;15:155-169.
26. O'Neil BG, Manderfeld TB. *MedPartners.* Minneapolis, Minn: Piper Jaffray; December 1996.
27. MedPartners, Inc to acquire Aetna U.S. Healthcare's physician practice management business; companies enter into strategic national provider relationship [press release]. Birmingham, Ala: MedPartners; March 5, 1997.
28. MedPartners, Inc and InPhyNet complete merger [press release]. Birmingham, Ala: MedPartners; June 26, 1997.
29. MedPartners announces acquisition of Talbert medical management [press release]. Birmingham, Ala: MedPartners; August 14, 1997.
30. Rundle RL. FPA plans to buy Health Partners for $115 million. *Wall Street Journal.* July 3, 1997:B6.
31. FPA Medical Management, Inc announces agreements with Prudential HealthCare and Carolina Health Care Group [press release]. San Diego, Calif: FPA Medical Management; August 5, 1997.
32. Robinson JC. The dynamics and limits of corporate growth in health care. *Health Aff (Millwood).* 1996;15:155-169.
33. Schenkin B. The independent practice association in theory and practice. *JAMA.* 1995;273:1937-1942.
34. Jensen MC. Eclipse of the Public Corporation. *Harvard Bus Rev.* 1989;67:61-74.
35. Medimetrix. *A National Initiative: The Survey of Hospital-Sponsored Management Service Organizations.* Cleveland, Ohio: Medimetrix; 1997.
36. Gold MR, Hurley R, Lake T, Ensor T, Berenson R. A national survey of the arrangements managed care plans make with physicians. *N Engl J Med.* 1995;333:1678-1683.
37. FPA Medical Management, Inc and Foundation Health Systems, Inc enter into letter of intent for national HMO contract [press release]. San Diego, Calif: FPA Medical Management; May 1, 1997.
38. FPA Medical Management, Inc signs agreement for national contracts with PacifiCare Health Systems [press release]. San Diego, Calif: FPA Medical Management; May 21, 1997.
39. FPA Medical Management, Inc signs new agreements with HealthSource, Inc [press release]. San Diego, Calif: FPA Medical Management; July 9, 1997.
40. Kerr EA, Mittman BS, Hays RD, Siu AL, Leake B, Brook RH. Managed care and capitation in California: how do physicians at financial risk control their own utilization? *Ann Intern Med.* 1995;123:500-504.
41. Wachter RM, Goldman L. The emerging role of hospitalists in the American health care system. *N Engl J Med.* 1996;335:514-517.
42. Iglehart JK. National Committee for Quality Assurance. *N Engl J Med.* 1996;335:995-999.
43. Shortell SM, Gillies RR, Devers KJ. Reinventing the American hospital. *Milbank Q.* 1995;73:131-160.
44. Robinson JC. Physician-hospital integration and the economic theory of the firm. *Med Care Res Rev.* 1997;54:3-24.

movie passes were given to each participant as an incentive.

Prior to the movie, participants were assigned to 1 of the 2 test groups via a separate randomization schedule generated for each of 6 sex and age strata (13-17, 18-34, and >34 years) (Figure). Each participant was then given a plain, white, coded 369-g (13-oz) bag of test chips (either regular Frito-Lay Ruffles or Frito-Lay MAX Ruffles made with olestra) by study staff, who were blinded to test group assignment. Participants also received their choice of beverage (various 960-mL [32-oz] soft drinks) and were asked to be seated in the theater at least 1 seat apart from other participants. They were instructed to consume as much or as little of their potato chips and beverage as they liked and not to share with anyone else. The theaters were monitored by several study staff during the movies.

At the conclusion of the movie, participants clipped their bags of potato chips shut; noted the approximate amount of beverage they had consumed; and completed a brief questionnaire regarding product acceptance, subjective satiety, and sensory attributes. Bags of chips were subsequently weighed to determine amounts of consumption.

Beginning 40 hours after the movie, trained telephone interviewers (Elrick & Lavidge, Chicago) began collecting information on any adverse events experienced since the movie. All participants were specifically asked if they had any digestive symptoms during or since the movie and, if so, to specify those symptoms. The participant's own words were captured; additional information, including timing and severity, was completed for each reported symptom. Symptom severity, was rated on a scale of mild, moderate, or severe, based on no, partial, or complete impairment of daily activities, respectively. Each participant was also asked about preexisting food intolerances or GI medical conditions. Multiple attempts were made to telephone all participants within 4 days of the movie. Attempts to contact those individuals not reached continued for another week.

The study was designed to provide 80% power (at .05 level) for detecting true differences in proportions of symptoms of 10% vs 15%, based on 700 subjects per group. All symptoms were classified blinded according to an adverse event coding dictionary.[6] Incidence of GI symptoms by category was compared between the olestra and triglyceride (TG) potato chip groups using the Fisher exact test. Treatment comparisons of consumption, satiety, and preference data were made using a 2-sample t test or Wilcoxon rank-sum test. All P values listed are 2-sided and were not adjusted for the multiplicity of variables being compared. Approximate 95% confidence intervals for the difference in 2 proportions were constructed using the standard, large-sample normal approximation method.

Results

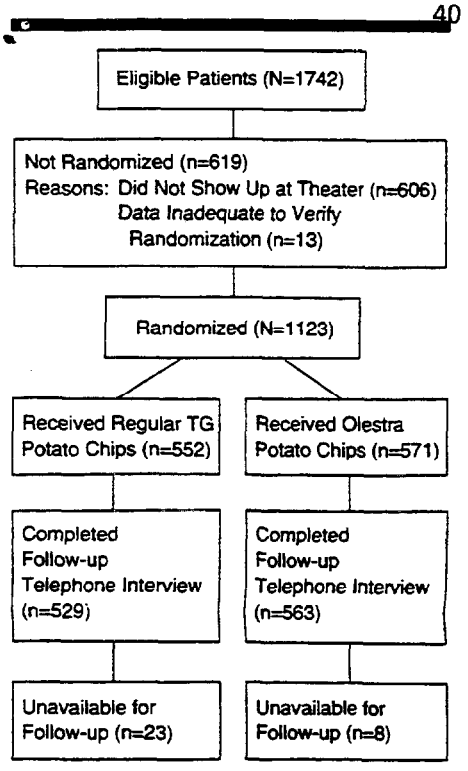
Of the 1742 individuals qualified for the study, 1123 kept their appointment times and viewed a movie. There were 31 individuals who could not be recontacted, leaving a total of 1092 evaluable subjects for data analysis. Follow-up telephone interviews had been completed by day 4 for 89% and by day 10 for 99% of these participants.

There were no significant differences between the olestra and TG groups in sex, race, or age composition (56% vs 58% female and 87% vs 86% white, with a mean age of 35.4 vs 34.7 years, respectively; $P>.40$). There was a broad range of chip consumption in both groups, with the median consumption of TG chips somewhat higher than that of olestra chips (77 g vs 60 g [2.7 oz vs 2.1 oz]; $P<.001$). Overall chip consumption was similar across age groups, but males generally consumed more chips than females (median, 80 g vs 60 g [2.8 oz vs 2.1 oz]; $P<.001$). The overall palatability of the TG chips was also rated higher than the olestra chips, with a mean score of 6.4 vs 5.6 on a 9-point overall preference scale ($P<.001$). However, there were no significant differences between the groups in satiety, as indicated by mean satiety scores of 5.9 vs 5.7 for TG and olestra chips, respectively, on a 9-point fullness scale, with 9 being "extremely full" ($P=.07$), nor were any significant differences seen in beverage consumption, choice of beverage, or time since last meal prior to the movie.

There were 3 adverse events reported prior to the scheduled recall: (1) a participant had nausea and vomiting during the movie after eating 14 g (0.5 oz) of olestra chips (she reported feeling ill prior to the movie); (2) a participant had nausea and vomiting after eating 51 g (1.8 oz) of TG chips (the only individual in the study who reported seeking the care of a physician); and (3) a participant had cramping, diarrhea, and fecal incontinence the morning after the movie after eating 289 g (10.2 oz) of TG chips. The remaining experiences were collected as part of routine "callbacks."

Analysis of the incidence of GI adverse events indicated no significant difference between the 2 groups, with 17.6% and 15.8% of the TG and olestra subjects, respectively, reporting 1 or more GI complaints ($P=.47$) (Table). There were also no significant differences or trends between groups in the incidence of any of the 14 individual GI symptoms reported. The overall mean symptom severity for any GI event was not different between groups (mean, 1.3; $P=.83$), nor was there a significant difference in symptom severity for any GI event between olestra and TG in individuals eating more than 113 g (4 oz) of chips (mean, 1.5 vs 1.3; $P=.49$). The percentage of individuals with any GI symptom and with each of the specific symptoms (gas, diarrhea, abdominal pain, upset stomach, abdominal cramping, and loose stool) was compared between olestra and TG groups across 4 chip-consumption levels (0-57, 57-113, 113-170, and 170-369 g [0-2, 2-4, 4-6, and 6-13 oz). There was no indication of increasing symptom incidence with greater consumption in either the olestra or TG group. Also, there were no significant differences between the 2 groups in incidence within 7 symptom and 4 consumption categories (28 comparisons), except for 2 isolated findings of increased incidence of any GI symptom for the TG group in the 57- to 113-g (2- to 4-oz) category (20.6% vs 11.3%; $P=.001$) and increased upset stomach for the olestra group in the 0- to 57-g (0- to 2-oz) category (2.6% vs 0%; $P=.05$).

In subjects with a history of GI disorders, there was no greater frequency of GI complaints in those receiving olestra than TG (6/33 [18%] vs 6/29 [21%], $P>.99$).



Progress of study participants during randomization and follow-up. TG indicates triglyceride.

Comment

We found no increased incidence or severity of GI symptoms of any type in a

Adverse Events Summary*

Adverse Event	Treatment Group: TG (n=529)	Olestra (n=563)	P Value	Difference (95% CI)†
Any GI event	93 (17.6)	89 (15.8)	.47	−1.8 (−6.2 to 2.7)
Gas	34 (6.4)	27 (4.8)	.29	−1.6 (−4.4 to 1.1)
Diarrhea	14 (2.6)	17 (3.0)	.72	0.4 (−1.6 to 2.3)
Abdominal pain	19 (3.6)	13 (2.3)	.22	−1.3 (−3.3 to 0.7)
Upset stomach	11 (2.1)	11 (2.0)	>.99	−0.1 (−1.8 to 1.5)
Abdominal cramping	10 (1.9)	11 (2.0)	>.99	0.1 (−1.6 to 1.7)
Loose stools	6 (1.1)	9 (1.6)	.61	0.5 (−0.9 to 1.8)
Other GI events‡	21 (4.0)	19 (3.4)	.63	−0.6 (−2.8 to 1.6)

*TG indicates triglyceride; CI, confidence interval; and GI, gastrointestinal. All treatment group values are number (percentage) of subjects reporting 1 or more events.
†Values are the difference (95% CI) in symptom frequency between olestra and TG groups.
‡Other GI events included nausea, bloating, indigestion, aftertaste, belching, constipation, vomiting, or bloody stool.

large group of subjects consuming olestra chips ad libitum during 1 sitting in a movie theater. While this setting may be unique for a clinical trial, the study was structured to meet rigorous controlled clinical trial standards under conditions typical for the use of the snack foods.

Overall preference for olestra potato chips was slightly lower, and this is probably reflected in the 22% lower chip consumption in the olestra group. Despite lower consumption, the olestra group reported being no less satiated than the TG chip group. This suggests a previously reported[7] possibility that olestra use will reduce energy and fat intake, aiding weight control in those who consume potato chips. While the median consumption of olestra chips was less than TG chips, it was more than 57 g (2 oz), which is more than a typical single-serving snack-sized bag of chips, and there were 155 subjects who consumed more than 113 g (4 oz) of olestra chips (>33 g of olestra). Thus, the consumption levels were adequate to ensure that enough olestra was consumed to evaluate potential GI effects. However, even in the participants consuming more than 113 g (4 oz), there were no differences observed in the frequency or severity of reported GI symptoms between groups, nor was there any indication of a dose-response relationship of increasing symptoms with higher consumption levels in either test group. The 2 statistically significant findings (increased upset stomach in the 0- to 57-g [0- to 2-oz] olestra group and increased incidence of any symptom in the 57- to 113-g [2- to 4-oz] TG group) appear likely to be due to random variation.

The information label on olestra products states that "olestra may cause loose stools and abdominal cramping." The current study findings do not support this statement. The label primarily reflects the results from 2 clinical studies in which subjects were required to consume olestra at every meal for 56 consecutive days. In those studies there were statistically significant increases (19%-42%) in mild to moderate GI symptoms in persons eating 20 or 32 g of olestra per day in foods (equivalent to 68-111 g [2.4-3.9 oz] of chips relative to the current study) compared with placebo subjects.[8,9] However, in other studies conducted under ad libitum home-use conditions that included more than 3500 participants, no differences were found in the reporting of GI symptoms compared with TG snack control groups.[10]

The manufacturer of olestra is currently conducting postmarketing surveillance via toll-free telephone numbers on packages of olestra-containing snack products. Reporting frequency has been related to news media coverage on the controversy about potential GI effects. While the current study was designed to evaluate symptom occurrence under conditions at 1 sitting, this type of consumption constitutes the majority of consumer complaints to the manufacturer to date (81%). These same individuals report a median consumption of 48 g [1.7 oz] of chips.[11] Thus, these reports would not appear to be supported by the findings in the present study.

What, then, are alternative explanations for the symptoms experienced by these consumers and by the participants in the present study? It has been demonstrated in a large-scale survey that functional GI symptoms are quite common in the general population, with up to 69% of individuals reporting 1 or more symptoms during a 3-month period.[12] Food intolerances are also commonly reported in the population.[13] Of note, however, are our findings that increased symptom rates were not observed in individuals consuming more chips and that there was a lack of association between reported history of GI problems and symptoms in the present study. Finally, because possible GI symptoms were mentioned in the informed consent, a potential "nocebo," or negative placebo effect, may be increasing the rate of reporting. For example, in 1 published study, a 6-fold increase in the number of patients withdrawing from a trial because of minor GI symptoms was found when a statement outlining these possible adverse effects was included in the informed consent.[14]

Regardless of the potential explanations for the high rate of GI symptoms reported, we were unable to demonstrate any increase in the frequency of GI symptoms when participants ate as many olestra potato chips as they cared to at 1 time. Previous and ongoing studies address GI symptom incidence under a variety of other consumption settings. The present findings provide practical information on the effects of olestra consumed in a typical fashion.

Funding for this study was provided by Procter & Gamble Company, Cincinnati, Ohio.

