

The Nutritional Effects of Olestra

Assessment of the Nutritional Effects of Olestra, a Nonabsorbed Fat Replacement: Summary^{1,2}

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ABSTRACT Olestra is a zero-calorie fat replacement intended to replace 100% of the fat used in the preparation of savory snacks. Olestra can affect the absorption of other dietary components, especially highly lipophilic ones, when ingested at the same time. The potential effects of olestra on the absorption of essential fat-soluble and water-soluble dietary components have been investigated in pigs and in humans. In these studies, subjects were fed daily amounts of olestra up to 10 times the estimated mean intake from savory snacks and the olestra was eaten each day of the studies. In real life, snacks are eaten on average five times in a 14-d period. Olestra did not affect the availability of water-soluble micronutrients or the absorption and utilization of macronutrients. Olestra reduced the absorption of fat-soluble vitamins A, D, E and K; however, the effects can be offset by adding specified amounts of the vitamins to olestra foods. Olestra also reduced the absorption of carotenoids; analysis of dietary patterns showed that in real life the reduction will likely be <10%. Any effect on vitamin A stores caused by a reduction in carotenoid uptake is offset by the addition of vitamin A to olestra foods. Because of the olestra-to-nutrient ratios fed and the nutritional requirements of the test subjects, the effects of olestra on nutritional status of subgroups of the population are unlikely to be different than those measured in the studies. An analysis of lipophilicity showed that olestra is unlikely to significantly affect the uptake of potentially beneficial phytochemicals from fruits and vegetables. Some people eating large amounts of olestra snacks may experience common GI symptoms such as stomach discomfort or changes in stool consistency, similar to symptoms accompanying other dietary changes. These symptoms present no health risks. *J. Nutr.* 127: 1719S–1728S, 1997.

KEY WORDS: • olestra • nutrition • subgroups • water-soluble vitamins

An extensive research program was conducted to assess the potential of olestra, a zero-calorie fat replacement, to affect nutritional status. Olestra (Olean, Procter & Gamble, Cincinnati, OH) is approved for use in replacing 100% of the cooking oil used in the preparation of savory snacks such as potato and corn chips and crackers (Federal Register 1996). Key studies conducted as part of this program are described in the preceding articles in this supplement. This paper provides an overall summary of the integrated findings from the program.

Because olestra is lipophilic, nondigestible and nonabsorbable, it has the potential to interfere with the absorption of other components of the diet, especially lipophilic ones, eaten at the same time as olestra. This interference occurs because a portion of those components may partition into the olestra

in the gastrointestinal (GI)³ tract and be excreted with the olestra (Jandacek 1982). Because it is lipophilic, olestra is expected to interfere with the absorption of only lipophilic molecules by this mechanism; water-soluble substances do not partition into olestra. An important aspect of this partitioning mechanism is that it is a physical interaction that occurs in the lumen of the gut. Olestra does not affect the physiological processes involved in nutrient digestion, absorption and metabolism, as discussed in the introductory article in this supplement (Peters et al. 1997). Olestra has no effect on nutrient stores accumulated prior to the consumption of olestra (i.e., olestra does not deplete the body of nutrients), or the utilization of those stores, and any effect that olestra might have on nutritional status can be prevented by the addition of extra amounts of the affected nutrient to olestra foods.

Because olestra has this potential to affect the availability of certain dietary components, and thus nutritional status, an essential part of the overall evaluation of the safety of olestra included a thorough investigation of the potential effects of olestra on the availability of dietary components. The dietary components that were assessed included macronutrients, essential vitamins and minerals, and other components of the diet such as phytochemicals. The focus of the nutrition program was to determine to what degree olestra affected the absorption of key dietary components and how the effects could be offset.

The broad objectives of the olestra nutrition research pro-

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³ Abbreviations used: FDA, Food and Drug Administration; GI, gastrointestinal; Gla, γ -carboxyglutamic acid; $\log_{10} P_c$, octanol-water partition coefficient; 25(OH)D, total 25-hydroxyvitamin D; 25(OH)D₂, 25-hydroxyergocalciferol; 25(OH)D₃, 25-hydroxycalciferol; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; PT, prothrombin time; PTT, partial thromboplastin time; RDA, recommended dietary allowance; RDI, recommended daily intake; TA, *d*- α -tocopheryl acetate.

gram were as follows: 1) to define the nature and magnitude of olestra's effect on the absorption of the fat-soluble vitamins and other lipophilic dietary components; 2) to determine if the effects of olestra on the absorption of fat-soluble vitamins could be offset by adding the affected vitamins to foods containing olestra; and 3) to investigate whether olestra might interfere with the absorption or utilization of macronutrients or water-soluble micronutrients by a mechanism or mechanisms other than the partitioning mechanism. Other facets of the program included a determination of how much olestra people would ingest from eating olestra snacks, the frequency and context (with or without meals) of snack consumption, an assessment of the potential for olestra to affect the availability of dietary phytochemicals, and an assessment of the nutritional safety of olestra for subgroups of the population who might have either unique dietary patterns or unique nutritional needs.

APPROACH AND SCOPE OF THE PROGRAM

Animal studies were a key element of the nutrition program for several reasons. Olestra intake and frequency of consumption can be exaggerated in animal studies relative to what actually occurs when people consume olestra in savory snacks. In addition, invasive techniques of measuring changes in nutrients stores that cannot be used with humans can be used with animals. Further, and importantly, studies can be conducted over time periods that cover major growth and development phases, essentially from birth to adulthood. The domestic pig was chosen as the animal in which to conduct the studies for reasons discussed elsewhere in this issue (Cooper et al. 1997d, Peters et al. 1997).

Clinical studies in adult male and female subjects were used to confirm and extend the results from the pig studies. For example, measurement of the effects of olestra on carotenoid absorption and on vitamin K function, using parameters that are more sensitive than clotting times, were made in the human studies as were the direct measurements of the effect of olestra on the absorption of triglyceride, vitamin A and vitamin B-12. In the human studies, olestra was provided in foods representative of its intended use, primarily in potato chips, and, as with the pig studies, the human studies were conducted with daily olestra intakes and eating frequencies that were extreme relative to real-life dietary patterns for savory snacks. In all human studies except one, a study in a free-living population, the diet and eating habits of the subjects were strictly controlled and monitored. In both human and pig studies, nutritionally or physiologically meaningful parameters that reflect overall status were measured when possible; in some cases direct measurements of absorption were made. **Table 1** illustrates key design elements of the pig and human studies.

In addition to the pig and human studies, other studies or assessments were conducted to help place the results of the studies in perspective relative to real life, or to assess the potential effects of olestra on substances not included in the studies. An integral and important part of the program was a study that estimated potentially how much and how often people would eat olestra. Others studies estimated the magnitude of the effect of olestra on carotenoid absorption when olestra snacks and carotenoid-containing foods are eaten in real life and assessed the potential of olestra to affect the availability of dietary phytochemicals. Finally, the results from the pig and human studies were examined to determine their relevance to subgroups of the population who might have nutritional needs or dietary habits different than those of the subjects used in the studies.