References

1. US Department of Health and Human Services, Food and Drug Administration. Food additives permitted for direct addition to food for human consumption; olestra. *Federal Register*. 1996;61:3118-3173.
2. Mattson FH, Volpenhein RA. Hydrolysis of fully esterified alcohols containing from one to eight hydroxyl groups by the lipolytic enzymes of rat pancreatic juice. *J Lipid Res*. 1972;13:325-328.
3. Mattson FH, Nolen GA. Absorbability by rats of compounds containing one to eight ester groups. *J Nutr*. 1972;102:1171-1176.
4. Bergholz CM. Safety evaluation of olestra, a nonabsorbed, fatlike fat replacement. *Crit Rev Food Sci Nutr*. 1992;32:141-146.
5. Levine A. Food fight in Indianapolis. *US News & World Report*. May 5, 1997:53-54.
6. US Food and Drug Administration. *COSTART: Coding Symbols for Thesaurus Adverse Reaction Terms*. 5th ed. Rockville, Md: US Food and Drug Administration; 1995.
7. Miller DL, Hammer VA, Shide DJ. et al. Consumption of fat-free potato chips by obese and restrained males and females. *FASEB J*. 1995;9:A190.
8. Schlagheck TG, Riccardi KA, Zorich NL, Torri SA, Dugan LD, Peters JC. Olestra dose response on fat-soluble and water-soluble nutrients in humans. *J Nutr*. 1997;127(suppl 8):1646S-1665S.
9. Schlagheck TG, Kesler JM, Jones MB, et al. Olestra's effect on vitamins D and E in humans can be offset by increasing dietary levels of these vitamins. *J Nutr*. 1997;127(suppl 8):1666S-1685S.
10. Peters JC, Lawson KD, Middleton SJ, Triebwasser KC. Assessment of the nutritional effects of olestra, a nonabsorbed fat replacement: summary. *J Nutr*. 1997;127(suppl 8):1719S-1728S.
11. Zorich NL, Biedermann D, Riccardi KA, Bishop LJ, Filloon TG. Randomized, double-blind, placebo-controlled consumer rechallenge test of Olean salted snacks. *Regul Toxicol Pharmacol*. 1997;26:200-209.
12. Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders. *Dig Dis Sci*. 1993;38:1569-1580.
13. Kang JY, Tay HH, Guan R. Chronic upper abdominal pain: site and radiation in various structural and functional disorders, and the effect of various foods. *Gut*. 1992;33:743-748.
14. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. *Clin Pharmacol Ther*. 1987;42:250-253.

BIBLIOGRAPHIC DATA SHEET	1. Report No. FDABF-GRAS-119	2.	3. Recipient's Accession No. PB 221 951
4. Title and Subtitle: EVALUATION OF THE HEALTH ASPECTS OF SORBITOL AS A FOOD INGREDIENT			5. Report Date: December, 1972
			6.
7. Author(s)			8. Performing Organization Rept. No. SCOGS-9
9. Performing Organization Name and Address: Life Sciences Research Office, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, Maryland 20014			10. Project/Task/Work Unit No.
			11. Contract/Grant No. FDA 72-85
12. Sponsoring Organization Name and Address: Bureau of Foods, U.S. Food and Drug Administration, 200 "C" Street, S.W., Washington, D.C. 20204			13. Type of Report & Period Covered
			14.

15. Supplementary Notes

16. Abstracts

This report by a group of qualified scientists, designated the Select Committee on GRAS Substances (SCOGS), provides an independent evaluation on the safety of sorbitol in food at its present or projected levels of use.

17. Key Words and Document Analysis. 17a. Descriptors

17b. Identifiers/Open-Ended Terms

Reproduced by
NATIONAL TECHNICAL INFORMATION SERVICE
US Department of Commerce
Springfield, VA. 22151

17c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report) UNCLASSIFIED	21. No. of Pages
	20. Security Class (This Page) UNCLASSIFIED	22. Price

SCOGS-9

EVALUATION OF THE HEALTH ASPECTS OF SORBITOL AS A FOOD INGREDIENT

DECEMBER 1972

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 72-85

Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

ia

NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology under contract with the Food and Drug Administration of the U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their competence and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

C. Jeffe Carr

C. Jeffe Carr, Ph.D., Director
Life Sciences Research Office
FASEB

CONTENTS

		Page
I.	Introduction	1
II.	Background information	1
III.	Consumer exposure data	2
IV.	Biological studies	4
V.	Opinion	6
VI.	References cited	7
VII.	Scientists contributing to this report	10

I. INTRODUCTION

Under the terms of FDA Contract 72-85, dated March 30, 1972, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using sorbitol as a food ingredient, primarily on the basis of information contained in a monograph summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents available as of December 1972. The LSRO Select Committee on GRAS Substances has reviewed these materials and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of sorbitol under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Sorbitol, which is one of the hexahydric alcohols derived commercially by the catalytic reduction of glucose, is a normal constituent of such fruits as cherries, plums, pears, apples, and many berries (1, 2).

The Food Chemicals Codex specifies that the food grade product should contain not less than 91 percent sorbitol, and the food grade solution, not less than 64 percent sorbitol. Maximum limits are specified for arsenic, heavy metals, chloride, sulfate, total sugars, and reducing sugars (3).

In the food industry, sorbitol is used to promote retention of original food quality during storage and shipment or to endow foods with improved quality or texture, because of its capacity to function as a crystallization modifier, humectant, softening or plasticizing agent, sweetness or viscosity controller, or rehydration aid (2).

Sorbitol is present in amounts ranging from 93.5 to 0.001 percent in the following categories of foods, arranged in decreasing order of sorbitol content: hard candy, chewing gum, soft candy, baked goods, frozen dairy products, milk products, poultry products, fish products, nonalcoholic beverages, meat products, frostings, snack foods, processed fruits, nut products, fats and oils, gelatin puddings, alcoholic beverages, sweet sauces, and seasonings and flavors (4).

It should be noted that the Federal Food and Drug Administration's GRAS list indicates a tolerance of 7 percent for sorbitol in foods for special dietary use (23). In a conflicting order (24), FDA states that sorbitol may be safely used in food provided the amount used does not exceed that reasonably required to accomplish the physical or technical effect.

Sorbitol is reported to have been first used as a food ingredient in the United States in 1929. The total amount of sorbitol used in foods in 1970 is reported to be about seven times that used in 1960 (4). However, there is no information now available to the Select Committee that permits it to determine the extent to which there has been significant change in the sorbitol content of the foregoing food categories over the past decade.

III. CONSUMER EXPOSURE DATA

A comprehensive survey by a National Research Council subcommittee has provided information on the possible daily human intake of sorbitol in the total diet, as shown in the following table for individuals in various age groups (4). The Select Committee has converted these figures to possible intakes per kilogram of body weight.

Age group	Possible daily intake			
	Total		Per kilogram of body weight*	
	Average	Maximum	Average	Maximum
	mg	mg	mg	mg
0-5 months	770	2,096	154	419
6-11 months	6,959	17,223	870	2,153
12-23 months	13,670	27,419	1,243	2,493
2-65+ years	30,191	55,439	503	924

*Calculations based on an average weight of 60 kg for an adult (5) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (6).

It is recognized that the figures calculated for the daily intake of sorbitol per kg of body weight in the age group 2-65+ years could be deceptively low, since the majority of individuals from age 2 to maturity will probably weigh less than 60 kg. Thus the daily intake of sorbitol for children could be significantly higher than the figures indicated. For example, a child weighing 20 kg could consume, on the average, 1,510 mg per kg rather than 503 mg, and at a maximum, 2,772 mg per kg per day rather than 924 mg.

However, such deviations from the figures in the table must also be considered in respect to total production and use of sorbitol. The data developed by the NRC subcommittee are based on (a) a survey of the frequency of eating various food products, (b) a determination of the portion size of these food products, and (c) a survey of food producers to determine the percentage use of sorbitol in these food products (4). The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins.* That human intakes are undoubtedly overstated in the case of sorbitol is borne out by the following two calculations.

The NRC subcommittee has also provided data (4) to show that the use of sorbitol for food purposes in the United States was 7,622,141 pounds (3.46 million kg) in 1970. This figure is reported to comprise between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (12.70 million pounds or 5.77 million kg), and a U.S. population of 200 million, the per capita per day average intake would be only 79 mg rather than the 30,191 mg given in the foregoing table.

U.S. Tariff Commission figures (21) show that 105 million pounds (47.7 million kg) of sorbitol were produced in the U.S. in 1970 for all purposes. Even if all of the 105 million pounds were used in food, the per capita per day average intake of sorbitol would be only 654 mg rather than the 30,191 mg given in the foregoing table.

---

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC succommittee report (4). The Select Committee finds this explanation reasonable and concurs in the first recommendation of Section XII of the same report that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."

On the basis of these considerations, the Select Committee regards the figures given in the table as levels that are highly unlikely to be achieved by any of the age groups, but more likely, are generous over-estimates of the sorbitol content of the daily diet.

IV. BIOLOGICAL STUDIES

Orally administered sorbitol is absorbed and metabolized rapidly by man through normal glycolytic pathways, ultimately to carbon dioxide and water (7, 8, 9, 10). After a 35 g dose (equivalent to 583 mg per kg) in normal and in diabetic adults, for example, less than 3 percent of the sorbitol was excreted in the urine in any case and the concentration of sorbitol in the blood was found to be immeasurably small. No evidence of toxicity was reported (7).

The oral LD_{50} of sorbitol in male and female mice is reported to be 23,200 and 25,700 mg per kg respectively; in male and female rats, 17,500 and 15,900 mg per kg respectively (11). The oral LD_{100} for the male rat is separately reported as 26,000 mg per kg (12).

The following short term studies of the oral administration of sorbitol are relevant:

> In 40 g male rats, fed 5 percent sorbitol in a balanced diet, no toxic effects were observed during the three months of feeding (13). Feed consumption is not reported, but estimates based on other data presented indicate that sorbitol was being fed at a level of approximately 5 g per kg per day.
>
> Rhesus monkeys fed sorbitol at a level of 8 g per kg per day for 3 months remained unaffected (13).
>
> Man, consuming 10 g of sorbitol each day (equivalent to 167 mg per kg) for one month remained unaffected (13).
>
> Normal children, 5-6 years old and normal infants, 20-35 months old, fed 9.3 g of sorbitol (equivalent to 500 or more mg per kg) remained unaffected except for the appearance of diarrheal stools in the younger group (14).

The laxative threshold for sorbitol, established in 12 normal adults, has been reported to be 50 g (equivalent to 833 mg per kg) (13). It is also reported, in a study involving 86 volunteers, that a dosage level of 25 g per day in two doses does not cause laxation (22).

The following long-term studies of the oral administration of sorbitol are relevant:

> Rats fed 5 percent sorbitol (equivalent to 5 g per kg per day) through three generations showed no deleterious effects on growth rate or liver glycogen storage capacity. There were no gross or histological abnormalities in kidney, liver, spleen, pancreas, or duodenum attributable to sorbitol (15). A subsequent report has indicated that weanling rats, given sorbitol at levels of 10 to 15 percent in the diet for 17 months and observed over 4 successive generations, showed no evidence of deleterious effects on weight gain, reproduction, lactation, or histological appearance of the main organs (11).
>
> Rats fed 16 percent sorbitol for 19 months showed a tendency to become hypercalcemic after one year, with the appearance in some animals of bladder concretions and a generalized thickening of the skeleton (16). No feed consumption or animal weight figures were reported, but sorbitol level was estimated to be of the order of 16 g per kg.
>
> No oral studies of the carcinogenic activity of sorbitol have been reported. However, studies in rats revealed that injected sorbitol, in the form of an iron-sorbitol citric acid product (Jectofer), produced no injection site tumors.

Sorbitol, at dose levels of 5 g per kg did not produce any measurable mutagenic response in the host-mediated assay in mice, in the metaphase chromosomes of rat bone marrow, or in the dominant lethal test in the rat. A slight increase was noted in the mitotic recombination frequency for Saccharomyces cerevisiae in the host-mediated assay, and a moderate, dose-related adverse effect was exhibited by human embryonic lung cells scored at anaphase (19).

Sorbitol elicited no teratogenic response in pregnant mice or rats fed a daily dose of 1600 mg per kg for 10 days, or in hamsters fed 1200 mg per kg per day for 5 days (20).

The Joint Food and Agriculture Organization/World Health Organization Committee on Food Additives indicates the acceptable daily intake of sorbitol for man as follows: "Conditional acceptance (as a food additive or as a food) not limited" (11).

V. OPINION

The available information reveals that there are no short-term toxicological consequences in rats, mice, monkeys, or man, and no long-term toxicological consequences in rats, of consuming sorbitol in amounts exceeding those currently consumed in the normal diet of the U.S. population. There is no evidence that consumption of sorbitol as a food ingredient has had adverse effects on man in the many years it has been so used.

It is to be noted that sorbitol begins to exert a laxative effect at levels that are about twice the estimated average adult intake level and about equal to the estimated maximum adult intake level. It should be noted also that the average consumption levels of children in the age groups 6-11 months and 12-23 months are now estimated to be close to, or in excess of, those capable of exerting a laxative effect. However, because the reported average and maximum intake levels are known to be generous overestimates, it is the opinion of the Select Committee that the use of sorbitol in food in the present or reasonably foreseeable amounts poses no problem in this regard.

The Select Committee is concerned that the actual consumption of sorbitol may be considerably higher than average consumption in certain segments of the population. These individuals, for dietary reasons, may select foods containing particularly high levels of sorbitol. Currently available food consumption data do not permit the Select Committee to determine the extent and significance of this problem in regard to sorbitol.

The Select Committee has weighed the foregoing and concludes that:

> There is no evidence in the available information to show that sorbitol as a food ingredient constitutes a hazard to the general public when used at levels that are now current or that might reasonably be expected in future.

VI. REFERENCES CITED

1. Informatics, Inc. 1972. Monograph on sorbitol. Submitted under DHEW contract no. FDA 72-104. Rockville, Md.

2. Griffin, W.C., and M.J. Lynch. 1968. Polyhydric alcohols. Pages 447-460 *in* T.E. Furia, ed. Handbook of food additives. The Chemical Rubber Co., Cleveland, Ohio.

3. National Research Council. 1972. Sorbitol. Pages 786-791 *in* Food chemicals codex, 2nd ed. National Academy of Sciences, Washington, D.C.

4. Subcommittee on Review of the GRAS List (Phase II). 1972. A comprehensive survey of industry on the use of food chemicals generally recognized as safe (GRAS). Prepared under DHEW contract no. FDA 70-22, Committee on Food Protection, Division of Biology and Agriculture, National Research Council. National Academy of Sciences, Washington, D.C.

5. Nelson, A.A. 1954. Approximate relation of parts per million in diet to mg/kg/day (table). Assoc. Food Drug Officials Quart. Bull. 18: 66.

6. Altman, P.L., and D.S. Dittmer, editors. 1972. Pages 201-202 *in* Biology data book, 2nd ed., vol. 1. Federation of American Societies for Experimental Biology, Bethesda, Md.

7. Adcock, L.H., and C.H. Gray. 1957. The metabolism of sorbitol in the human subject. Biochem. J. 65: 554-560.

8. Blakley, R.L. 1951. The metabolism and antiketogenic effects of sorbitol. Sorbitol dehydrogenase. Biochem. J. 49: 257-271.

9. Hers, H.G. 1955. The conversion of fructose-1-C^{14} and sorbitol-1-C^{14} to liver and muscle glycogen in the rat. J. Biol. Chem. 214: 373-381.

10. Steinke, J., F.C. Wood, L. Domenge, A. Marble, and A.E. Renold. 1961. Evaluation of sorbitol in the diet of diabetic children at camp. Diabetes 10: 218-227.

11. Joint FAO/WHO Expert Committee on Food Additives. 1964. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents. 7th rept. Food and Agriculture Organization of the United Nations, Geneva, Switzerland. 189 pp.

12. Carr, C.J., and S.E. Forman. 1939. Sugar alcohols. XX. The fate of d-sorbitol, styracitol, and l-sorbose in the animal body. J. Biol. Chem. 128: 425-430.

13. Ellis, F.W., and J.C. Krantz, Jr. 1941. Sugar alcohols. XXII. Metabolism and toxicity studies with mannitol and sorbitol in man and animals. J. Biol. Chem. 141: 147-154.

14. Gryboski, J.D. 1966. Diarrhea from dietetic candies. New Engl. J. Med. 275: 718.

15. Ellis, F.W., C.J. Carr, E.J. Wiegand, and J.C. Krantz, Jr. 1943. Sugar alcohols. XXIII. Effect of sorbitol feeding on successive generations of rats. Proc. Soc. Exp. Biol. Med. 52: 260-261.

16. Fournier, P.L., J. Gambier, and N. Fontaine. 1967. The effects of prolonged ingestion of sorbitol on calcium utilization and ossification of the rat. C.R. Acad. Sci. Paris 264: 1301-1304. (In French; translation supplied with reference #1.)