SUMMARY AND DISCUSSION OF RESULTS

When considering the results of the pig and human studies, it is important to keep in mind the study conditions, conditions designed to exaggerate the effects of olestra. The primary exaggerating factor in the studies was the eating pattern. Eating pattern has a strong influence on the olestra effect because olestra must be present in the GI tract with other dietary components in order to affect the absorption of the components. In the pig studies, the animals ate olestra at every feeding throughout the studies. In the 8-wk human studies, subjects ate olestra at every meal (i.e., 42 times in repeating 14-d periods) and were not allowed to eat anything between meals. In the 16-wk human study, subjects ate olestra foods every day (i.e., up to 42 times in each 14-d period) but not necessarily at every meal and were allowed to eat between meals if they desired.

In contrast to these patterns, savory snacks are eaten by the average consumer five times in a 14-d period, and 8% of this consumption occurs with meals (Webb et al. 1997). At the 90th-percentile consumption level, snacks are eaten 10 times in a 14-d period; 18% of that consumption is with meals. **Figure 1** compares the eating frequency used in the human studies with the eating frequency of individuals who consume snacks at various levels. In real life, most of an individual's nutrients will be consumed at times other than when olestra is eaten.

An additional exaggerating factor in the pig studies was the method of feeding olestra; it was mixed in the diet when the diet was prepared. This increases the opportunity for the olestra-nutrient interaction to occur and thus for olestra to affect absorption. The result of mixing olestra in the diet is illustrated by findings from a study in which pigs were fed the same amount of olestra either mixed in the diet or in potato chips (Daher et al. 1997a). The effects of olestra on the absorption of fat-soluble vitamins were 1.7–4.5 times greater, depending on the vitamin, when olestra was mixed in the diet relative to being fed in potato chips.

The daily olestra intakes used in the studies were also exaggerated in relation to estimated potential intakes of olestra. The mean chronic intake of 18- to 44-y-old adults, the age range covering the majority of the subjects in the studies, was estimated to be 3.7 g/d; the 90th-percentile intake was estimated to be 8.1 g/d. In the human studies, olestra doses as high as 32 g/d were used. Even more exaggerated intakes were used in the pig studies.

The effects of olestra on the absorption of dietary components observed in pigs and humans were consistent. In both kinds of studies, the results were consistent with the partitioning mechanism, a strong indication that this mechanism is the only significant mechanism by which olestra exerts an effect on nutritional status. **Table 2** illustrates how the data from the human and pig studies were used to define the effects of olestra on water-soluble and fat-soluble nutrients.

Effects on water-soluble nutrients micronutrients and macronutrients. Olestra did not affect the absorption of water-soluble nutrients (Cooper et al. 1997a, 1997b and 1997c, Schlagheck et al. 1997a and 1997b). These included nutrients such as vitamin B-12 and folate, which are digested and absorbed via complex multistep processes, and nutrients that are limiting in the U.S. diet such as calcium, zinc and iron. In view of the extreme conditions used in the studies, it can be concluded with high certainty that consumption of snacks made with olestra will not affect the status of water-soluble nutrients.

Olestra did not affect the digestion, absorption or utilization

TABLE 1

Design elements of the olestra nutrition studies in the domestic pig or adult humans

Study	Amounts of olestra tested ¹	Length (wk)	Frequency of eating	Reference
With pigs				
Model validation	4.8%	4	3 times/d	Cooper et al. 1997d
Dietary context	2.2%	4	1 or 3 times/d	Daher et al. 1997a
Dose response	1.1, 2.2, 3.3, 4.4, 5.5, 7.7%	12	3 times/d	Cooper et al. 1997c
Vitamin restoration	1.1, 4.4, 7.7% with extra vitamins A, D and E	12	3 times/d	Cooper et al. 1997a
Dose response and vitamin restoration	0.25% and 5.5% with and without extra vitamins A and E, 0.5, 1.1, 3.3%	26	3 times/d	Cooper et al. 1997b
Vitamin restoration	0.25% with and without extra vitamins A and E	39	3 times/d	Cooper et al. 1997b
With humans				
Free-living	18 g/d with and without extra vitamin E	16	3 times/d	Koonsvitsky et al. 1997
Dose response	8, 20, 32 g/d	8	3 times/d	Schlagheck et al. 1997b
Vitamin restoration	8, 20, 32 g/d with extra vitamins A, D, and E	8	3 times/d	Schlagheck et al. 1997a
Vitamin A absorption	8, 20, 32 g/d with ³ H-retinyl palmitate	2	at breakfast of d 3	Daher et al. 1997b
Triglyceride absorption	8, 20, 32 g/d with ¹⁴ C-triolein and ⁵¹ CrCl ₃	2	at breakfast of d 7	Daher et al. 1997c

¹ Weight/weight % in the diet for the pig studies.

of macronutrients. This was evidenced by the fact that olestra did not affect growth or digestible energy intake of the pigs (Cooper et al. 1997a, 1997b and 1997c). Fat absorption was measured directly, and the small effect of olestra was not nutritionally significant (Daher et al. 1997c). Of the macronutrients, fat is the most lipophilic; its digestion and absorption involve processes (i.e., lipolysis and micelle formation) that are the most likely to be affected by olestra. Failure of olestra to affect fat absorption is important evidence that olestra does not affect the digestion or absorption of other macronutrients.

Effects on fat-soluble vitamins and restoration results. The pig and human studies showed that olestra can affect the absorption of fat-soluble nutrients, as would be expected from a consideration of the partitioning mechanism. The more lipophilic the nutrients, the larger the effect, consistent with the partitioning mechanism. The 16-wk study in free-living human subjects demonstrated that the effect of olestra on the absorption of fat-soluble vitamins can be offset by adding extra amounts of the vitamins to olestra or olestra foods (Koonsvitsky et al. 1997). This was confirmed in pig and other human studies. The pig studies established the relationships between the dietary concentrations of olestra and the amounts of extra vitamins required to offset the olestra effects. Both pig and human studies allowed a determination of the amounts of vitamins required to maintain tissue concentrations at control (no olestra) levels. The effects of olestra on the absorption

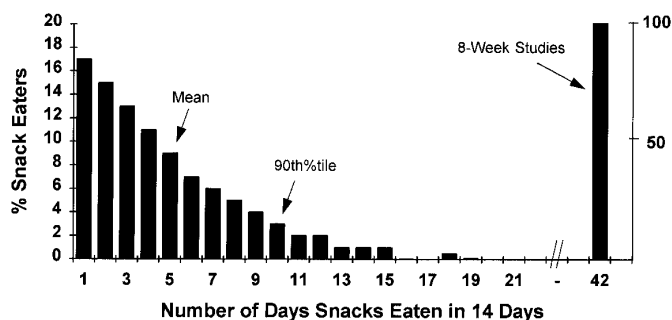


FIGURE 1 Estimated frequency of consumption of olestra by the general population of snack consumers, all ages, and the consumption frequency in the 8-wk human studies.

of the fat-soluble vitamins and the amounts required to offset those effects are summarized below for each specific vitamin.

Vitamin A. Liver vitamin A concentration was reduced by about 45% in pigs fed 0.25% olestra (wt/wt) in a diet that provided about 75% of vitamin A as retinyl palmitate and about 25% as provitamin A carotenoids (Cooper et al. 1997b). A dietary olestra concentration of 0.25% is similar to the 90th-percentile chronic human intake from savory snacks, 6.9 g/d. Feeding olestra mixed in the diet increases the effect on liver vitamin A by about three times relative to the situation in which it is eaten as potato chips (Daher et al. 1997a), which means that, had the pigs been fed olestra in chips, the effect of 0.25% olestra on liver vitamin A concentration would have been a reduction of ~15%.

The dose response of olestra on liver vitamin A concentration in the pig was fully manifested during the 12-wk studies. **Figure 2** compares 12-wk data (Cooper et al. 1997c) and 26-wk data (Cooper et al. 1997b). The magnitude of the effect did not change as the pigs aged through their most rapid growth period and sexual maturity.

At intakes likely to result from the consumption of olestra savory snacks, olestra does not significantly affect the absorption of preformed vitamin A (Daher et al. 1997b); therefore the reduction in liver vitamin A results primarily from a reduction in carotenoid absorption. In the 8-wk studies, 20 g/d olestra reduced the absorption of β -carotene by ~58% (Schlagheck et al. 1997a and 1997b). Other carotenoids, with the exception of lutein, were similarly affected. The absorption of lutein, a less lipophilic carotenoid, was reduced by ~48%. In the 16-wk study in free-living subjects, 18 g/d olestra reduced the absorption of β -carotene by ~27% (Koonsvitsky et al. 1997). In both the 8-wk and 16-wk studies, serum carotenoid concentrations declined rapidly after olestra ingestion was started and reached a new steady-state level in <4 wk. These results indicate that daily consumption of olestra may reduce the steady-state circulating concentrations of carotenoids but does not lead to depletion as occurs when people consume carotenoid-free diets. This is illustrated in **Figure 3**, which shows the change in serum carotenoids concentration, plotted as a percentage of the base-line value, observed in the 16-wk study (Koonsvitsky et al. 1997) and the change when subjects consumed a low-carotenoid diet, in this case <4 mg/d (Rock et al. 1992).

TABLE 2

How data from the human and pig studies were used to accomplish the objectives of the program and define the effects of olestra on water-soluble and fat-soluble nutrients¹

Objective	Data from human studies	Data from pig studies
Determine the effect on macronutrient absorption and utilization	Weight stability	Growth, digestible feed efficiency
Determine the effect on fat absorption	Absorption of ¹⁴ C-triolein	Growth, digestible feed efficiency
Determine the effects on folate status and vitamin B-12 absorption	Folate: plasma, RBC folate Vitamin B-12: ⁵⁷ CO-vitamin B-12 absorption	Folate: plasma folate Vitamin B-12: liver vitamin B-12
Determine the effects on calcium, zinc and iron status	Calcium: serum calcium Zinc: urinary zinc Iron: serum ferritin, TIBC, hematology	Calcium: Bone ash, phosphorus, and calcium, PTH Zinc: liver, bone and serum zinc Iron: liver iron, serum ferritin, total iron, TIBC, hematology
Determine the effects on the status of vitamins A (including carotenoids), E, D, and K	Vitamin A: retinyl palmitate absorption, serum carotenoids Vitamin E: serum tocopherol Vitamin D: serum 25(OH)D ₂ , 25(OH)D, and 1,25(OH) ₂ D Vitamin K: serum phyloquinone, plasma prothrombin and <i>des</i> - γ -carboxylated prothrombin, urinary Gla Vitamin E: serum tocopherol	Vitamin A: liver vitamin A Vitamin E: serum, adipose and liver tocopherol Vitamin D: serum 25(OH)D ₂ , 25(OH)D, and 1,25(OH) ₂ D; bone ash, calcium and phosphorus Vitamin K: PT, PTT
Determine the amounts of vitamins A, E, D and K required to offset the effects of olestra	Vitamin D: serum 25(OH)D ₂ Vitamin K: serum phyloquinone	Vitamin A: liver vitamin A Vitamin E: liver, serum tocopherol

¹ Abbreviations used: Gla, γ -carboxyglutamic acid; 25(OH)D₂, 25-hydroxyergocalciferol; 25(OH)D, total 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; PT, prothrombin time, PTH, parathyroid hormone, PTT, partial thromboplastin time; TIBC, total iron-binding capacity.

The amount of vitamin A required to offset the effect of olestra was determined from direct measurements of liver stores of the vitamin in pigs. The pigs were fed diets that provided vitamin A as a 3:1 ratio of retinyl palmitate and β -carotene in terms of retinol equivalents. The amount of vitamin A required to offset the effects of olestra was found to be an essentially a linear function of the amount of olestra in the diet over the range of olestra tested, 1.1–7.7% (Cooper et al. 1997a). A 26-wk study, which tested dietary concentrations of olestra that encompassed estimated daily intakes of olestra by humans from savory snacks prepared with olestra, showed that restoration of liver vitamin A concentration to control

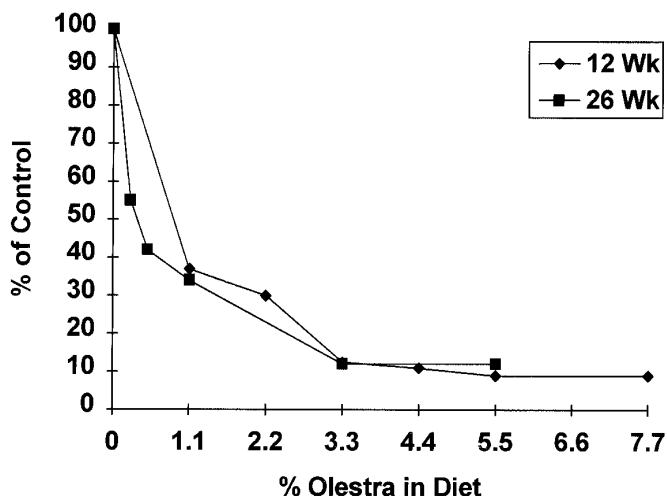


FIGURE 2 The liver concentration of vitamin A in pigs fed olestra for 12 or 26 wk.

required 93 μ g retinyl palmitate/g olestra (Cooper et al. 1997b).

Because of the similarities between pig and human GI physiology and because the diet used in the pig studies modeled the human diet with respect to vitamin A sources and fat intake, the restoration result obtained in the pig for vitamin A is appropriate for humans. Further evidence of the appropriateness of the pig as a surrogate for humans comes from the data on vitamin E discussed below.