17. Roe, F.J.C., and A. Haddow. 1965. Test of an iron sorbitol-citric acid complex (Jectofer) for carcinogenicity in rats. Brit. J. Cancer 19: 855-859.

18. Wrba, H., and U. Mohr. 1968. Cancer produced by injections of iron complexes. Muenchen. Med. Wochenschr. 110: 139-140. (In German; translation supplied with reference #1.)

19. Stanford Research Institute. 1972. Study of mutagenic effects of sorbitol (71-31). Compound report no. 10 prepared under DHEW contract no. FDA 71-267. Menlo Park, Calif. [122 pp.].

20. Food and Drug Research Laboratories, Inc. 1972. Teratologic evaluation of FDA 71-31 (sorbitol) in mice, rats, and hamsters. Report prepared under DHEW contract no. FDA 71-260. Maspeth, N.Y. [43 pp.].

21. U.S. Tarriff Commission. 1972. Page 213 *in* Synthetic organic chemicals. United States Production and Sales, 1970. TC Publ. 479. Government Printing Office, Washington, D.C.

22. Peters, R., and R.H. Lock. 1958. Laxative effect of sorbitol. Brit. Med. J. 5097: 677-678.

23. Office of the Federal Register, General Services Administration. 1972. Page 24 *in* Code of Federal Regulations. Title 21, Food and drugs, parts 120-129, rev. Government Printing Office, Washington, D.C.

24. Office of the Federal Register, General Services Administration. 1972. Page 140 *in* Code of Federal Regulations. Title 21, Food and drugs, parts 120-129 rev. Government Printing Office, Washington, D.C.

VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

Aaron M. Altschul, Ph. D., Professor, Department of Community Medicine and International Health, School of Medicine, Georgetown University, Washington, D. C.

Joseph F. Borzelleca, Ph. D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Va.

Bert N. La Du, Jr., M. D., Ph. D., Professor and Chairman, Department of Pharmacology, New York University School of Medicine, New York, N. Y.

John R. McCoy, V. M. D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, N. J.

Sanford A. Miller, Ph. D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass.

Gabriel L. Plaa, Ph. D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Ralph G. H. Siu, Ph. D., Consultant, Washington, D. C.

John L. Wood, Ph. D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tenn.

George W. Irving, Jr., Ph. D. (Chairman), Research Associate, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.

2. Ex officio:

C. Jelleff Carr, Ph. D., Director, LSRO/FASEB

Samuel B. Detwiler, Jr., Research Associate, LSRO/FASEB

Report Submitted by:

January 22, 1973
Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances

The Nutritional Effects of Olestra

Estimated Consumption and Eating Frequency of Olestra from Savory Snacks Using Menu Census Data[1,2]

D. Ronald Webb, Gail G. Harrison,* Min-June Lee* and Mei-Hua Huang*

*The Procter & Gamble Company, Winton Hill Technical Center, Cincinnati, OH 45224 and *University of California, School of Public Health, Los Angeles, CA 90095*

ABSTRACT Potential chronic (14-d average) and acute (single-day) estimated daily intakes (EDI) were computed for olestra, a fat replacement intended for use in preparing savory snacks. The EDI were computed from eating occasions reported during a 14-d Menu Census survey among 4741 consumers; values were increased by 10% for conservatism. The eating occasions included all meals and in-between meal occasions eaten at home or away. Data from only those individuals who ate savory snacks at least once during the 14 d were used; this included 3820 individuals (81% of the sample) and represented a total of 16,067 eating days (24% frequency). The estimated mean chronic intake ranged from 1.8 to 4.7 g/d, depending on age and gender; at the 90th percentile, the range was 4.1–11.0 g/d. For all ages and both genders, the estimated mean intake was 3.1 g/d. Estimated acute intakes at the mean and 90th percentile ranged from 5.5 to 16.5 g/d and from 10.2 to 24.0 g/d, respectively, depending on age and gender. For all ages and both genders, the estimated mean intake was 10.2 g/d. The lack of parity in the chronic and acute intake estimates indicates that savory snacks are not eaten on a daily basis by the majority of snack eaters. The survey data were analyzed to understand the potential temporal eating patterns of olestra from savory snacks. When snacks were consumed, on average, 69% of the eating occasions were with main meals and 31% were between meals. Savory snacks did not contribute a major fraction of total food to the diet; only 7 and 18% of main meals contained a savory snack food at the 50th and 90th percentile, respectively. For the 50th-percentile consumer (all ages, both genders), savory snacks were eaten four times during the 14-d survey period, and the eating occasions occurred on 3 d. Comparable results for 90th-percentile consumers were 10 eating occasions and 8 eating days. J. Nutr. 127: 1547S–1554S, 1997.

KEY WORDS: • *olestra* • *intake* • *human* • *menu census*

Olestra is a mixture of sucrose polyesters formed from the addition of fatty acids to six, seven or eight of the hydroxyl positions on a sucrose backbone. Saturated and unsaturated fatty acids with a chain length ranging from C_{12} to C_{20} and higher can be used in the manufacture of olestra if the final product meets established fatty acid compositional specifications and the fatty acids are derived from edible sources (Federal Register 1996). The fatty acids used to produce olestra impart the same physical properties, taste and cooking characteristics, and heat stability profiles to olestra as found in the starting triglyceride (Gardner and Sanders 1990, Henry et al. 1992, Kester 1993).

Olestra (Olean, Procter & Gamble, Cincinnati, OH) is approved as a replacement for up to 100% of the fats and oils used in the preparation of savory (i.e., salty or piquant but not sweet) snacks such as flavored and unflavored chips and crisps, flavored and unflavored extruded snacks, and crackers (Federal Register 1996).

The purpose of the dietary assessment study described here was to determine the potential estimated daily intake (EDI)[3] of olestra from the consumption of savory snacks prepared with olestra and to determine how (i.e., how often, in what context) savory snacks are consumed. This was done by analyzing 14-d food diaries collected by Market Research Corporation of America (MRCA) Information Services (Des Plaines, IL) from 4741 individuals during 1991–92. The data were analyzed to provide estimates of the following: *1*) potential chronic (14-d average) and acute (amount eaten in a single day) EDI of olestra from the consumption of savory snacks, *2*) potential frequency at which olestra will be eaten as defined by the number of times and the number of days savory snacks are normally eaten over a 14-d period, and *3*) potential pattern of olestra consumption as defined by main meal and in-between meal eating occasions for savory snacks within a 14-d period. The EDI were determined on a gram per person per day basis but for simplicity will be referred to in gram per day (g/d) throughout this paper.

The MRCA Menu Census method was chosen because of its large size (e.g., about 2000 households and 5000 individu-

[1] Published as a supplement to *The Journal of Nutrition*. Guest editors for this supplement were John W. Suttie, University of Wisconsin, Department of Biochemistry and Nutritional Sciences, 420 Henry Mall, Madison, WI and A. C. Ross, Pennsylvania State University, 126 S. Henderson Bldg., University Park, PA 16802.

[2] Address correspondence to Suzette J. Middleton, Ph.D., The Procter & Gamble Company, Winton Hill Technical Center, 6071 Center Hill Road, Cincinnati, OH 45224.

[3] Abbreviations used: CSFII, Continuing Survey of Food Intake by Individuals; EDI, estimated daily intake; FDA, Food and Drug Administration; GRAS, generally recognized as safe; NAS, National Academy of Sciences; MRCA, Market Research Corporation of America; NFCS, Nationwide Food Consumption Survey.

0022-3166/97 $3.00 © 1997 American Society for Nutritional Sciences.

als), its duration of assessment (14 consecutive days/subject), its overall time frame (i.e., the survey is conducted annually and runs continuously throughout a calendar year to capture seasonal changes in eating habits) and the similarity of the survey's demographics (e.g., geographic location, age, gender, race, income, education and household size) to U.S. census statistics.

METHODOLOGY AND RESULTS

MRCA Menu Census survey methodology. Potential olestra EDI, eating frequency and eating patterns were derived from 1991–92 Menu Census survey data collected and analyzed by MRCA Information Services. This survey represented the most recent Menu Census data available at the time the assessment was made, 1993. The MRCA methodology was originally developed by the National Academy of Sciences (NAS) generally recognized as safe (GRAS) Review Committee Phase I, and has been refined substantially in continued work with the U.S. Food and Drug Administration (FDA), with subsequent NAS GRAS Review committees, and with many commercial organizations (Abrams 1992).

The MRCA Menu Census survey has been described in detail by Abrams (1992) and will be described only briefly here. As an overview, the survey tracks all foods and beverages (except table salt, table pepper and tap water) consumed by individuals daily, at home and away, at main meals and in between meals throughout a consecutive 14-d period. Key elements of the survey are provided below.

Survey population. The food diaries were collected from a population sample of 4741 men, women and children, representing about 2000 households, throughout the year. The daily diaries are completed by homemakers who were also long-term members of MRCA's National Consumer Panel and Weekly Purchase Diary Panel and who were trained and experienced in reporting personal and family eating habits in great detail.

Households included in the survey were nationally representative according to such criteria as geographic location, household size and household income. An average of 5.5 new households started their biweekly reporting every day of the year, so that each day of the week and of the year was equally represented. The demographic characteristics of the households were comparable with U.S. census demographics (**Table 1**). A final questionnaire included the self-reported age, gender, pregnancy status, weight, height and diet status of each household member. Other household demographic characteristics are collected separately in an annual questionnaire. Compared with the U.S. population in general, the survey population contained an adequate representation of children and a representation of individuals ≥55 years of age greater than that found in the U.S. population (**Table 2**). These two subpopulations might be of greatest concern with respect to the effects of olestra on nutritional status.

Data collected. The diaries included a detailed description of each dish eaten and items added to it at the time of preparation or at the time it was eaten, whether it was eaten at home or away from home, whether it was eaten at breakfast, lunch or dinner or consumed at a morning, afternoon, evening or bedtime snack eating occasion, the position of the dish in the meal (i.e., first, second or third course) and which household members ate the dish. Portion sizes were not reported directly by the homemakers, but rather were estimated from the 1987–88 Nationwide Food Consumption Survey (NFCS) as described below.

Procedure for estimating EDI values. The potential EDI values for olestra were computed daily for each household member of the survey by multiplying the number of times a savory snack was eaten by that person on a given day by the average portion size of that snack food for a person of that age and gender. This result is then multiplied by the potential concentration of olestra in the snack food, assuming 100% replacement of the fat with olestra. Acute (single-day) intake and chronic (14-d average) intakes are derived. The acute intakes reflect the daily intakes for each of the 14 d of the survey period. Thus, an individual contributes 14 acute intake values to the data set, whose values are zero for days in which no savory snacks were eaten. The acute sample size was 14 times 4741 persons or 66,374. The chronic intake is equal to the cumulative intake ove the 14-d period divided by 14, yielding only one chronic intake valu for an individual. In essence, the chronic value is equal to the averag of the 14 daily acute intakes by that person. How the three compo nents of the procedure (i.e., number of times snacks were eate amount consumed per eating occasion and the potential amount olestra in the snack food) were derived is described in more deta below.

Number of times savory snacks were eaten. Determination of th frequency of savory snack consumption was based on a detaile list of all commercial products that could contain olestra as define

TABLE 1

Demographic characteristics of households in the 1991–92 MRCA Menu Census survey and the U.S. census[1]

Demographic characteristic	Percentage of households in MRCA survey	Percentage of households in U.S. cens
Census area		
Northeast	19.9	20.5
North Central	26.2	24.7
South	33.7	34.6
West	20.3	20.2
Census region		
New England	4.6	5.3
Mid-Atlantic	15.4	15.2
East North Central	18.4	17.3
West North Central	7.8	7.4
South Atlantic	17.1	17.8
East South Central	6.9	6.2
West South Central	9.8	10.6
Mountain	5.9	5.5
Pacific	14.4	14.7
Metro area size		
Farm	4.8	3.9
Under 2500	12.4	10.1
2500–50,000	8.3	7.8
50,000–250,000	10.1	9.8
250,000–500,000	10.6	11.1
500,000–1 million	16.1	15.2
1 million–2 million	16.9	17.2
Over 2 million	21.1	24.9
Household annual income		
≤$5,000	2.6	5.2
$5,000–$9,999	6.8	9.7
$10,000–14,999	12.4	9.5
$15,000–19,999	10.7	8.8
$20,000–29,999	21.8	17.0
≥$30,000	45.8	49.8
Education (household head)		
≤9th Grade	3.6	12.8
9th–12th Grade	42.0	43.3
≥13 Years	54.5	43.9
Occupation (household head)		
White collar	34.2	38.9
Blue collar	27.1	30.7
Farmer	1.9	2.4
Not a worker	36.9	28.0
Homemaker employment		
Employed	47.6	54.2
Not employed	52.5	45.8
Household size		
1 Person	28.0	24.6
2 Persons	38.9	32.3
3–4 Persons	25.4	32.8
≥5 Persons	7.8	10.3
Race		
White	91.0	86.1
Nonewhite	9.0	13.9

[1] The U.S. census population estimates include institutional popula tion; the MRCA Menu Census population does not.

TABLE 2

Person characteristics of the households in the 1991–92 MRCA menu census survey and the U.S. census[1]

Person characteristic	Percentage of households in	
	MRCA survey	U.S. census
Males (y)		
Total	44.5	48.7
<2	0.9	1.6
2–5	2.9	3.1
6–12	5.1	5.3
13–17	2.8	3.5
18–24	2.6	4.9
25–34	4.4	8.5
35–44	6.9	7.6
45–54	6.1	5.0
55–64	5.8	4.1
≥65	7.1	5.1
Females (y)		
Total	55.5	51.3
<2	0.9	1.6
2–5	2.5	2.9
6–12	4.1	5.0
13–17	2.5	3.3
18–24	2.7	5.1
25–34	6.5	8.7
35–44	8.9	7.9
45–54	7.8	5.3
55–64	7.8	4.5
≥65	11.8	7.0

[1] The U.S. census population estimates include institutional population; the MRCA Menu Census population does not.

in MRCA's code book of over 20,000 commercial products. The list was continuously updated as new products came on the market. The type of savory snacks tracked in the survey included: curls, puffs and extruded snacks; corn chips; tortilla, nacho and taco chips; potato chips; baked crackers and chips; saltine and oyster crackers; butter- and other-flavored snack crackers; and filled and sandwich-type crackers.

Determination of average amount (i.e., portion size) of savory snacks consumed per eating occasion. The savory snack portion sizes used to estimate olestra EDI were computed by MRCA, for children by age groups, and for adults by age within sex groups, from the USDA/NFCS detailed eating records according to the weighted grams eaten and smoothing these averages over age groups with the use of a method developed under the direction of the FDA and The National Academy of Sciences Food Additives Review Committee. The 1987–88 NFCS (U.S. Department of Commerce 1988) study collected food eating data from each respondent for up to three consecutive days. The data for d 1 were obtained by a trained interviewer by the 24-h assisted recall method. The data for the next 2 d were self-reported by adults, and by the homemaker for children, in separate daily diaries, and collected by the interviewer on a following day. MRCA used only those respondents who reported their eatings for all 3 d, for whom weights were available to balance the sample to the demographic characteristics of the U.S. census and to the days of the week.

The portion sizes ranged from 11 g per person per eating occasion for 2 to 5-y-old children eating crackers to 64 g per person per eating occasion for 45- to 54-y-old males or females eating sandwich-type crackers (Table 3). The portion sizes for males were greater than those for females with one exception; females 18–24 y of age ate larger portion sizes of flavored crackers. The portions sizes for sandwich crackers were the same for males and females. MRCA did not separate children's portion sizes by gender.

The reasonableness of using the 1987–88 NFCS average portion sizes for savory snacks was assessed by analyzing savory snack portion size data from the 1994 Continuing Survey of Food Intake by Individuals (CSFII) (USDA 1996) and comparing those sizes with the NFCS sizes. The distribution of portion sizes reported by those respondents to the 1994 CSFII who reported eating chips and/or crackers on any of the two, widely separated, nonconsecutive days of that survey was examined. The CSFII data are from quantitative 24-h recall of food intake, probed for detail by trained interviewers. Chips were reported in the 1987–88 NFCS as two separate categories, namely, white potato chips, favored and unflavored, and a second category that included corn-based puffs and twists, tortilla chips and corn chips. The entire combined second category was used for examination of the 1994 CSFII data. **Figure 1** shows the mean portion sizes for white potato chips (identified as Chips 1) and tortilla and corn chips and corn puffs (identified as Chips 2) for the 3-d average of the 1987–88 NFCS and for all chips on d 1 and d 2 of the CSFII survey for males and females. **Figure 2** shows the same data for crackers.

The mean CSFII portion size of crackers was slightly greater than the NFCS portion size for the same snacks. There was no clear trend for chips. The serving sizes were similar for females; the CSFII serving sizes for teenage and young adult males tended to be greater than the NFCS sizes.

Determination of the potential olestra concentration in savory snacks. To define the potential olestra content of savory snacks, snack products representative of the different types and methods of manufacture in the industry were analyzed for total replaceable fat content. The percentage (wt/wt) of replaceable fat for each type of snack product was determined by using methods approved by the Association of Official Analytical Chemists (AOCS 1980). Duplicate samples were analyzed and the results were averaged for each type of product. The samples analyzed were selected to include the unflavored and flavored market leaders and additional products, as necessary, to represent the range of taste and texture within each type of savory snack (e.g., sliced potato chip or sandwich cracker).

The fat content of reduced-fat products was not analyzed but rather assumed to be the same as the content of their full-fat counterparts. In addition, any snack food captured in the MRCA census survey and not analyzed directly was assumed to have a replaceable fat content equal to the greatest measured value in that particular product category.

The replaceable fat content (wt/wt %) for the savory snack products assessed in the MRCA survey is summarized in **Table 4**. The replaceable fat content for potato chips, fabricated chips, corn and tortilla chips, and extruded puffs and curls averaged 35% with a range of 27–43%. The replaceable fat content for soda crackers, flavored and unflavored crackers, cracker chips and filled crackers averaged 19% with a range of 1–27%.

Estimated olestra daily intakes. Only the subjects in the Menu Census survey who reported eating savory snacks at least once during 14 consecutive days were used to compute the potential olestra EDI. This was done so that the intake estimates would not be diluted by the presence of the noneaters in the survey. Of the 4741 survey participants, 3820 individuals (81%) met this criterion. For these individuals, frequency distributions of olestra acute (single-day) and chronic (14-d average) intake were produced and intakes tabulated at the mean and 90th percentile. To be conservative, these intake values were then increased by 10%. The distributions of acute and chronic EDI, broken out by age, are presented in **Table 5** for the total survey population and for males and females > 12 y of age separately. Values for children < 13 y of age are not broken out by gender. In addition, estimated intakes for pregnant women and for low calorie and low fat dieters are presented.

The estimated mean acute olestra intake for males and females combined ranged from 6.3 to 14.5 g/d, depending upon age. For the total population, all ages, the mean value was 10.2 g/d. For the 90th-percentile consumer, acute intakes for males and females combined ranged from 11.7 to 23.9 g/d, depending on age; for all ages combined the estimated intake was 18.3 g/d. Males and females in the age range 13–44 y had the largest intakes. Males had larger estimated intakes than females at each age group. The estimated mean and 90th-percentile acute olestra intakes for pregnant females 12–55 y of age were similar to the estimated intakes for nonpregnant females of the same age range. Dieters, both those attempting to control calorie intake (low calorie) and those attempting to control fat intake (low fat), had slightly lower estimated intakes than the average nondieter.

The estimated chronic (14-d average) intakes were less than the

TABLE 3

Range of 50th-percentile portion sizes of savory snacks based upon 3-d reporters in the USDA Nationwide Food Consumption Survey of 1987–88

	Amount consumed per eating occasion[1]				
Age group	Potato chips	Corn-based products	Saltine crackers	Flavored crackers	Sandwich crackers
y	*g*	*g*	*g*	*g*	*g*
2–5	23	23	11	19	34
6–12	30	31	17	27	50
13–17	32–42	40–52	18–26	23–28	56–56
18–24	32–45	37–50	18–28	28–22	54–54
25–34	35–41	34–58	18–20	27–28	51–51
35–44	35–38	23–56	17–29	23–30	53–53
45–54	25–34	30–48	14–25	21–35	64–64
55–64	27–27	23–43	16–21	20–28	54–54
≥65	22–24	25–42	16–22	18–28	59–59

[1] For males and females. The first number is for females, the second for males. Children were not broken out by gender.

estimated acute intakes, as might be expected from the inclusion of their noneating days in their averages. For males and females combined, the mean intakes ranged from 2.0 to 4.4 g/d, depending on age. The mean value for the total population (all ages) was 3.1 g/d. The estimated 90th-percentile chronic intakes for males and females combined ranged from 4.6 to 10.0 g/d, depending on age; the value was 6.9 g/d for all ages combined.

As with the acute intakes, the largest chronic intakes were found for 13- to 44-y-old individuals, either male or female, with males having larger intakes than females at each age group. Pregnant females had estimated chronic intakes somewhat lower than those o

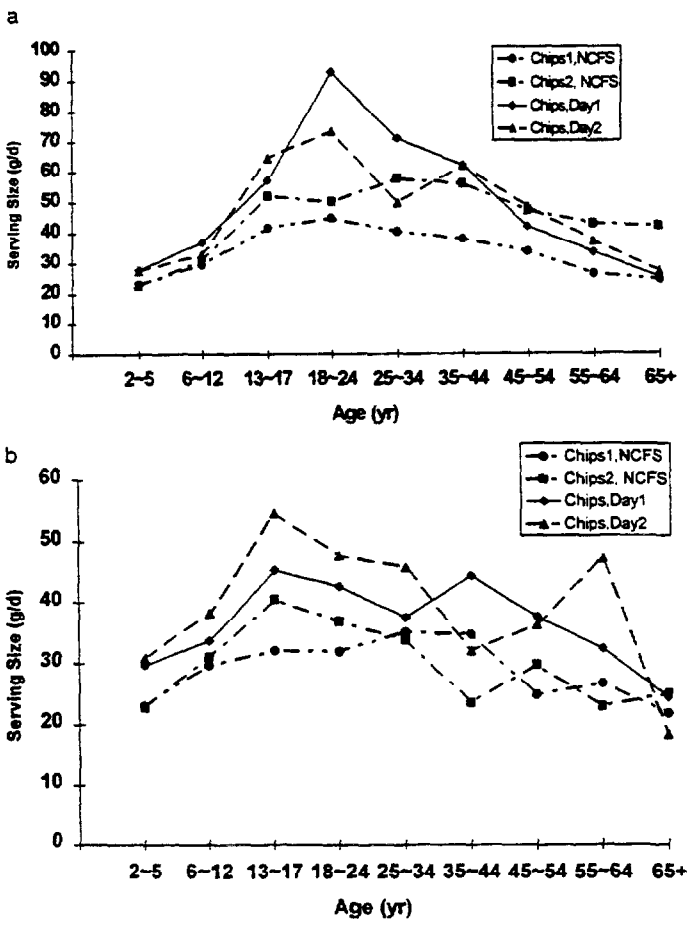


FIGURE 1 Mean portion sizes of white potato chips (Chips 1) and tortilla chips, corn chips and corn puffs (Chips 2) from the 3-d 1987–88 NFCS reporters and d 1 and 2 of the 2-d 1994 CSFII for (*a*) males and (*b*) females.

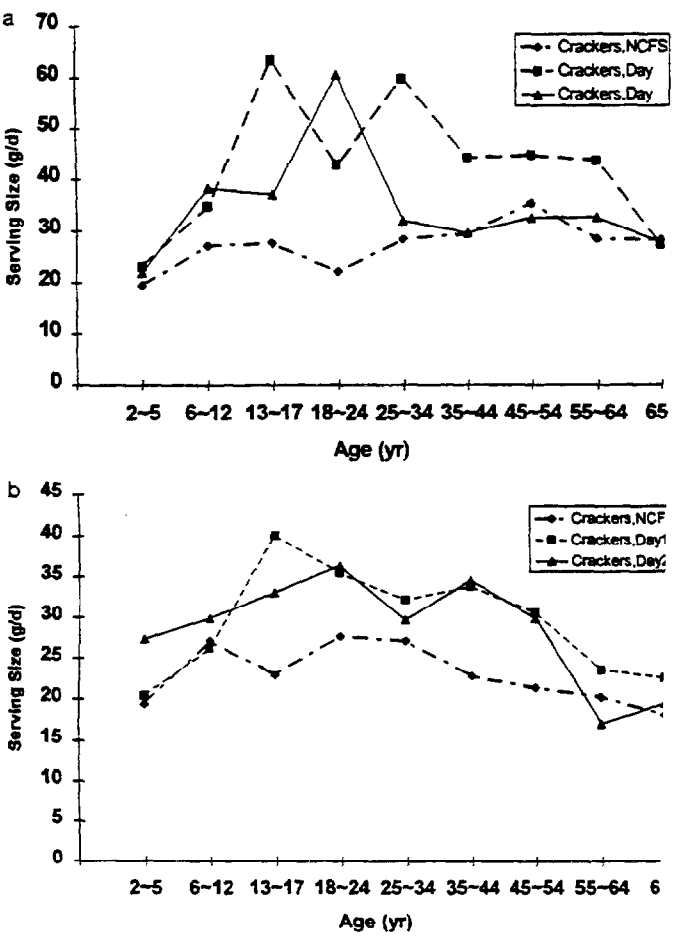


FIGURE 2 Mean portion sizes of crackers from the 3-d 1987–NFCS reporters and d 1 and 2 of the 2-d 1994 CSFII for (*a*) males a (*b*) females.

TABLE 4

Range of replaceable fat content of savory snacks as determined from analytical measurements

Snack category	Replaceable fat content
	% wt/wt
Potato chips	29–43
Corn and tortilla chips	27
Extruded puffs and curls	35
Soda crackers	1–14
Plain crackers	19–21
Flavored crackers	21–27
Filled crackers	23–27
Cracker chips	16–20

nonpregnant females of the same age range, and dieters tended to have slightly lower intakes than the average nondieter.

Olestra eating frequency and meal pattern of consumption. For persons of all ages, savory snacks were eaten on 16,067 d out of a total of 66,374 observed eating days (4741 persons times 14 d), which reflects an eating frequency of about 24%. Age-specific frequency distributions were computed for the number of times and the number of days savory snacks were eaten over the 14-d survey period. The frequency at which savory snacks were consumed at either main meals or in-between meal occasions was also determined.

The number of times savory snacks were consumed out of the 14-d survey period is presented as a histogram in **Figure 3**. Among savory snack eaters only (all ages, both genders), savory snacks were eaten four times in 14 d by the 50th-percentile consumer and about five times by the average consumer. The 90th-percentile consumer ate savory snacks 10 times in 14 d. The maximum number of eatings in 14 d was 35.

The number of days savory snacks were eaten during the 14-d survey period (all ages, both genders) is shown in **Figure 4**. Savory snacks were eaten 3 d out of the 14 by the 50th-percentile consumer. This value increased to 8 d for the 90th-percentile consumer. The maximum number of days was 14 of 14.

On average, 69% of savory snack eatings were with main meals,

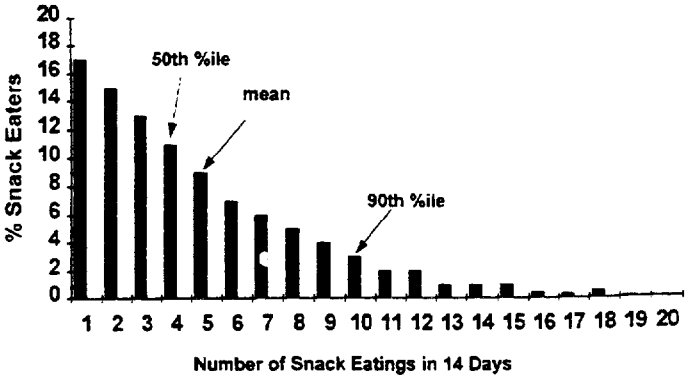


FIGURE 3 Frequency at which savory snacks are consumed in a 14-d period by snack eaters (all ages, both genders).

whereas the remainder were consumed as in-between meal snacks. For the 50th-percentile consumer, only 7% of main meals included savory snack products and for the average consumer, only 8% of main meals. At the 90th percentile, savory snacks were included with 18% of main meals.

DISCUSSION

Menu Census survey data were used to estimate acute and chronic olestra EDI values. The greatest acute intake of olestra for individuals (13- to 17-y-old males or females) consuming savory snacks at the 90th percentile was estimated to be about 24 g/d, equivalent to about 3 ounces of olestra potato chips. The mean acute intake (all ages, both genders) was estimated to be 10.2 g/d. Savory snacks are not eaten on a daily basis; at the 90th-percentile consumption level, they were eaten 10 times in 14 d, and on only 8 of the 14 d. Because of this eating frequency, the estimated chronic (lifetime) daily intake potential for olestra is lower than the acute (single-day) intake. The chronic mean intake (all ages, both genders) is estimated to be 3.1 g/d. The

TABLE 5

Estimated mean and 90th-percentile (90th %) intakes of olestra from the consumption of savory snacks, eaters only

		Estimated acute intake[1]			Estimated chronic intake[2]		
Sample	Age	Eaters	Mean	90th %	Eaters	Mean	90th %
	y	*n*	*g/d*	*g/d*	*n*	*g/d*	*g/d*
Total	2–5	1,189	8.3	13.5	238	3.0	6.4
	6–12	1,826	11.3	18.4	381	3.9	8.0
	13–17	874	14.5	23.9	206	4.4	10.0
	18–44	4,640	13.3	21.7	1,186	3.7	8.1
	45–64	4,090	9.0	16.6	1,034	2.5	5.9
	>64	3,240	6.3	12.5	725	2.0	4.6
	All ages	16,067	10.2	18.3	3,820	3.1	6.9
Adult males	13–17	415	16.5	23.9	103	4.7	10.9
	18–44	2,099	16.0	22.2	507	4.7	11.0
	45–64	1,847	10.8	18.3	455	3.1	7.2
	>64	1,234	7.5	16.2	271	2.4	5.4
Adult females	13–17	459	12.8	24.0	103	4.1	8.9
	18–44	2,541	11.1	16.4	679	3.0	6.3
	45–64	2,243	7.7	13.5	579	2.1	4.7
	>64	2,006	5.5	10.2	454	1.8	4.1
Pregnant females	12–55	45	10.1	15.7	15	2.2	4.2
Low calorie dieters	All ages	2,213	8.9	16.7	576	2.4	5.3
Low fat dieters	All ages	2,764	8.4	16.5	670	2.5	5.6

[1] Single day.
[2] 14-d average.

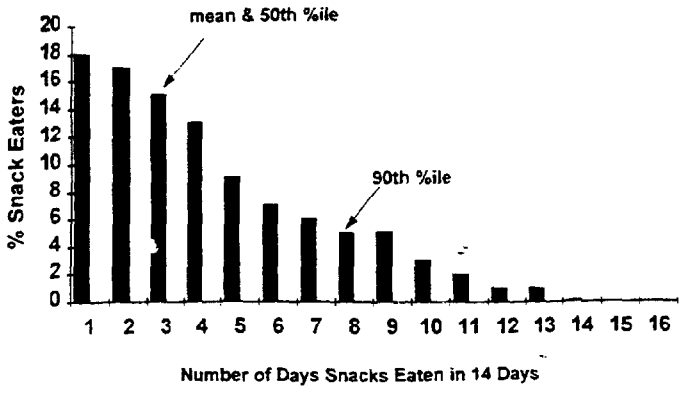


FIGURE 4 Frequency of the number of days savory snacks are consumed during a 14-d period by snack eaters (all ages, both genders).