Vitamin E. The pig studies showed that serum and liver concentrations of vitamin E were similarly affected by olestra (Cooper et al. 1997b and 1997c). For pigs fed 0.25 or 0.5% olestra, liver vitamin E was reduced by 24 and 31%, respectively, and serum vitamin E was reduced by 26 and 49%, respectively (Cooper et al. 1997b). These dietary concentrations of olestra provided daily intakes that ranged from 4 to 10 g/d by the end of the study, intakes similar to the mean

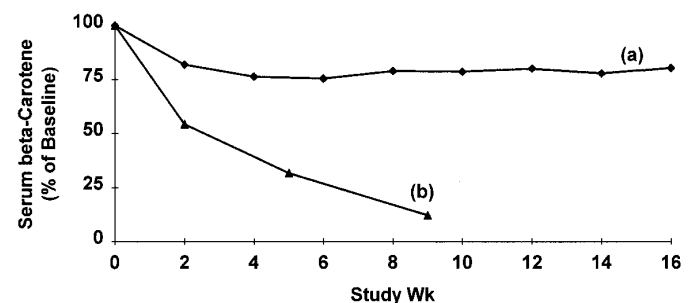


FIGURE 3 Changes in the serum concentration of carotenoids (a) in subjects fed 18 g/d olestra for 16 wk (Koonsvitsky et al. 1997) and (b) in subjects fed a diet low (<4 mg/d) in carotenoids for 9 wk (Rock et al. 1992).

90th-percentile human intake, 3.7–10.0 g/d, from savory snacks depending on gender or age (Webb et al. 1997). Results from a study in which pigs were fed olestra either mixed in the diet or in potato chips indicate that these effects on vitamin E status would have been ~50% less (i.e., 12–25%) had the pigs been fed olestra in potato chips (Daher et al. 1997a).

Data from pigs showed that the relationship between the amount of vitamin E required to maintain tissue concentrations at control concentrations and the amount of olestra in the diet was essentially linear, as was also true for vitamin A.

Restoration of serum vitamin E concentration to control level in the pig required 2.2 mg *d*- α -tocopheryl acetate (TA)/g olestra, and restoration of liver vitamin E concentration required 2.1 mg TA/g olestra (Copper et al. 1997a). The finding that serum and liver concentrations respond in the same way to olestra intake and to the addition of extra vitamin E to the diet was important because it supports the use of serum vitamin E as a measure of vitamin E status in humans.

In humans, 8 and 20 g/d olestra, eaten in potato chips, reduced serum vitamin E by ~6 and 18%, respectively, in reasonable agreement with the effects measured in the pig had the pigs been fed olestra in potato chips (Schlagheck et al. 1997b).

The linear relationship between the amount of additional vitamin E required to restore serum vitamin E to control concentration and the amount of olestra in the diet was confirmed in humans, and it was found that 2.1 mg TA/g olestra was required to offset the effect of olestra (Schlagheck et al. 1997a). This value agrees with that found for the pig. The finding of similar restoration values for vitamin E in humans and pigs provides further evidence of the appropriateness of the pig model for establishing the restoration level for vitamin A in humans, for whom direct measures of vitamin A tissue stores cannot be made.

Vitamin D. The serum concentration of 25-hydroxyergocalciferol [25(OH)D₂] was used as a measure of the effect of olestra on the absorption of dietary vitamin D. In addition, serum concentrations of 25-hydroxycalciferol [25(OH)D₃], total 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25(OH)₂D] were measured to provide an assessment of total vitamin D status. In the pig, bone concentrations of ash, calcium and phosphorus were also measured.

The combination of pig and human data showed how olestra affected circulating concentrations of the metabolites with different relative contributions of dietary vitamin D to total vitamin D status. Serum 25(OH)D₂ was reduced by 20–25% by olestra in humans, depending on olestra dose, and the effect was essentially the same in the absence and presence of a 20 μ g/d supplement of ergocalciferol (Schlagheck et al. 1997a and 1997b). The supplement resulted in a dietary contribution of ~68% to total vitamin D status. In the nonsupplemented study, the dietary contribution was ~20%. Also, the effect of olestra on serum 25(OH)D₂ was essentially the same in pigs exposed or not exposed to UV light (Cooper et al. 1997a and 1997b).

The contributions of dietary vitamin D-2 to overall vitamin D status in these studies encompassed and exceeded the dietary contribution for the general population. The majority of people obtain <20% of their vitamin D from the diet (Haddad and Hahn 1973, Jones 1978, Jones et al. 1991). In more extreme climatic conditions, such as winter in Canada, the contribution of dietary vitamin D to overall status may be no more than 50% (Delvin et al. 1979).

Measures of overall vitamin D status such as serum 1,25(OH)₂D and 25(OH)D concentrations were not significantly affected by olestra in either the pig or the human stud-

ies, including the 16-wk human study in free-living subjects (Koonsvitsky et al. 1997).

The amount of vitamin D required to offset the effect of olestra was determined from the 8-wk human study (Schlagheck et al. 1997a). This study showed that 0.06 μ g ergocalciferol/g olestra offset the effect of olestra on serum 25(OH)D₂ concentration.

Vitamin K. Both pig and human studies showed that olestra, at any of the intakes tested, did not affect vitamin K function. Neither prothrombin time (PT) nor partial thromboplastin time (PTT) was affected in pigs fed vitamin K near the NRC requirement for 12 wk (Cooper et al. 1997c) or about one fifth of the requirement for 39 wk (Cooper et al. 1997b). In humans, plasma concentrations of *des*- γ -carboxyprothrombin and prothrombin, and urinary excretion of γ -carboxyglutamic (Gla) were used as measures of vitamin K function. Urinary Gla excretion reflects vitamin K-dependent carboxylation of glutamic acid residues in proteins produced by the liver and by other tissues; plasma *des*- γ -carboxyprothrombin reflects incomplete carboxylation of plasma prothrombin. Both measures are considerably more sensitive to changes in vitamin K function than are clotting times (Suttie 1992). In the 16-wk human study, plasma concentration of functional prothrombin was measured (Simplastin-Ecarin assay). No significant changes were observed in any of these functional parameters.

Olestra did reduce serum phylloquinone concentration in humans by 36–47%, depending on dose (Schlagheck et al. 1997a and 1997b). However, changes in serum phylloquinone do not necessarily reflect changes in overall vitamin K status. Because the half-life of circulating phylloquinone is ~104 min (Shearer et al. 1974), serum phylloquinone reflects mainly short-term intake of the vitamin. Evidence of this was found in the 8-wk dose-response study in which the subjects ate different amounts of phylloquinone on the days immediately before blood draws (Schlagheck et al. 1997b). The intake of phylloquinone on the day immediately before the four blood draws was 235, 43, 78 and 235 μ g/d, respectively. Serum phylloquinone concentration for the control group (no olestra) at the four draws was 1.3 \pm 0.13, 0.51 \pm 0.13, 0.64 \pm 0.07 and 1.6 \pm 0.18 nmol/L, respectively.