90th-percentile intake (all ages, both genders) is estimated to be 6.9 g/d, or about 1.2 ounces of olestra potato chips per day. These intake values represent snack eaters only; they are not diluted by the noneaters in the survey population.

This methodology was also used to assess olestra eating patterns in the context of frequency of consumption at main meals. Although savory snacks are eaten on average about 69% of the time with main meals, these snack foods are eaten infrequently in the overall context of the total diet. The 50th-percentile snack consumer eats savory snacks with only 7% of main meals across a 14-d period; the 90th-percentile consumer eats them with 18% of main meals in 14 d.

The MRCA Menu Census methodology provides a realistic estimate of the consumption of savory snacks, and the intake estimates are sufficiently conservative to be useful in nutritional safety evaluation. The method is realistic because the survey relies upon the determination of the frequency of food consumption over 14 continuous days for each survey participant. In contrast, other surveys such as the NFCS or the CSFII evaluate food intake over a period of only 1–3 d (Anderson 1988). Because of the longer observation period, the MRCA method provides a relatively more representative long-term perspective on eating patterns and therefore is well suited to the estimation of chronic intake levels of dietary components such as olestra. The MRCA consumption data are collected yearly, providing an up-to-date resource of food consumption patterns that are inherently dynamic and were current at the time of this assessment, 1993. In addition, the survey runs continuously throughout the year to capture seasonal changes in eating habits. Data are also recorded for specific brands and types of foods such as savory snacks, which maximizes the accuracy and specificity of the intake estimates. Further, new brands and types of snack foods are continuously added to the survey as they come onto the market.

The methodology used in this assessment provides conservative intake estimates because the MRCA model assumes that 100% of all savory snacks available in the marketplace, including stores, restaurants or vending machines, are replaced by olestra-containing savory snacks and thus yields intake estimates much greater than can be reasonably expected from introduction of a new product line into the savory snack food category. In addition, the derived intake estimates were adjusted upward by 10% to provide more conservative estimates. The degree of conservatism inherent in the method has been assessed by evaluating the intake of aspartame in Canada on the basis of a premarket "theoretical" model, which, like the MRCA Menu Census Survey, assumed that aspartame foods captured 100% of market share. For comparison, aspartame intake was also estimated on the basis of a postmarket "actual monitoring" program. The results of this analysis demonstrated that mean aspartame intake estimates derived in the postmarketing monitoring program were one tenth (10%) of the premarket, total market penetration model estimates (Butchko and Kotsonis 1991, Lauer and Kirkpatrick 1991).

Despite the strengths and conservatism of the MRCA methodology noted above, any method applied to estimating potential food or nutrient intake has inherent weaknesses that may, if significant in nature, undermine the ultimate value of the assessment outcome. Potential weaknesses of the MRCA survey are the use of the 1987–88 NFCS data to estimate portion sizes of savory snacks and the possible underreporting of savory snack consumption in the Menu Census survey. An assessment of each of these follows.

The MRCA Menu Census survey does not include quantitation of portion sizes; instead it relies on other appropriate and current data bases for that information. At the time this assessment was made, 1993, that data base was the 1987–88 NFCS. The 1987–88 NFCS has been criticized because of its low response rate relative to other USDA national food consumption surveys. For example, the response rate was 38% compared with a target of 74%, and lower than the 61% response rate for the 1977–78 NFCS. In addition, the response rate was variable over both time and geography. Another criticism of the 1987–88 NFCS is the lack of availability of data on the sociodemographic characteristics of the nonresponding households.

An analysis of the effects of the structure of household-level nonresponse has been conducted by Aickin et al. (1992) using selected intake variables. Briefly, these researchers used the 1977–78 NFCS as an external data base with the same sampling design and examined the relationship of area segment-level nonresponse to the differences in intake estimates and in their variability between the 1987–88 and 1977–78 surveys. The variables examined were as follows: *1*) in each case separately for individuals < 19 y and ≥19 y of age, energy intake and the proportion of meat, poultry and fish intake, which was assumed to change throughout the population in the interval between the two surveys, and *2*) for women 19–50 y of age and children 1–5 y of age, intake of the 10 food groups most commonly reported in the 1985 CSFII. For women, these were milk, eggs, white bread, cucumber, lettuce, onion, butter, margarine, salad dressings/mayonnaise, sugar, coffee, tea and soft drinks. For children, they were milk, bologna, sausage, eggs, white bread, potato, butter, margarine, sugar, soft drinks, orange juice and fruit-flavored drinks.

This analysis showed no consistent effects of the nonresponse structure (i.e., the attributes and demographics of the nonresponders) on intake. It would not be expected that the household-level nonresponse rates or the geographical or time-related structure of nonresponse would affect the estimation of the average amount of food consumed per eating occasion unless there was a systematic bias toward nonparticipation of households in which this average amount of food consumed was different than that of other households. Although it is not empirically possible

TABLE 6

Total energy intake and the percentage from fat for the 1987–88 NFCS and the 1991–92 MRCA surveys and the percentage differences between the two data sets

Sample population	Age	NFCS intake	MRCA intake	Difference of MRCA intake from NFCS intake
		Total energy intake		
	y	*MJ/d*	*MJ/d*	%
Males	≥19	495	485	−2.2
Females	≥19	347	366	+5.5
Children	4–10	389	404	+3.9
Teenagers	11–18	472	456	−3.4
Total sample	All ages	421	423	+0.7
		Percentage of energy intake from fat		
	y	%	%	%
Males	≥19	37.6	38.4	+2.1
Females	≥19	36.8	37.5	+1.9
Children	4–10	35.9	36.1	+0.6
Teenagers	11–18	36.8	37.5	+1.9
Total sample	All ages	37.0	37.7	+1.9

to ascertain that this did not occur, it is unlikely that it did because subsequent population intake surveys (e.g., 1996 CSFII) have had good household response rates. This demonstrates that nonresponse is not a secular trend but rather an indication that, in the NFCS, the survey team may have failed to follow procedures designed to ensure a good response rate. Therefore, the portion size estimates from the 1987–88 NFCS reasonably represent portion sizes of the U.S. population.

Examination of the distribution of portion sizes for savory snacks in the 1994 CSFII data shows a larger average portion size for crackers, but not for chips, relative to the 1987–88 NFCS data. Males 18–24 y of age, for example, averaged 22.1 g crackers/serving in the NFCS and 42.8 and 60.5 g on d 1 and 2 of CSFII, respectively. It is not possible to ascertain whether the difference is due to differential reporting accuracy, differences in the sample or a secular trend toward larger portion sizes of crackers between the two time periods. These differences in cracker portion sizes may also be due to the fact that personal interviewing concerning eating habits by trained individuals was done on each of the 2 d of the CSFII study. In contrast, this approach was used only on d 1 of the NFCS study, then followed by 2 d of self-reporting in diaries by the untrained respondents. The significance of these differences in estimating olestra intakes is likely to be minimal in light of the conservative assumptions applied in the analysis.

A common criticism of any population dietary survey is that the respondents may have bias for not accurately reporting the frequency of consumption of certain foods or beverages. This potential may be especially problematic for the MRCA survey given that underreporting could be characterized as an eating occasion that occurs without the knowledge of the head-of-household responsible for recording food consumption frequency for all household members. If the consumption of savory snacks was not accurately reported to the head-of-household by other household members, then olestra intake might be understimated.

As noted above, the MRCA survey method assumes that 100% of all savory snacks are replaced by olestra-containing savory snacks. This can lead to a significant (i.e., likely an order of magnitude) overestimation of potential olestra intake among savory snack consumers. Although this magnitude of conservatism would appear to negate any concern for underreporting of savory snack food intake, further perspective on this issue is provided below.

It is reasonable to assume that if MRCA survey participants underreport savory snack consumption, then they do so consistently. There is general recognition that people tend to overestimate, on either report or recall, intake of food items they believe to be good for them and, conversely, underestimate those they believe to be bad. However, MRCA estimates for both total energy intake and fat intake are generally within 5% of averages from the 1987–88 NFCS (**Table 6**). Reported energy intakes showed no consistent differences across age or gender. The percentage energy from fat was consistently higher in the MRCA survey but the differences were slight, from 0.6 to 2.1%, depending on age or gender.

An additional characteristic of the MRCA data is that the food intake data are collected as one component of a multidimensional consumer purchasing and behavior inventory. There is not a particular focus on food or on savory snacks, thus possibly decreasing any reporting bias that might be present if the main issue were food intake and the individual or organization requesting the intake information represented the health profession.

The assessment described here provides a conservative estimate of potential olestra intake from savory snacks. The methodology used to derive the estimated intakes was demographically balanced, representative of U.S. households and provided the best perspective available on long-term eating habits among U.S. consumers. The estimated intakes served as the basis for evaluating the safety of olestra for use as a replacement of fat in savory snacks and were used to choose appropriate intake levels for the human and pig nutrition studies described elsewhere in this issue. The overall objective of these studies was to assess the potential for olestra to interfere with the absorption and utilization of macronutrients and water- and fat-soluble micronutrients. Toward that end, it was paramount to have not only an estimate of potential olestra intake on a gram per day basis but also an understanding of how olestra will be consumed (e.g., the number of times likely to be eaten per day, the number of days per week olestra is likely to be eaten and the likely frequency of consumption with main meals).

ACKNOWLEDGMENTS

The authors wish to acknowledge Johanna Dwyer, Tufts University, Boston, MA and I. Jack Abrams, MRCA, Des Plaines, IL for their technical input and K. D. Lawson for assistance in preparing the manuscript.

LITERATURE CITED

Abrams, I. J. (1992) Using the menu census survey to estimate dietary intake: postmarket surveillance of aspartame. In: ACS Symposium Series no. 484: Food Safety Assessment (Finley, J. W., Robinson, S. F. & Armstrong, D. J., eds.), pp. 201–213, American Chemical Society, Washington, DC.

Aickin, M., Harrison, G., Guillen, J. & Shaheen, M. (1992) Exploratory adjustment method for the 1987–88 NFCS, final report of cooperative agreement no. 58-3198-9-048 to the U.S. Department of Agriculture.

Anderson, S. A. (1988) Estimation of exposure to substances in the food supply. Life Science Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD.

Association of Official Analytical Chemists (1980) Methods 7.058 and 16.225, Official Methods of Analysis (Horwitz, W., ed.), 13th ed. AOAC, Washington, DC.

Butchko, H. H. & Kotsonis, F. N. (1991) Acceptable daily intake vs. actual intake: the aspartame example, J. Am. Coll. Nutr. 10: 258–266.

Federal Register, Part III, Department of Health and Human Services, Food and Drug Administration, 21 CFR Part 172, Food additives permitted for direct addition to food for human consumption: olestra; final rule. 62: 3118–3173, January 30, 1996.

Gardner, D. R. & Sanders, R. A. (1990) Isolation and characterization of polymers in heated olestra and an olestra/triglyceride blend. J. Am. Oil Chem. Soc. 67: 788–796.

Henry, D. E., Tallmadge, D. H., Sanders, R. A. & Gardner, D. R. (1992) Characterization of used frying oils. Part 2: Comparison of olestra and triglyceride Am. Oil Chem. Soc. 69: 509–519.

Kester, J. J. (1993) Food product development using olestra as a fat sub tute. In: Science for the Food Industry of the 21st Century (Yalpani, M., e pp. 37–50, ATL Press, Mt. Prospect, IL.

Lauer, B. H. & Kirkpatrick, D. C. (1991) Food additive intake: estimated ve actual, In: Monitoring Dietary Intakes (Macdonald I., ed.), pp. 170–182, Monographs, Springer-Verlag, New York, NY.

U.S. Department of Agriculture, Food Surveys Research Group (1996) 1 Continuing survey of food intakes by individuals, Agricultural Research vice, CD-Rom.

U.S. Department of Commerce (1988) 1987–88 Nationwide Food Consu tion Survey. National Technical Information Service, Springfield, VA.

EFFECTS OF FIBER LAXATIVES AND CALCIUM DOCUSATE ON REGIONAL WATER CONTENT AND VISCOSITY OF DIGESTA IN THE LARGE INTESTINE OF THE PIG.

J. McRorie, Ph.D.[1],

S. Pepple, A.S.[1],

C. Rudolph, M.D., Ph.D.[2],

The Procter & Gamble Company,

6071 Center Hill Avenue

Cincinnati, OH 45224[1]

Current Address:

Children's Hospital Medical Center
Department of Pediatric Gastroenterology
Children's Hospital Medical Center
3333 Burnet Ave.
Cincinnati, Ohio 45229[2]

Corresponding Author:

Dr. John McRorie
The Procter & Gamble Company
6071 Center Hill Avenue
Cincinnati, OH 45224
Tel: (513)634-3663 Fax: (513)634-4600

This study was sponsored by The Procter & Gamble Company.

Abstract

This aim of this study was to determine how bulk fibers and calcium docusate affect regional dehydration and digesta viscosity throughout the large intestine. METHODS: 52 pigs were fed a chow diet supplemented with a bulk laxative, placebo, or calcium docusate for 3 days, after which the pigs were sacrificed and the contents of the large bowel were analyzed. RESULTS: Digesta occurred as a continuum from liquid (cecum, 91.2% water content) to solid (rectum, 70.5% water content). The observed 20.7% difference in water content resulted in a 240-fold increase in viscosity. Half of this water is reabsorbed in the first 18% of the large bowel length where viscosity remains relatively low. Compared to placebo, calcium docusate and calcium polycarbophil had no significant effect on digesta water content or viscosity, polycarbophil exhibited significantly ($p < 0.05$) lower digesta viscosity in 3 bowel segments, and psyllium exhibited significantly ($p < 0.01$) lower viscosity in 6 bowel segments and higher water content in 9 bowel segments. Conclusions: The majority of digesta dehydration occurs early in the proximal large bowel, while the greatest increases in viscosity occur in the distal bowel. Relatively small decreases in digesta water content result in large increases in digesta viscosity. Psyllium, and to a lesser extent polycarbophil, are able to resist dehydration, resulting in a softer digesta.

Key Words: viscosity, large intestine, digesta, water content, bulk laxative, stool softener

INTRODUCTION

The mammalian large intestine is responsible for the mixing, dehydration, storage, transport and evacuation of intestinal contents. The pattern of regional dehydration in the large bowel and the mechanical effects of regional dehydration on the viscosity of digesta are not known. Further, the regional effects of bulk laxatives and stool softeners on the water content and viscosity of digesta are not known. Chronic idiopathic constipation is common in the general population, especially in women (1) and the elderly(2), and is the most common gastrointestinal complaint in the United States(3). The symptoms most often associated with constipation are straining with bowel movement (52%) and hard stools (44%)(3). This suggests that a significant digesta/stool softening effect would provide a major benefit in the treatment of chronic idiopathic constipation. This study was conducted to define progressive dehydration and regional changes in viscosity of digesta throughout the large intestine of the pig. Further, the effects of bulk fiber laxatives and a stool softener on regional digesta water content and viscosity were determined compared to control.

METHODS

Animals

Fifty two female Yorkshire Pigs (Butterfield Farms, Ross, Ohio) were group-housed (4 per indoor/outdoor pen). The pigs acclimated to the facility at least five weeks prior to study initiation. Throughout the acclimation and testing periods, water was available *ad libitum*. Purina Porcine Chow (#5084) was rationed at 500 grams/pig twice daily. For each cohort, pigs were randomly allocated to a placebo group or one of four treatment groups. At study initiation, pigs were housed individually in adjacent pens. This study was approved by the Institutional Animal Care and Use Committee (Procter & Gamble) and was conducted under Good Laboratory Practice guidelines.