The data from this study also allowed the amount of vitamin K required to offset the effect of olestra on serum phylloquinone to be calculated as follows. For each treatment group (0, 8, 20 or 32 g/d olestra) a best-fit linear regression equation describing the relationship between serum phylloquinone concentration and the previous day's vitamin K intake was derived. Then, the serum concentration of phylloquinone that would result from eating 80 μ g [1 recommended dietary allowance (RDA)] of vitamin K in the absence of olestra was calculated from the equation derived for the control group, 0.69 nmol/L. As a next step, this value was inserted into the regression equations for the olestra groups, and the amount of vitamin K required to maintain serum phylloquinone at the control value in the presence of 8, 20 or 32 g/d olestra was calculated. These calculated values were then adjusted for the 1 RDA vitamin K intake by the control group by subtracting 80 μ g from each. These calculations showed that 31, 68 and 82 μ g of vitamin K were required to offset the effects of 8, 20 and 32 g/d olestra, respectively. These values were converted to μ g/g olestra and averaged to produce a restoration value of 3.3 μ g vitamin K/g olestra.

As part of the olestra approval process, the Food and Drug Administration (FDA) carefully considered the effects of olestra on the absorption of the fat-soluble vitamins. The studies, conducted under exaggerated dietary conditions as discussed above, showed no significant effects of olestra on overall vita-

TABLE 3

The amounts of fat-soluble vitamins that will be added to savory snacks to offset the potential effects of olestra on the absorption of these vitamins. The amounts are expressed in terms of the recommended daily intakes (RDI) of the vitamins added to a single serving of savory snacks

Vitamin	RDI added to a single serving of savory snacks ¹
A	0.3
D	0.3
E	0.9
K	1.0

¹ Based on the maximum amount of olestra in the savory snack product with the greatest replaceable fat content, potato chips, which can contain up to 10 g of replaceable fat per 1-ounce serving. The typical range of olestra in savory snacks will be 4–10 g/serving, depending on the type of snack.

min D status or vitamin K function. Further, the effects of olestra on the absorption of vitamin A and vitamin E are likely to be small and not nutritionally significant for most people eating savory snacks made with olestra. However, the fat-soluble vitamins are essential nutrients, and there may be individuals whose dietary patterns would lead to larger effects than those measured in the test subjects, or individuals whose vitamin status is marginal or inadequate and in whom any decrease would therefore be undesirable. Because of these possibilities, the FDA concluded that the potential benefit of adding all four fat-soluble vitamins to olestra snacks in sufficient amounts to offset any olestra effects outweighed any potential risk from such additions (Federal Register 1996).

Addition of the required amounts of fat-soluble vitamins to olestra will pose no risk of vitamin toxicity. The added amounts of the vitamins, even if all were absorbed, are well below amounts known to product toxic effects (Federal Register 1996, Schlagheck et al. 1997a). Table 3 lists the vitamin addition levels recommended by the FDA in terms of recommended daily intakes (RDI) that would be contained in a single serving of olestra savory snacks, in this case a 1-ounce serving of potato chips, the snack food that would contain the greatest amount of olestra per serving, 10 g. The total amounts of added vitamins will not all be absorbed and, most importantly, the added vitamins simply maintain tissue concentrations at control values and do not increase them.

Relationship between effects observed in the human and pig studies and effects that might occur in real life. The effects of olestra on the absorption of dietary components measured in the human and pig studies are significantly greater than those likely to occur when olestra snacks are eaten in real life. The dietary conditions used in the studies (i.e., the eating frequency and olestra intake) were intentionally selected to maximize the interaction between olestra and the dietary components and thereby maximize the responses to olestra, were there any. Because of the mechanism by which olestra can interfere with the absorption of dietary components, by physical interaction in the gut, eating pattern (i.e., whether olestra is eaten together with other foods or at a different time) is the primary factor that can maximize olestra effects. A comparison of the effect of olestra on the absorption of vitamin E measured in the 16-wk study in free-living subjects with that measured in the 8-wk studies illustrates how dietary pattern can influence the effect of olestra on the absorption of fat-soluble nutrients. In the 16-wk study, in which

subjects ate olestra with meals but were not restricted from eating between meals and were permitted to eat their habitual diets, 18 g/d of olestra reduced vitamin E absorption by 6% (Koonsvitsky et al. 1997). In the 8-wk study, in which the subjects ate olestra at every meal as part of a predefined diet and were not allowed to eat anything between meals, 20 g/d olestra reduced vitamin E absorption by 18%, an effect three times greater than that measured in the free-living study (Schlagheck et al. 1997b). However, the results from the free-living studies are still exaggerated relative to what might occur in real life because the subjects ate olestra daily (i.e., up to 42 times in a 14-d period) in that study.

A further perspective on the importance of dietary pattern comes from comparison of the effects of olestra on the absorption of β -carotene measured in the 8-wk studies and the 16-wk study with the effect calculated from real-life eating patterns of snack foods and carotenoid-containing foods (Cooper et al. 1997e). To what extent olestra might affect carotenoid absorption when people eat olestra snacks and carotenoid-containing foods in their habitual eating pattern was estimated as follows. First, analysis of menu census data showed that an individual eating savory snacks at the 90th-percentile level eats snacks and carotenoid-containing foods together about five times in a 14-d period. The intake of β -carotene, used as a marker of carotenoid intake in general, was calculated for the general population from the menu census data. Then, the intake was recalculated assuming that the β -carotene intake would be reduced by the amount measured in the 8-wk human studies each time a savory snack and a carotenoid-containing food were eaten together. The calculated average reduction in β -carotene intake (all ages, males and females) from eating olestra snack foods was 5.9% (Cooper et al. 1997e). For the top 10% of snack eaters (all ages), the reduction was calculated to be 9.5%. These estimates are still exaggerated because it was assumed in the analysis that all snack foods eaten were snacks made with olestra, an unlikely situation.

Figure 4 illustrates the effect of eating pattern on β -carotene absorption. This figure shows the effects of olestra on serum β -carotene measured when 1) olestra snack foods and foods containing β -carotene are eaten in real-life dietary patterns, the analysis discussed above, 2) when olestra was eaten every day with meals but carotenoids were eaten ad libitum (Koonsvitsky et al. 1997, Weststrate and van het Hof 1995), and 3) when carotenoids and olestra were always eaten together (Schlagheck et al. 1997b).

The likely effect of olestra on the availability of other carotenoids would be expected to be similar to, or less than that calculated for β -carotene because β -carotene is one of the most lipophilic carotenoids (Cooper et al. 1997e). Calculations similar to those discussed above were not made for other dietary components such as the fat-soluble vitamins. However, the effect of olestra on these nutrients in real life would be expected also to be considerably less than the effects measured in the pig and human studies because the foods containing these nutrients are only occasionally eaten together with snack foods.

The interaction of olestra with carotenoids and other dietary components is not different than many other interactions that occur between many other dietary components. For example, carotenoid absorption can be reduced by as much as 50% when carotenoids are eaten with large amounts of fiber (Rock and Swendseid 1992), and β -carotene absorption is reduced by more than 70% from meals containing only small amounts of fat (Dimitrov et al. 1988). A normal serving of milk can reduce whole-body retention of iron from a standard breakfast by as much as 50% (Deehr et al. 1990), and drinking tea with

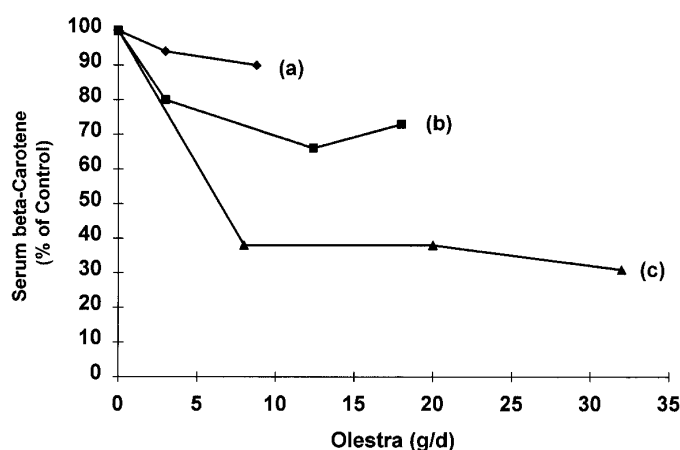


FIGURE 4 Effect of olestra on the serum concentration of β -carotene under the following different dietary contexts: (a) calculated from the frequency of co-consumption of olestra snacks and foods containing β -carotene when olestra is eaten ad libitum, as snacks, at the mean (3.1 g/d) and 90th percentile (8.8 g/d) and the foods containing β -carotene are eaten ad libitum; (b) measured when olestra was eaten every day with meals and β -carotene was eaten ad libitum; [the 3 and 12.4 g/d points are taken from Weststrate and van het Hof (1995) and the 18 g/d point is taken from Koonsvitsky et al. (1997)]; and (c) measured when olestra and β -carotene were always eaten together (Schlagheck et al. 1997b).

a typical breakfast has been shown to reduce the absorption of iron from that meal by as much as 60% (Rossander et al. 1979). Although such effects might be significant at any one meal, because of variations in dietary components and eating patterns, they are generally not nutritionally significant over time.

The variation in carotenoid bioavailability for people eating olestra snacks is likely to be within the normal variation of dietary carotenoid bioavailability and likely not be nutritionally meaningful. Further, any effect of a decrease in carotenoid availability on vitamin A stores will be offset by the addition of vitamin A to the snack food. The FDA concluded, on the basis of the scientific evidence available, that the effects of olestra on carotenoid absorption is "reasonably certain" to be nutritionally insignificant and that there is currently no need or justification to add carotenoids to olestra snack foods (Federal Register 1996).

Potential of olestra to affect the availability of phytochemicals. Studies of the association between diet and health have shown that increased consumption of fruits and vegetables is associated with reduced risk of certain kinds of cancer and cardiovascular diseases (Block et al. 1981, Doll and Peto 1981, Gaziano 1996, Peto et al. 1981). It has been hypothesized that the beneficial effects of diets rich in fruits and vegetables come from fiber as well as various phytochemicals, including carotenoids (Institute of Food Technologies 1993, Steinmetz and Potter 1991, Tanka 1994).

Because of the observed associations and hypothesis, the potential of olestra to affect the absorption of phytochemicals was assessed (Cooper et al. 1997e). As a first step in making the assessment, octanol-water partition coefficients ($\log_{10} p_c$) for those molecules shown to be affected, or not affected by olestra were compiled. Octanol-water partition coefficients provide a measure of the lipophilicity of a molecule (i.e., its equilibrium distribution between an aqueous phase and an oil phase). Comparison of $\log_{10} p_c$ values of those molecules for which olestra does not affect absorption with those of molecules that are affected showed that olestra affects the absorp-

tion only of molecules with $\log_{10} p_c$ values < 7.5 (Cooper et al. 1997e). The effect of olestra on the absorption of molecules with $\log_{10} p_c$ values in the 7.5–9 range is minimal. As a next step, $\log_{10} p_c$ values for almost 400 phytochemicals, making up all of the major classes, were calculated. Only two classes contained molecules with $\log_{10} p_c$ values > 7.5 and thus likely to be affected by olestra. These were the carotenoids and the phyosterols.

Carotenoids are only one of many phytochemicals found in fruits and vegetables, and it is unlikely that they are the only component responsible for the apparent beneficial effects of high fruit and vegetable intake. As discussed above, the effect of olestra on carotenoid absorption when olestra snack foods are eaten in real life is estimated to be $< 10\%$. A reduction in the absorption of one component by $< 10\%$ is unlikely to affect the beneficial effects associated with diets rich in fruits and vegetables.

The other class of phytochemicals that contains molecules sufficiently lipophilic that their absorption might be affected by olestra is the phyosterols. Phyosterols, when taken in large amounts, can reduce cholesterol absorption (Linscheer and Vergrosen 1988). A small reduction in the absorption of these phytochemicals by olestra is unlikely to pose a risk because large intakes of olestra also have the potential to reduce cholesterol absorption (Jandacek et al. 1990). Further, the absorption of large amounts of phyosterols themselves is undesirable inasmuch as it may result in increased risk of hypercholesterolemia (Linscheer and Vergrosen 1988).

Application of the results of the pig and human studies to subgroups of the population. The human nutrition studies were conducted with healthy male and female adults. Hypothetically, certain subgroups of the population might exhibit greater effects from eating olestra than those observed in the studies, either because of their dietary pattern or because they have nutrient needs that exceed those of the subjects tested in the studies. A dietary pattern that results in olestra-to-nutrient intake ratios (i.e., amounts of olestra relative to the amounts of nutrients in the GI tract) greater than those used in the studies might produce either greater effects than those measured in the studies or effects not seen in the studies. Any effect on nutrient availability for subgroups with a particularly high metabolic need for that nutrient could also potentially place them at risk for nutritional inadequacy.

To ensure that the results from the pig and human studies can be used to assess the potential for olestra to affect the nutritional status of such subgroups, the nutrient needs and dietary patterns represented in the olestra studies were compared with those of potentially at-risk subgroups (Middleton et al. 1997). The first step was to identify subgroups potentially at-risk either because of unique dietary patterns or nutrient needs different than those of the test subjects. This was done by compiling requirements for and intakes of the nutrients selected for evaluation in the studies for subgroups of the population. Olestra intakes were estimated for the same subgroups. This analysis showed that children, teenager and young adults, women from low-income families and vegetarians had dietary patterns that produced olestra-to-nutrient intake ratios greater than those of adults. Subgroups identified with high nutrient requirements included children, teenagers, and pregnant or lactating women.