Cohort 1 (n = 4-5 pigs per treatment group) determined the regional viscosity of digesta throughout the large intestine (control group), and compared these values to 4 psyllium treatment groups in a dose-responsive manner. Psyllium was delivered as Sugar-free, Smooth Texture, Orange-flavored Metamucil®.

Cohort 2 (n = 5 pigs per treatment group) compared the viscosity and water content of digesta throughout the large intestine of pigs dosed with psyllium, polycarbophil, calcium polycarbophil or calcium docusate as compared to control (see table 2). Preliminary tests of calcium polycarbophil and calcium docusate showed no change in digesta viscosity at the recommended human daily dose (data not shown). A dose level of 4-times the maximum recommended daily human dose was selected for all treatment groups to maximize the observed effects of calcium polycarbophil and calcium docusate.

Test materials were weighed in the amounts shown in Tables 1 and 2, then hydrated in 321 ml tap water to form suspension. These suspensions were admixed to 500 g Porcine Chow and fed to pigs twice daily for three consecutive days.

Necropsy Procedure

At completion of the three day dosing period, each pig was sedated with an intra-muscular injection of Telazol (1mg/kg) followed by immediate euthanasia with intra-venous Beuthanasia (1ml/4.5kg). The abdominal viscera were exposed and the large bowel was isolated by double ligatures (umbilical tape) into 13 sequential segments by anatomical landmarks. The cecum (≅20cm) was isolated at the ileo-cecal junction (segment 1). The proximal colon of the pig is a conical mass comprised of 3 large diameter centripetal coils forming the outside of the cone and 3 smaller diameter centrifugal coils forming the inside of the cone. The first two (largest diameter) centripetal coils were divided in half (≅ 30cm/segment, segments 2 - 5). The last centripetal coil (≅40cm) and the three centrifugal coils (≅30cm/segment) comprised segments 6 through 9. The transverse colon (≅25 cm) was segment 10. The descending colon was divided in two (≅20cm/segment, segments 11 and 12). The rectum (≅20cm) was segment 13. Following isolation, each segment was excised and the luminal contents collected for viscosity and water content evaluation. Aliquots were obtained for water content measures, sealed in an airtight container and stored at -70° C. Samples for viscosity measures were sealed in air-tight containers, transferred to a 38° C water bath, and peak force measures were made within 1 hour.

Viscosity Measures

The 'Stevens QTS 25 Texture Analyzer' (Michael G. Brown & Assoc., Newtown, PA) is a food-grade rheometer that was used to measure the relative viscosity of digesta by a back extrusion technique. The instrument is comprised of a stage plate, a 60 cm vertical tower, a mobile beam, and a beam head that contains a load-cell. During back extrusion, the beam descends at a constant rate, and the force required to back extrude the sample is recorded over time. The sample container is a spherical aluminum cup that holds the test sample (I.D. 2.54cm, 5.0cm deep), and the spherical probe (1.90cm diameter teflon ball mounted on a 2mm O.D. threaded rod) is attached to the beam. The diameters of the cup

and probe were selected to accommodate a wide range of viscosity (liquid to solid digesta) without approaching the maximum capacity of the rheometer (25kg). During a test, the beam thrusts the probe into the test sample at a constant rate (1 cm/second) for a 2 cm stroke, forcing the sample to back-extrude around the equatorial region of the probe. The peak force for back extrusion at a controlled stroke rate is proportional to the viscosity of the sample(9). Three samples from each segment were tested, and a mean peak force/segment was determined.

Water Content

Water content was determined by lyophilizing (Woodson-Tenent Laboratories, Inc., Dayton, Ohio) an aliquot of each sample and subtracting the dry weight from the wet weight of the aliquot.

Statistical Analyses

Statistical analyses were conducted using the Pharm PCS program (Pharm PCS, Version 4, Microcomputer Specialists, Philadelphia, PA). Data results for groups receiving fiber supplementation were compared to the chow fed control using a One-Way Analysis of Variance (ANOVA), and Grouped t-test. Differences $\leq$ 0.05 were considered significant.

RESULTS

Peak Force Measures

Cohort 1

Peak force measures, which are proportional to viscosity, were made by obtaining digesta from each bowel segment and measuring the peak force for back extrusion. Table 3 summarizes mean (± standard error of the mean) data for cohort 1 for 13 bowel sequential bowel segments, from cecum to rectum. The viscosity of digesta is significantly lower (softer) in distal bowel regions for all four psyllium treatment groups versus control. These differences generally increase in a dose-responsive manner.

Figure 1 provides a graphic display of the data presented in Table 3. The peak force for back-extrusion is proportional to the viscosity of large intestine luminal contents. The peak force is similar for all treatment groups within the cecum and proximal half of the colon. The viscosity of digesta in the distal half of the colon is lower for all psyllium treatment groups compared to control, and lowest (softest) for the high-dose (4X) psyllium.

Cohort 2

Cohort 2 compared the effects of psyllium, polycarbophil, calcium polycarbophil, calcium docusate and control on regional viscosity and water content of digesta throughout the large intestine. Table 4 shows that calcium polycarbophil and calcium docusate were not different from control for digesta viscosity throughout the large intestine. The peak force for polycarbophil was significantly lower in 3 distal bowel segments compared to control and for psyllium was significantly lower in 6 distal bowel segments compared to control.

The peak force for back-extrusion is proportional to the viscosity of large intestine luminal contents. The peak force is similar for all treatment groups in the cecum and most-proximal colon. At segment 6, note the apparent change in slope for the control, calcium docusate, calcium polycarbophil, and polycarbophil treatment groups. This increase in slope occurs at a water content of approximately 77 to 78%. The psyllium treatment group showed a less dramatic change in slope at segment 10, at a similar water content (78.6%). Calcium polycarbophil and calcium docusate were not significantly different from control in peak force throughout the large intestine. Polycarbophil was significantly lower ($p \leq 0.05$) than control in peak force for the distal three bowel segments. Psyllium was significantly lower ($p \leq 0.01$) than control in peak force for the distal six bowel segments.

Digesta Water Content

Digesta water content, expressed as percent water, was obtained for each bowel segment by lyophilizing an aliquot of the digesta. Table 5 summarizes mean data from 13 pigs. Figure 3 is a graphic display of the data presented in Table 5. Dehydration of digesta appears to occur most rapidly in the first three segments of the large bowel. By bowel segment 3, approximately 48% of the total dehydration that will occur in the large intestine has occurred for all treatment groups (control 43.5%, docusate 49.7%, psyllium 43.5%, polycarbophil 54.8%). By the 6th bowel segment, approximately 70% of the total dehydration that will occur in the large intestine has occurred for control, docusate and polycarbophil groups. For all except the psyllium treatment group, digesta continues to dehydrate in a relatively linear fashion throughout the remainder of the bowel. For the psyllium treatment group, percent water content remains relatively constant throughout the middle bowel segments, then dehydration resumes in the distal bowel, resulting in a higher percent water content in the rectum.

Psyllium was the only treatment group that demonstrated a significant difference from control for water content, retaining significantly more water in 9 of 13 bowel segments. The 3.4-fold difference in peak force (viscosity) observed for rectal samples in the psyllium versus control groups (1185g versus 4011g, respectively) correlates with a difference in water content of only 5%. Regardless of the treatment group, the relationship between the viscosity and the water content remains relatively constant. A semi-log plot of the data would yield the constants for the equation: $\ln(y) = \ln(A) - bx$, which, when converted, becomes: $y = Ae^{-bx}$, where y = Mean Peak Force, x = Per Cent Water Content, A = Force Constant (g), and b = Dimensionless Constant. A plot of the data and the regression equation is shown in Figure 4.

DISCUSSION

This study was designed to determine the pattern of dehydration of digesta throughout the large intestine of the pig, and to determine how regional dehydration affects the viscosity of digesta. Digesta in the large intestine of control pigs occurs as a continuum from liquid (cecum, 91.2% water content) to solid (rectum, 70.5% water content). This 20.7% decrease in water content results in a 240-fold increase in viscosity. Dehydration of digesta occurs more rapidly in the proximal bowel, where the water-like consistency of digesta in the cecum becomes semi-solid within 20-40cm of proximal bowel. The first centripetal loop of the pig proximal colon is approximately 60cm in length, representing 18% of the length of the large bowel. In this segment, 48% of the total dehydration accomplished in the large intestine has occurred. The pig and human large intestines are approximately 3.3 and 1.5 meters in length, respectively. If a similar dehydration pattern is present in man, it suggests that half of the dehydration process in the large intestine of man is accomplished by the hepatic flexure (approximately 18% of the length of the large bowel in man)(4).

In more distal regions of the large bowel, relatively small decreases in water content resulted in large increases in digesta viscosity. In control animals, a decrease of 0.5% water content in rectal samples (from 71.0% to 70.5%) resulted in a 15% (520.6g) increase in viscosity. A water content difference of only 5% between control (70.5%) and psyllium (75.6%) treatment groups resulted in a 3.4-fold difference in peak force. This shows that relatively small increases in stool water content can have a dramatic effect on stool softening.

This study was also designed to determine the regional effects of bulk fiber laxatives (calcium polycarbophil, polycarbophil and psyllium) and calcium docusate (marketed as a

stool softener) on digesta viscosity and water content as compared to control. There were no significant differences in viscosity or water content between calcium docusate and control, suggesting that calcium docusate exhibits no efficacy as a laxative or stool softener in pigs. Similar results were obtained in studies in man(2,5), rat(6,7), and dog(8), suggesting that docusate is not efficacious as a stool softener/laxative. Polycarbophil directionally increased digesta water content in eight bowel segments and significantly lowered digesta viscosity in three distal bowel segments compared to control. Polycarbophil delivered as calcium polycarbophil was not different from control for viscosity, suggesting that the calcium is not liberated, leaving the polycarbophil inactive.

Psyllium directionally increased water content in the proximal 4 bowel segments and significantly increased water content in the remaining 9 bowel segments compared to control. Psyllium also significantly decreased viscosity in 6 distal bowel segments compared to control. These data suggest that psyllium exerts its laxative and stool softening effects by resisting the dehydrating effects of the bowel, maintaining a higher water content throughout the bowel resulting in a softer digesta/stool. This is supported by the observation that, regardless of the treatment group, the relationship between viscosity and water content remains relatively constant. Under conditions of a controlled diet, digesta/stool viscosity is a function of water content. These data also demonstrate that, once water content falls below 75%, a small decrease in water content results in a relatively large increase in digesta/stool viscosity.

Viscosity is can be qualitatively defined as a measure of resistance to deformation and flow(9). Lowering the viscosity of digesta, therefore, should have the effect of increasing the rate of flow, or transit rate. Extreme examples of this phenomenon in the bowel are gas and solids. Studies of intestinal gas in healthy individuals show whole gut transit times of 20 to 35 minutes(10) and jejunum to anus transit times of 15 to 20 minutes(11). This is

in contrast to whole gut transit of solids, which is reported to be an average of 33 to 56 hours in healthy individuals(12,13). This study has demonstrated that the bowel must accommodate a wide range of digesta viscosity, from liquids to formed stool. We have previously demonstrated that propagating contractions exhibit a wide range of propagation rates (0.4 to 16.7cm/s), waveform durations (5 to 40s) and peak amplitudes (10 to 116mmHg)(14). Slowly propagating, high amplitude, long duration contractions, known as High Amplitude Propagating Contractions (HAPCs)(15,16), have been associated with the propulsion of solid luminal contents and the urge to defecate. The lower amplitude (10mmHg), shorter duration(5s), and more rapidly propagating contractions (up to 16.7cm/s) are likely to propel low viscosity substrates such as gas, but could not effectively propel solids. This concept is described mathematically using a rheological value known as the Deborah number(9).

The formula for the Deborah number is the time constant of the substance (proportional to viscosity) divided by the duration of the event. A Deborah number greater than 1.0 would exhibit a more 'solid-like' or plastic behavior. A Deborah number less than 1.0 would exhibit a more 'fluid-like' behavior. An example of the Deborah number is 'Silly Putty ®' (a viscoelastic polymer sold as a children's toy), which behaves like a solid when 'bounced' on a solid surface (duration of event <1s) and flows like a liquid when gradually pulled (duration of event >1s). The propulsion of luminal contents in the large intestine may be similarly affected by the numerator (viscosity of digesta) and denominator (propagation rate and duration of contraction). The Deborah number predicts that high viscosity substrates, such as hard stool, would only be propelled by a few slowly propagating, high amplitude, long duration contractions (HAPCs), resulting in relatively slow colonic transit rates (days)(12,13). Low viscosity substrates, such as gas, could be propelled by all propagating contractions, including low amplitude, short duration, rapidly propagating contractions(14), resulting in very fast colonic transit rates (minutes)(10,11).

Decreasing the viscosity (lowering the time constant) of digesta would decrease the Deborah number, predicting a more fluid-like behavior in response to a mechanical stress (propagating contractions). It is reasonable to speculate that decreasing the Deborah number (more 'fluid-like behavior, soft stool) with a bulk or osmotic laxative may allow a wider range and greater number of faster propagating contractions to become propulsive, resulting in a faster transit rate (laxation). Conversely, an increase in the Deborah number (more 'solid-like' behavior, hard stool) may result in a more narrow range of few, slowly propagating contractions that are propulsive, resulting in a slower transit rate (constipation).

This study has demonstrated that digesta in the large intestine normally occurs as a continuum, from liquid in the cecum to solid in the rectum. The majority of digesta dehydration occurs early in the large bowel, while the greatest increases in viscosity occur in the distal bowel. This study has also demonstrated that, when the diet is held constant, digesta/stool viscosity is a function of water content, suggesting that a stool softening agent must increase stool water content to be effective. Psyllium was the only product tested that significantly affected both digesta water content and digesta viscosity, leading to a significantly softer digesta/stool.

REFERENCES

1. Everhart, J., Go, V., Johannes, R., Fitzsimmons, S., Roth, H., and White, L. A Longitudinal Survey of Self-Reported Bowel Habits in the United States. Dig. Dis. Sci. 34(8):1153-1162, 1989.

2. Castle, S., Cantrell, M., Israel, D, and Samuelson, M. Constipation Prevention: Emperic use of stool softeners questioned. Geriatrics 46(11):84-86, 1991.

3. Goldfinger, S. The Hard Facts. Harvard Health Letter 16(4):1-4, 1991.

4. Moore, K. Clinically Oriented Anatomy, Second Edition, Williams & Wilkins, Baltimore, 1985.

5. Chapman RW, Sillery J, Fontana DD, Matthys C, Saunders DR. Effect of oral dioctyl sodium sulfosuccinate on intake-output studies of human small and large intestine. Gastroenterology 89:489–93, 1985.

6. Lish, P. and Dungan, K. Peristaltic-stimulating and fecal-hydrating properties of dioctyl sodium sulfosuccinate, danthron, and cascara extracts in the mouse and rat. J. Am. Pharm. Assoc. 47:371-375, 1958.

7. Lundholm, L. and Svedmyr, N. The incluence of dioctyl sodium sulfosuccinate on the laxative action of some anthraquinone derivatives. Acta Pharmacol. Toxicol. 15:373-383, 1959.

8. Case, M., Smith, J. and Nelson, R. Acute mouse and chronic dog studies of danthron, dioctyl sodium sulfosuccinate, poloxalkol and combinations. Drug Chem. Toxicol. 1(1):89-101, 1977-78.

9. Barnes, H., Hutton, J., and Walters, K. An Introdution to Rheology, Third Edition, Elsevier Science Publishers, New York, 1993.