A comparison of nutrient needs and olestra-to-nutrient intake ratios of the identified subgroups with those covered in the studies showed that the nutrient needs of the rapidly growing pigs used in the studies were greater than those of any of the subgroups for any nutrient. Also, olestra-to-nutrient intake ratios fed in the studies were greater than the ratios calculated

for any subgroup for all nutrients except calcium, a micronutrient not affected by olestra. Thus, the effects (or lack of effects) of olestra on fat-soluble and water-soluble nutrients observed in the studies are applicable to these subgroups and indicate that no subgroup of the population will be placed at nutritional risk from eating olestra snacks.

Tolerance of olestra. No medically significant health-related conditions were observed or reported during the olestra clinical studies. Common GI symptoms such as abdominal discomfort (gas, cramps, bloating) and changes in stool consistency (soft, loose, diarrhea-like) were reported by all groups, including the placebo groups, in the 8- and 16-wk clinical studies (Koonsvitsky et al. 1997, Schlagheck et al. 1997a and 1997b). Subjects in the olestra groups did not report symptoms different than those reported by the subjects in the placebo groups.

Detailed information on the nature of these GI symptoms was obtained in the two 8-wk studies in which subjects used questionnaires to identify each GI symptom they experienced, indicated the length of each episode of each symptom and graded the severity. Because the demographics of the subject populations in the two 8-wk studies, a total of 192 adults, 18–44 y of age, were essentially the same and the protocols were identical, it is appropriate to combine the GI symptom data from the two studies.

The average severity of the GI symptoms is shown in Figure 5 for all symptoms, abdominal cramping and diarrhea for those subjects reporting symptoms in both studies (1 = mild, 2 = moderate, 3 = severe). Abdominal cramping and diarrhea were broken out because they are the symptoms of most concern. Similarly, the percentage of possible symptom-days is shown in Figure 6 for the combined studies. A symptom-day is defined as a day in which one or more symptoms were experienced with more than usual frequency, as reported by the subjects. Symptom-days were used to characterize the symptoms because they were transient in nature, abating and recurring. The maximum possible number of symptom-days for a given test group is obtained for a given symptom by multiplying the number of subjects in the group by 56, the number of days in the study.

Generally, the symptoms were mild to moderate in severity, and the severity was not dose responsive with respect to olestra intake. There was only 1 wk in which the average diarrhea grade was severe and that was in the placebo group at wk 3. The percentage of symptom days was generally dose responsive with respect to olestra intake; however, the placebo and 8 g/d olestra groups reported GI symptoms, including diarrhea and cramping, to essentially the same extent. Subjects eating 8 g/d olestra, an amount more than twice the estimated mean chronic olestra intake (3.1 g/d, all ages, males and females) from savory snacks (Webb et al. 1997) reported no symptoms on 90% or more of the days on which they were eating olestra snacks.

Many of the GI symptoms reported during the olestra studies were related to changes in stool consistency. In view of its properties (e.g., lipophilic, nondigestible, nonabsorbed), it is not surprising that olestra affects stool consistency. Large amounts of a highly lipophilic substance in the bowel can disrupt the fecal matrix and produce soft or loose stools. In extreme cases, this can be perceived as diarrhea. This stool-softening phenomenon may be akin to the stool-softening effects observed with liquid petrolatum and oils such as olive oil (Curry 1986). In the pig studies, variations in fecal consistency were noted with larger numbers of pasty feces being associated with higher dietary concentrations of olestra (Cooper et al. 1997a, 1997b, 1997c and 1997d).

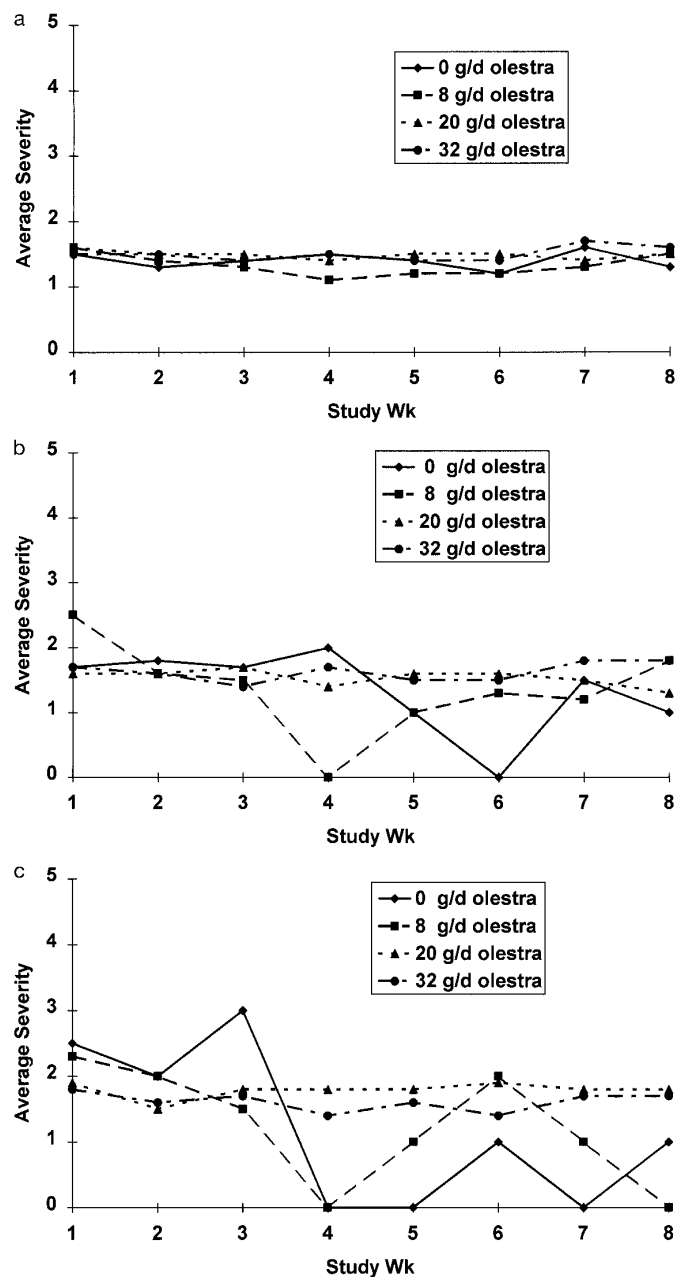


FIGURE 5 Average severity of the gastrointestinal (GI) symptoms reported during the two 8-wk olestra clinical studies (a) for all symptoms, (b) for abdominal cramping and (c) for diarrhea (1 = mild, 2 = moderate, 3 = severe).