10. Danhof, I.E. The Clinical Gas Syndromes: a Pathophysiological Approach. Ann. N.Y. Acad. Sci. 150:127-140, 1968.

11. Lasser, R.B., Bond, J.H., and Levitt, M.D. The Role of Intestianl Gas in Functional Abdominal Pain. N. Engl. J. Med. 293:524-526, 1975.

12. Sarna, S. Colonic Motor Activity. Surgical Clinics of North America, 73(6):1201-1223, 1993.

13. Basile, M., Neri, M., Carriero, A., Casciardi, S., Comani, S., Del Gratta, C., Di Donato, L., Di Gratta, S., Di Donato, L., Di Luzio, S., and Macri, M. Measurement of Segmental Transit Through the Gut in Man; A Novel Approach by the Biomagnetic Method. Digestive Disease Science 37(10): 1537-1543, 1992.

14. Pepple, S. and McRorie, J. Manometric Recordings of Propagating Contractions in Proximal Colon of Ambulatory Yucatan Mini Pigs. Gastroenterology 107(4):1244, 1994.

15. Crowell, M., Bassotti, G., Cheskin, L., Schuster, M., and Whitehead, W. Method for Prolonged Ambulatory Monitoring of High-amplitude Propagated Contractions from Colon. Am. J. Physiol. 261:G263-G268, 1991.

16. Bassotti, G., Crowell, M., and Whitehead, W. Contractile Activity of the Human Colon: Lessons From 24 Hour Studies. Gut. 34:129-133, 1993.

Table 1 Cohort 1 Test Articles

Treatment Group	Maximum Recommended (Human) Daily Dose	Daily Dose	Dose Administered Twice Daily
Control (n=5 pigs)	—	—	Metamucil Excipients
Psyllium (n=5 pigs) (Procter & Gamble)	10.2 g	10.2 g (1X)	5.1g
Psyllium (n=4 pigs) (Procter & Gamble)	10.2 g	20.4 g (2X)	10.2g
Psyllium (n=4 pigs) (Procter & Gamble)	10.2 g	30.6 g (3X)	15.3g
Psyllium (n=4 pigs) (Procter & Gamble)	10.2 g	40.8 g (4X)	20.4g

Table 2 Cohort 2 Test Articles

Treatment Group	Maximum Recommended (Human) Daily Dose	Daily Dose	Dose Administered Twice Daily
Control (n=5 pigs)	—	—	water vehicle
Psyllium (n=5 pigs) (Procter & Gamble)	10.2 g	40.8 g	20.4g
Polycarbophil (n=5 pigs) (B.F. Goodrich)	4.0 g	16.0 g	8.0 g
Calcium Polycarbophil (n=5 pigs) (B.F. Goodrich)	5.0 g	20.0 g	10.0 g
Calcium Docusate, (n=5 pigs) (Cytec Industries)	240 mg	960 mg	480 mg

Table 3

Dose-response Effects of Psyllium on Digesta Viscosity Throughout the Large Bowel

Bowel Segment	Control Mean ± sem	Psyllium 1x Mean ± sem	Psyllium 2X Mean ± sem	Psyllium 3X Mean ± sem	Psyllium 4X Mean ± sem
Cecum	10.07 ± 1.25	14.57 ± 4.31	23.17 ± 5.51	****100.00 ± 61.17**	****59.06 ± 15.78**
2	30.80 ± 12.69	55.80 ± 20.18	72.71 ± 20.51	****174.44 ± 44.45**	****129.98 ± 27.86**
3	118.70 ± 73.65	152.79 ± 57.75	116.04 ± 41.80	200.54 ± 47.89	135.52 ± 18.59
4	152.17 ± 55.45	208.86 ± 42.45	143.08 ± 10.34	488.25 ± 368.11	115.25 ± 22.39
5	165.73 ± 60.38	228.36 ± 88.97	117.13 ± 28.83	158.25 ± 35.05	110.96 ± 23.63
6	263.87 ± 126.39	288.19 ± 93.51	235.51 ± 59.94	257.65 ± 17.06	161.54 ± 43.95
7	604.47 ± 378.50	483.83 ± 179.61	347.88 ± 110.60	320.71 ± 38.42	214.42 ± 61.63
8	913.27 ± 454.71	613.57 ± 153.84	599.87 ± 148.92	452.77 ± 39.42	286.84 ± 108.58
9	1761.37 ± 562.90	964.27 ± 172.29	1016.08 ± 253.58	***798.46 ± 108.76**	****448.25 ± 150.67**
10	2846.00 ± 1214.22	***1341.00 ± 97.73**	***1396.25 ±274.01**	****899.00 ± 60.11**	****777.92 ± 299.42**
11	2516.75 ± 450.41	***1352.50 ± 59.54**	2006.00 ± 667.75	***1228.63 ± 176.85**	****1122.00 ± 202.56**
12	4942.90 ± 1392.78	****1764.62 ± 334.86**	***2096.88 ± 599.93**	****1416.38 ±163.47**	****1003.02 ± 453.40**
Rectum	5533.33 ± 320.74	****2662.75 ± 656.09**	****2995.00 ± 995.61**	****2225.63 ± 335.22**	****1823.56 ± 956.56**

bold = statistically significant (* = $p<0.05$, ** = $p<0.01$) compared to excipient control

Table 4 Mean Peak Force Values for Digesta in 13 Segments of the Large Intestine

	Chow	Calcium Docusate	Polycarbophil	Psyllium	Calcium Polycarbophil
Bowel Segment	**mean ± sem**	**mean ± sem**	**mean ± sem**	**mean ± sem**	**mean ± sem**
Cecum	16.7 ± 2.6	17.0 ± 2.6	30.7 ± 6.3	24.5 ± 5.1	12.1 ± 1.4
2	45.3 ± 15.0	75.1 ± 25.8	139.7 ± 50.7	41.4 ± 3.2	34.4 ± 6.2
3	115.9 ± 21.1	174.8 ± 40.6	268.0 ± 89.8	81.2 ± 14.7	210.3 ± 84.5
4	169.2 ± 48.0	276.5 ± 53.2	300.0 ± 78.9	94.7 ± 12.5	197.4 ± 58.5
5	243.9 ± 60.0	412.1 ± 75.0	386.2 ± 102.7	79.1 ± 11.7	316.6 ± 112.9
6	477.4 ± 201.5	579.3 ± 124.8	444.6 ± 81.8	91.6 ± 13.6	826.8 ± 254.0
7	749.7 ± 244.1	821.9 ± 92.6	696.3 ± 152.3	****123. 2 ± 21.2**	1102.9 ± 246.8
8	1193.7 ± 267.5	1194.6 ± 150.8	821.4 ± 185.7	****126.5 ± 21.9**	1552.8 ± 358.1
9	1828.2 ± 414.0	1509.0 ± 169.4	1066.1 ± 226.7	****199.7 ± 46.8**	1994.1 ± 370.4
10	2404.2 ± 550.8	2106.3 ± 259.1	***1451.7 ± 253.1**	****558.8 ± 262.4**	2396.4 ± 232.1
11	3535.0 ± 1033.0	3121.4 ± 574.3	****1564.7 ± 229.1**	****787.7 ± 285.8**	2816.9 ± 203.9
12	3490.6 ± 1068.9	3696.7 ± 814.7	***1635.7 ± 951.2**	****951.2 ± 226.9**	3115.4 ± 310.3
Rectum	4011.2 ± 968.9	5496.8 ± 978.5	2065.1 ± 314.1	1184.5 ± 163.5	4462.4 ± 1273.1

Mean peak force values for all treatment groups (n=6 pigs/group) in 13 segments of the large bowel, sequentially from cecum to rectum. Values in **bold** are significantly less than control (*$p \leq 0.05$, **$p \leq 0.01$). The rectum was empty in 8 (docusate 2, calcium polycarbophil 2, and psyllium 4) of 30 pigs, resulting in fewer available samples for these treatment groups and no statistically significant differences from control.

Table 5

Mean Percent Water Content Values for Digesta in 13 Segments of the Large Intestine

Bowel Segment	Control	Calcium Docusate	Psyllium	Polycarbophil
Cecum	91.2 ± 0.6	90.0 ± 1.3	92.4 ± 0.6	89.7 ± 0.9
2	87.8 ± 1.1	87.5 ± 1.0	89.7 ± 1.1	84.4 ± 0.8
3	83.7 ± 0.8	83.0 ± 2.0	86.2 ± 0.9	81.2 ± 0.8
4	82.2 ± 0.9	80.5 ± 1.9	85.1 ± 1.0	81.1 ± 0.5
5	80.2 ± 0.5	80.0 ± 1.1	****87.0** ± 0.8	80.0 ± 0.6
6	78.2 ± 1.8	79.8 ± 2.7	****86.9** ± 0.4	79.4 ± 0.4
7	77.1 ± 1.4	76.7 ± 0.9	****86.0** ± 1.5	78.4 ± 0.4
8	76.0 ± 0.9	75.4 ± 0.9	****85.6** ± 1.0	77.6 ± 0.5
9	74.8 ± 0.2	74.4 ± 0.7	****83.5** ± 0.7	77.2 ± 0.7
10	72.6 ± 0.9	75.1 ± 0.8	****80.1** ± 0.4	76.3 ± 0.6
11	70.4 ± 1.2	73.1 ± 1.1	****78.6** ± 0.2	76.0 ± 0.2
12	71.0 ± 1.3	71.9 ± 1.1	****76.0** ±0.6	74.8 ± 0.1
Rectum	70.5 ± 1.7	70.9 ± 1.1	***75.6** ± 0.4	74.0 ± 0.2

Mean percent water content (± standard error of the mean) for Control (Chow; 3 pigs), Calcium Docusate (CaDoc; 4 pigs), Polycarbophil (PC; 3 pigs), and Psyllium (Psy; 3 pigs) in 13 segments of the large bowel, sequentially from cecum (cec) to rectum (rect). Values in **bold** are significantly greater than control (*$p \leq 0.05$, **$p \leq 0.01$).

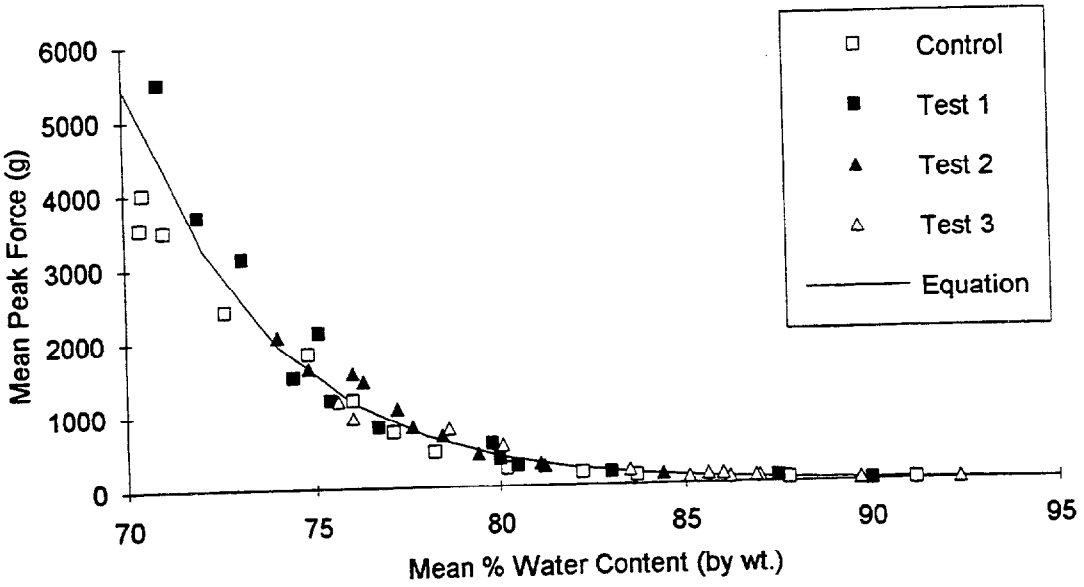
Figure 1. The mean peak force for back-extrusion (proportional to viscosity) for 13 bowel segments from cecum (cae) to rectum (rec) for control pigs and psyllium dosed at 1X, 2X, 3X and 4X the maximum recommended daily human dose.

Figure 2. Mean peak force values (n=6 pigs/treatment group) for Control (Chow), Calcium Docusate (CaDoc), Polycarbophil (PC), Psyllium (Psy), and Calcium Polycarbophil (CPC) in 13 segments of the large bowel, sequentially from cecum to rectum.

Figure 3. Mean percent water content for Control (Chow; 4 pigs), Calcium Docusate (CaDoc; 4 pigs), Polycarbophil (PC; 3 pigs), and Psyllium (Psy; 3 pigs) in 13 segments of the large bowel, sequentially from cecum to rectum.

Figure 4. Plot of mean percent water content versus mean peak force (g) for control, calcium docusate (Test 1), polycarbophil (Test 2), and psyllium (Test 3). Note that, for water content values $\leq$ 75%, small changes in water content result in relatively large changes in viscosity.

Figure 4


Control
Test 1
Test 2
Test 3
Equation
Mean Peak Force (g)
6000
5000
4000
3000
2000
1000
0
70
75
80
85
90
95
Mean % Water Content (by wt.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: December 16, 1995

From: Medical Officer, Epidemiology Branch, Division of Market Studies (HFS-728)

Subject: Review of Study Entitled "Measurement of Selected Fecal Parameters in Subjects Consuming Increasing Levels of Olestra" (FAP 3997, Volume 280)

To: Helen Thorsheim, Ph.D., Consumer Safety Officer, Office of Premarket Approval, (HFS-216)

Through: Raymond E. Schucker, Ph.D., Director, Division of Market Studies

Study Objectives: The purposes of this study were to quantitate the frequency, duration, and intensity of pre-defined GI symptoms as a function of dietary level of olestra, and to quantitate selected fecal parameters that might change in response to changes in olestra intake.

Study Design: The study consisted of two phases. A screening phase was conducted to identify subjects who reported GI symptoms in response to olestra consumption. This was followed by the study phase during which the identified subjects were given increasing dietary levels of olestra and GI symptoms were recorded and fecal measurements were made.

Screening Phase

This was a four-week, cross-over design with two treatment groups, 0 and 20 g/d olestra. The olestra substituted for 20 g of triglyceride in the three daily meals. Roughly one-third of the daily dose was provided in each meal.

Fifty-two adult subjects who had reported GI symptoms in previous product acceptance or olestra clinical studies were acclimated to the study procedures during a three-day baseline period in which they were given placebo meals. They were then divided into two groups and given placebo meals or meals which provided 20 g/d olestra for five days. After a seven-day washout period, the subjects were again given placebo meals (containing triglycerides) for three days, and then crossed-over to olestra or placebo meals for five days. After the second treatment period, the subjects were monitored for a four-day washout period.

The subjects were fed one of four meal sizes, based on four average body weights: 50, 65, 80, and 95 kg. The meals provided 30 kcal of energy per kg of body weight. The olestra was incorporated into the meals in french fries, ice cream,

4 severe). Total fecal collections were made for the last three days of each treatment period and the daily collections were pooled. To complete the study and have data included in the analyses, a subject had to provide at least one fecal sample for each three-day collection period.

Subject selection

Normal healthy males and females (18 to 60 years of age) were selected for the study from a population of subjects who had reported GI symptoms while consuming olestra in previous product acceptance studies. In addition, to be selected for the study phase, a subject had to report an increased frequency, severity, or duration of GI symptoms while on the 20 g/d olestra treatment, relative to the placebo treatment.

Stools were collected into plastic containers and immediately frozen at -20 degrees C. Sealable plastic bags and an ice chest containing dry ice were provided to the subjects for collection of stools at home. These samples were transferred to -20 degrees C as rapidly as possible. All fecal samples were kept frozen until analyzed.