The GI symptoms did not affect protocol compliance or the integrity of the findings from the studies. In the two 8-wk studies, the subjects ate more than 90% of the meals; only six subjects (in either the 20 g/d olestra groups or the 32 g/d olestra groups) temporarily stopped eating olestra foods because of the GI symptoms, and one subject withdrew because of persistent heartburn (Schlagheck et al. 1997a and 1997b). In the 16-wk study, only four of the 219 subjects enrolled withdrew because of GI symptoms, and olestra consumption was 98% of the targeted 18 g/d amount (Koonsvitsky et al. 1997).

The diarrhea reported by the individuals eating olestra was not pathological diarrhea, but rather an extreme case of stool softening. Pathological diarrhea could lead to malabsorption and thus cause changes in the absorption of

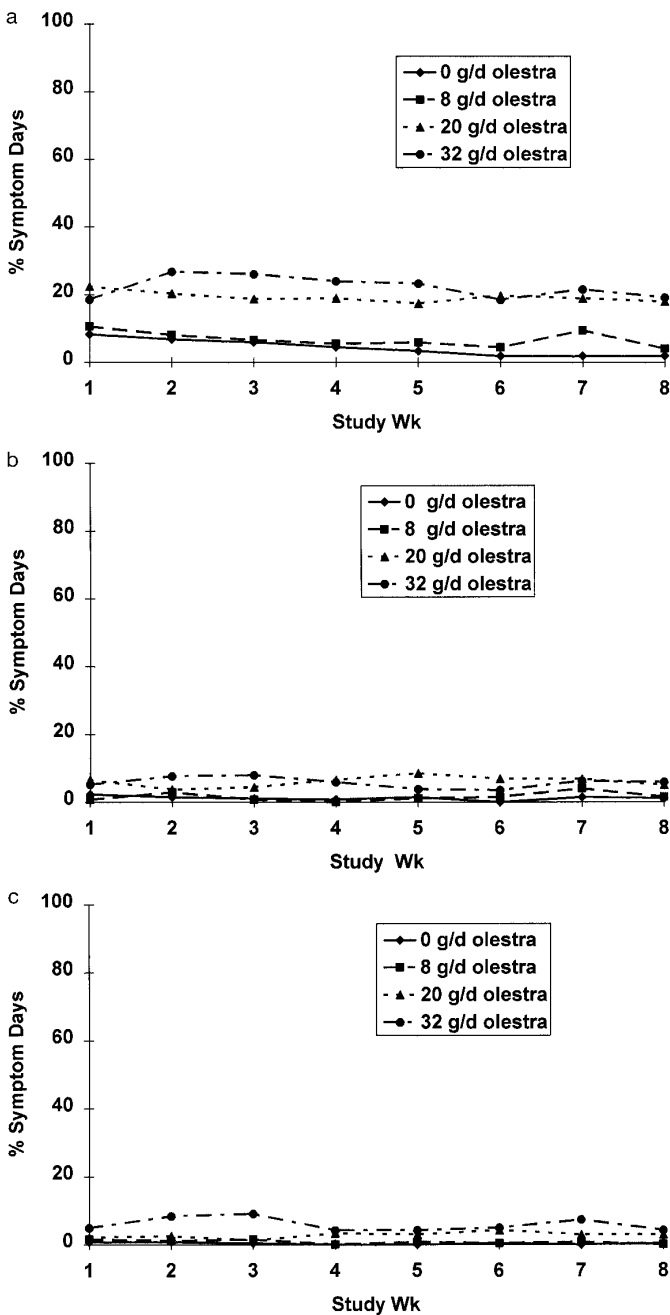


FIGURE 6 The percentage of symptom-days of gastrointestinal (GI) symptoms reported during the two 8-wk olestra clinical studies (a) for all symptoms, (b) for abdominal cramping and (c) for diarrhea. A symptom-day is defined as a day on which one or more GI symptoms were experienced with more than usual frequency, as reported by the subjects. For a test group, the total possible number of symptom-days for any given symptom is the number of subjects in the study multiplied by 56, the number of days of the studies.

water-soluble nutrients. The absorption of water-soluble nutrients was not affected by olestra in the subjects who reported diarrhea (Schlagheck et al. 1997a and 1997b). Further, clinical chemistry, hematology and urinalysis data collected on subjects who reported diarrhea on the day of or the day before blood and urine samples were taken showed no evidence of significant fluid loss such as hemoconcentration or electrolyte imbalance. Finally, no diarrhea was observed in pigs fed olestra at dietary concentra-

tions as high as 7.7% (Cooper et al. 1997a, 1997b, 1997c and 1997d).

The incidence of GI symptoms reported in these studies is greater than that likely to occur when olestra snacks are eaten in real life because olestra was present in the GI tract at all times in amounts that exceeded intakes estimated for savory snack consumption by severalfold. The nature and frequency of GI symptoms reported by people eating either snacks prepared with olestra or triglyceride under real-life conditions have been determined in several consumer tests. In one such test, female heads of households were allowed to choose potato chips prepared with either olestra or triglyceride, in an amount and at a frequency they desired, over a 5-mo period. In this test, more than 2,000 subjects ate chips prepared with olestra and more than 1,000 ate regular chips (Lawson et al. 1997). Of the subjects who ate either kind of chips, < 1% voluntarily reported GI symptoms and there were no significant differences between the groups in the reports of any of the symptoms except flatulence, which was increased for the group who ate the olestra chips.

GI symptoms that may be experienced by individuals eating olestra snacks present no health risks, a conclusion also reached by the FDA (Federal Register 1996). These symptoms are not different than the symptoms associated with the consumption of other dietary components such as fibers (Anderson and Akanji 1991) and food additives such as sorbitol (Corazza et al. 1988, Hyams 1983) and are not worse in individuals with diseased GI tracts. This is illustrated by the results of a study in patients with quiescent inflammatory bowel disease (Zorich et al. 1997). Patients given 20 g/d of olestra for 4 wk reported no more adverse events related to the GI tract than those given triglyceride, with one exception. An increase in the number of daily bowel movements on one or more days was reported by more patients in the olestra group than in the placebo group. An increase in the number of bowel movements is not unexpected for individuals eating large amounts of olestra because of the increased fecal bulk.

It is important for consumers to be aware of the potential for olestra to produce GI symptoms in order to preclude unnecessary concern, and perhaps inappropriate medical treatment. Therefore, olestra products will carry a label informing the consumer that certain GI effects may occur (Federal Register 1996).

Whenever any new ingredient is introduced into the food chain, postmarketing surveillance is prudent and commonly occurs. Such is the case with olestra. Procter & Gamble is carrying out a postmarketing surveillance program consisting of several components. The spontaneous reporting of alleged undesirable effects is being monitored via an 800 telephone number provided on the product label. Olestra exposure, both intake and frequency of consumption, is also being monitored. In addition, prospective observational epidemiologic studies are being conducted to determine the nature, severity, incidence and prevalence of any effects on nutritional status and any gastrointestinal effects among individuals who eat olestra snacks under free-living conditions.

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