Fecal samples were initially collected on an individual basis for each bowel movement and several measurements were made (e.g., wt weight, volume, density). Subsequently, all fecal samples from the three-day collection period were pooled (thus diarrheal, loose, and normal stools were pooled) for analyses of the remaining parameters (e.g., water concentration, dry weight, olestra analyses, Na, K, Cl, total and individual bile acids, free fatty acids, triglycerides, and total lipids by the Mayo Medical Laboratories (Rochester, MN). Because the analyses of stool electrolytes were conducted on pooled samples from the three-day collection period, separate daily values for an individual are not available.

Results

More than 99% of the olestra-containing test foods were consumed during both the 10 g/d olestra and 20 g/d olestra treatments.

Results: Screening period

Of the 52 subjects who enrolled in the study, 47 completed the screening phase. None of the five subjects who withdrew did so because of medical reasons. Ten different subjects reported adverse experiences during the screening phase, most commonly GI in nature. Two subjects reported diarrhea during the placebo period; one of these two reported loose stools also. During the olestra consumption period, one subject reported diarrhea and another reported loose stools.

Results: Study phase: Incidence of diarrhea and loose stools

Of the 47 subjects who completed the screening phase, 18 were selected to participate in the study phase. Two subjects withdrew prior to start of treatment, and one subject withdrew after the first treatment period (20 g/d olestra); none of the withdrawals was due to medical reasons. Therefore, 15 subjects completed the placebo arm of the study phase and the olestra 10 g/d arm, and 16 subjects completed the olestra 20 g/d arm of the study.

Figure 1 (attached) summarizes the number of study subjects who reported diarrhea or loose stools, by olestra dose. There was a steady increase in the number of subjects who reported diarrhea with increasing dose of olestra consumed. Three (20%) subjects reported diarrhea while eating 0 g/d olestra; 6 (40%) while eating 10 g/d olestra; and 11 (69%) while eating 20 g/d olestra. The difference in incidence of reported diarrhea during placebo and 20 g/d olestra treatment was statistically significant ($p=0.004$, Mantel-Haenzel chi square test). There was also an increase in the number of subjects reporting loose stools with increasing olestra dose, but this increase did not reach statistical significance ($p=0.08$ comparing placebo vs. 20 g/d olestra).

Figure 2 summarizes the number of diarrheal or loose stool episodes, by olestra dose consumed. There was a steady increase in the number of diarrheal bowel movements with increasing olestra dose eaten: 5 episodes of diarrhea among subjects while eating 0 g/d olestra; 14 episodes of diarrhea among subjects while eating 10 g/d olestra; and 40 episodes of diarrhea among subjects while eating 20 g/d olestra. The mean number of diarrheal bowel movements per subject reporting diarrhea during the study phase increased steadily with increasing olestra dose consumed: 1.7 diarrheal bowel movements per subject reporting diarrhea during placebo treatment [5 episodes of diarrhea among 3 subjects]; 2.3 diarrheal bowel movements per subject reporting diarrhea during 10 g/d olestra treatment [14 episodes of diarrhea among 6 subjects]; and 3.6 diarrheal bowel movements per subject reporting diarrhea during 20 g/d olestra treatment [40 episodes of diarrhea among 11 subjects]. The number of subjects experiencing diarrhea as reportedly "severe" increased with increasing doses of olestra consumed: none of the three subjects who experienced diarrhea while eating placebo reported the diarrhea as "severe"; two of the six subjects who experienced diarrhea while eating 10 g/d olestra reported the diarrhea as "severe"; and six of the 11 subjects who experienced diarrhea while eating 20 g/d olestra reported the diarrhea as "severe." The number of episodes of loose stools also increased with increasing amounts of olestra consumed.

In summary, both the incidence of diarrhea and the mean number of diarrheal bowel movements per subject reporting any diarrhea increased with increasing olestra consumed. Additionally, there was a steady increase in the incidence of diarrhea reported as "severe" with increasing olestra consumed.

Results: Fecal measurements during study phase

Six subjects reported a total of 13 episodes of diarrhea during the stool collection periods (i.e., the last three days of each treatment period). All episodes of diarrhea that were reported during the stool collection periods occurred among subjects eating either olestra 10 g/d or olestra 20 g/d. Summarized below are all reported bowel movements reported for the six subjects who experienced diarrhea during the stool collection periods; bowel movements not collected are noted.

<u>Placebo Stool Collection Period</u>

Subject # 103	1 episode of loose stools on day # 5 1 episode of loose stools on day # 6 1 episode of loose stools on day # 7
Subject # 125	1 episode of normal stools on day # 5 1 episode of loose stools on day # 6 1 episode of normal stools on day # 6 1 episode of normal stools on day # 7
Subject # 0139	1 episode of normal stools on day # 5 1 episode of loose stools on day # 6 1 episode of normal stools on day # 7
Subject # 0146	1 episode of normal stools on day # 5 1 episode of normal stools on day # 7
Subject # 0152	2 episodes of loose stools on day # 5 1 episode of loose stools on day # 6 1 episode of loose stools on day # 7

<u>Olestra 10 g/d Stool Collection Period</u>

Subject # 0103	1 episode of loose stools on day # 5 2 episodes of diarrhea on day # 7 **(one of these specimens was not collected)**
Subject # 0125	1 episode of normal stools on day # 5 1 episode of loose stools on day # 6 2 episodes of diarrhea on day # 7

Subject # 0139 — 1 episode of normal stools on day # 5
1 episode of normal stools on day # 6

Subject # 0146 — 1 episode of normal stools on day # 5
2 episodes of normal stools on day # 6
1 episode of normal stools on day # 7

Subject # 0152 — 1 episode of loose stools on day # 5
1 episode of normal stools on day # 6
1 episode of loose stools on day # 7 **(this specimen was not collected)**

<u>Olestra 20 g/d Stool Collection Period</u>

Subject # 0103 — 2 episodes of loose stools on day # 5
1 episode of diarrhea on day # 6
1 episode of loose stools on day # 7

Subject # 0122 — 3 episodes of diarrhea on day # 5
2 episodes of diarrhea on day # 6
1 episode of loose stools on day # 7

Subject # 0125 — 1 episode of normal stools on day # 5
1 episode of normal stools on day # 6
2 episodes of loose stools on day # 6
1 episode of loose stools on day # 7 **(this specimen was not collected)**

Subject # 0139 — 1 episode of diarrhea on day # 5
1 episode of loose stools on day # 6
1 episode of normal stools on day # 7

Subject # 0146 — 1 episode of diarrhea on day # 5
1 episode of loose stools on day # 6
2 episodes of normal stools on day # 6

Subject # 0152 — 2 episodes of loose stools on day # 5
1 episode of diarrhea on day # 6
1 episode of loose stools on day # 6 **(this specimen was not collected)**
2 episodes of loose stools on day # 7 **(one of these specimens was not collected)**

Thus, among the six subjects who reported diarrhea during the fecal collection period, there were five instances of stool samples not being collected. The ramifications of these omitted stools is discussed below.

Summarized below are the wet weights of stool (includes the 11 or 20 g/d of nonabsorbed olestra) for subjects who reported diarrhea and for subjects who did not report diarrhea during

the three days stools were collected; this data is abstracted from Exhibit 5.b. The mean wet weight of stool for persons who consumed olestra and reported diarrhea during the fecal collection periods ([140±36 for olestra 10 g/d] and [158±36 for olestra 20 g/d]) exceeded the mean wet weight of their stools during the placebo period (111±61), when none of the subjects reported diarrhea.

Mean (± SD) wet weight (g/24 hr) of stools, by olestra dose, for subjects who reported diarrhea and for subjects who did not report diarrhea during the three days stools were collected

Placebo	10 g/d Olestra		20 g/d Olestra	
Non-diarrhea stool	Non-diarrhea stool	Diarrhea stool	Non-diarrhea stool	Diarrhea stool
Subjects (n=6) reporting diarrhea during fecal collection periods				
111±61	88±39 (n=3)	140±36 (n=2)	None	158±36 (n=6)
Subjects (n=10) not reporting diarrhea during fecal collection periods				
89±67	79±36	None	79±76	None

Regarding subjects who reported diarrhea during the stool collection period, I asked Curtis Barton, Ph.D. (Division of Mathematics) to conduct a paired T-test to determine whether the wet weight of stools from subjects who reported having diarrhea while consuming 20 g/d olestra differed from the weight of nondiarrheal stools during the placebo period. Data for this t-test calculation was obtained from Exhibit 5.b. (This analysis was not done for the 10 g/d olestra subjects since only two subjects reported diarrhea on this dose of olestra.) Subject # 0122 was excluded from the analysis since he withdrew from the study without going through the placebo treatment period; thus, analysis was restricted to the paired results from five subjects. The mean daily weight of stools while consuming 20 g/d olestra was greater than that of stools while on placebo (T statistic 2.715, p-value 0.053). This value underestimates the true difference since three stool

episodes reported by two subjects during the olestra 20 g/d group (see above) were not collected. Results of the paired T-test after subtracting the weight of olestra (20 g) from the diarrheal stool weights for each subject yielded a p-value of 0.17.

In my opinion, the results of the paired T-test suggest that olestra-associated diarrheal stools were heavier than non-diarrheal stools (p=0.053). The presence of nonabsorbed olestra in the stool accounts for some, but not all, of this increase in stool weight. I assume that the remainder of this difference in weight is due to increased water in the diarrheal stool of olestra consumers.

The following values are the maximum stool weights for the five subjects who reported having diarrhea during the stool collection period and for whom data exist for both the placebo and the olestra 20 g/d treatment period:

Subject # g/d	Maximum daily stool weight on placebo	Maximum daily stool weight on olestra 20
103 (female)	213	279
125 (female)	281	456
139 (male)	70	170
146 (female)	115	257
152 (female)	103	281

This data suggests that, at least on some days while consuming olestra 20 g/d, stool weights for all four females exceeded the cutoff weight for diarrheal stool (235 g/d for men; 175 g/d for women) (reference provided by petitioner: Fine et. al.).

The stool weight data from the six subjects who reported diarrhea during the collection periods also suggests that there is a physiologic difference in the stools that subjects report as "diarrhea" versus that they call "loose" versus that they call "normal." The evidence for this is that the mean daily weight of stools described as "diarrhea" by persons consuming 20 g/d olestra was 177 g; the mean daily weight of stools described as "loose" for subjects consuming 20 g/d olestra was 137 g; by comparison, the mean daily weight of stools described as "normal" by the five subjects was 80 g. This data is summarized in the table below.

This data is summarized in the table below.

Mean daily weight of stools, by subjective description of stools, for subjects who reported having diarrhea during stool collection period

Stool type	Mean daily weight (grams)
"Diarrhea"	177
"Loose stools"	137
"Normal stools"	80

Data presented in Appendix G regarding the stool water concentration -- expressed as a percent of stools by weight -- suggests that the stool water concentration of subjects who reported having diarrhea during the olestra 20 g/d period did not differ from that of their nondiarrheal stools during the placebo period. However, even though the percent of stools composed of water may not have differed, it is possible that water loss was greater in subjects with olestra-associated diarrhea because of the greater mass (weight) of stool passed.

The data provided regarding stool electrolytes is presented in meq/day (Exhibits 7, 8, and 9), and suggests that the electrolyte concentration of persons eating olestra and reporting diarrheal stools did not differ from that of their nondiarrheal stools during the placebo period. As noted above, it was not possible to analyze stool electrolyte values for subjects by individual stools or by individual days since the stools were pooled from the three-day collection period prior to analysis for electrolytes.

I am not able to analyze the section on stool lipids without further information. Specifically:

1. Do the values in Appendix G under the column entitled "feces total lipid" include the weight of olestra?

A. If not, why does total feces lipid increase with olestra ingestion? In other words, does olestra interfere with lipid absorption in the gut?

Harvard Health Letter

WARNING: U.S. Copyright Law (Title 17) governs the making of photocopies of copyrighted materials. THIS WORK MAY NOT BE REPRODUCED WITHOUT PERMISSION.

UNIVERSITY OF CINCINNATI
FEB 08 1991
LIBRARY

VOLUME 16 • NUMBER 4 • FEBRUARY 1991

CONSTIPATION, PART I

The Hard Facts

The most common gastrointestinal complaint in the United States, constipation occasions 2.5 million visits to the doctor every year. And, according to one recent estimate, it induces a national expenditure of $400 million on laxatives annually. Yet despite the magnitude of the problem, it is not an easy one to define.

Among a group of people surveyed in the mid-1980s, straining to pass feces was the symptom most frequently linked to constipation (52%). Other symptoms were cited less commonly: hard stools (44%), inability to defecate when the desire is present (34%), infrequent bowel movements (32%), and abdominal discomfort associated with defecation (20%). Of course, as the percentages indicate, these complaints often occur together.

In thinking about constipation, physicians and researchers tend to focus on the frequency of defecation as the crux of the matter. There is probably more than one reason for linking the medical definition of constipation to frequency of bowel movements. If nothing else, it is the easiest aspect of constipation to quantify (although not as easy as one might think). Also, when frequency diminishes there may be a serious medical problem warranting further investigation (*see box, next page*).

Even so, the importance of regularity to health has been greatly overestimated in Western culture for at least 3,500 years. The Egyptians associated feces with decay, by which they were obsessed and horrified, and they therefore placed laxatives (including dried fruit, castor oil, and senna), suppositories, and enemas high on their list of therapeutic agents.

As recently as the 1930s, Sir William Arbuthnot Lane championed the notion that feces retained in the colon would release toxins into the system, leading to "autointoxication" and thus symptoms ranging from falling hair to premature senility. Lane was enormously influential in his time and no doubt persuaded the mothers or grandmothers of many of our readers that a bowel movement a day, more or less, is essential to good health.

The reality is different. Many adults defecate less than once a day and do fine. Around one of every 200 healthy adults has fewer than three bowel movements a week. It is also true, however, that such infrequent defecation is likely to be associated with a sense of bloating, distension, or other lower abdominal discomfort. Some people also link fatigue, achiness, and mental torpor to the sensation of retained feces. In general, defecation occurring anywhere from three times a week to three times a day is considered to be normal and not, in itself, anything to worry about.

The kinds of constipation

For practical purposes constipation can be divided into five main categories.

- *Normal bowel habits that change temporarily.* Function may be disrupted during travel, in the aftermath of diarrhea from a viral infection, or by a change in activity level or diet.

  For some women constipation is a premenstrual symptom, and it is often a problem in pregnancy, perhaps because the colon reacts to the changed in the level of sex hormones. There is, however, no direct evidence that this is the case.

INSIDE

Exercise and Aging
Gallstones
Botulinum Toxin
Hemolytic-Uremic Syndrome
Vegetable Estrogens

My conclusion is that the increased water loss in the stools of subjects reporting olestra-associated diarrhea or loose stools is of concern. The concern is not so much for young, healthy persons, but for the elderly and young children. The elderly are more likely than young, healthy persons to have underlying medical conditions that could be exacerbated if they become dehydrated (e.g., orthostatic hypotension leading to falls in an elderly person with cardiovascular disease). In addition, the elderly are more likely than young, healthy persons to be taking other medications that can have diarrhea as a side effect. For example, the Physicians Desk Reference-Drug Interactions and Side Effects Index lists 654 medications that can cause diarrhea (with frequencies ranging from less than 1 percent to 83 percent).

These conclusions reinforce the need to have a clear, informative label on all olestra-containing products. They also strongly suggest that aggressive post-marketing surveillance is required should olestra be approved so that the incidence of potential adverse effects can be monitored in subpopulations that were not studied at all prior to approval (i.e., the elderly) or in whom studies were very brief (i.e., children).

Karl C. Klontz

Karl Klontz, M.D., M.P.H.