

May 2, 2000

Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Food additive petition to amend 21 C.F.R. §172.867(e) and the “interim” label requirement for olestra (submitted by Procter and Gamble), and previous CSPI requests to revise the labeling of olestra-containing products [Docket No. 00F-0792].

Dear Sir or Madam:

The Center for Science in the Public Interest (CSPI) welcomes the opportunity to provide these comments on Procter and Gamble’s recent petition to the Food and Drug Administration (FDA) requesting that products that contain olestra no longer be required to bear a notice concerning nutrient losses and gastrointestinal symptoms.

The petition begins with a recap of the approval history of olestra. The petition states that the FDA relied in part on the Food Advisory Committee (FAC) for advice. We remind the FDA that that committee, which voted 17 to 5 in favor of approving olestra, was not an objective source of advice.¹ Despite our plea prior to the FAC meeting, the FDA did not appoint to the committee a single expert on carotenoids. Moreover, the committee was dominated by industry consultants. As CSPI discovered subsequently, at least nine of the 17 members who concluded that olestra presented a reasonable certainty of no harm had ties to industry. The petitioner states that “FDA had no meaningful concerns about the safety of olestra.”² Nevertheless, the FDA acknowledged in its notice approving olestra that the petitioner’s small clinical studies found that olestra could cause severe gastrointestinal symptoms.³

CSPI agrees with the petitioner that the current language of the notice may be confusing. But we urge that it be revised, not eliminated. In fact, significant concerns remain about adverse

¹ H.Blackburn, *Olestra and the FDA*, NEW ENGL. J. MED. 984 (1996).

² Procter & Gamble, Food Additive Petition to Amend 21 C.F.R. § 172.867(e) and the “Interim” Label Requirement for Olestra, Dec. 1, 1999 (hereinafter referred to as “Petition”), p. 6.

³ 61 Fed. Reg. 3,118, 3,153 (1996).

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effects of consuming olestra-containing products.

The petition before the FDA focuses on “real life” studies of gastrointestinal and nutritional effects of olestra on “free living” consumers. Focusing exclusively on those studies is inappropriate. Studies conducted by Procter and Gamble and other companies prior to approval provide crucial information that must be considered by the FDA if it is to make a decision that will protect the public health. The purported absence of major problems in the post-marketing studies may be due, in part, to the fact that very few subjects consumed large amounts of olestra-containing products. It is quite conceivable that in the future such products may become more popular due to a combination of factors. Those factors include removal of the olestra label notice, wider availability of olestra-containing snack foods beyond the current handful of brands and products, FDA approval of the use of olestra in foods other than snack foods, lowering of prices, and improvements in taste. Rules should be based not on the basis of the health effects of the few products currently on the market, but on the possibility that more olestra products would be consumed more frequently.

I. Interference with the absorption of nutrients

A. The current petition ignores data demonstrating that olestra can interfere with the absorption of nutrients.

Procter and Gamble’s recent petition states that “post-approval research provides strong, convincing evidence that consumption of foods containing olestra does not have a meaningful or significant adverse effect on health due to interference with the absorption of fat-soluble vitamins or other lipophilic substances.”⁴ That post-approval research consists of studies that involved much lower consumption of olestra than the controlled clinical studies submitted with the original food additive petition. Those earlier studies demonstrated clearly that olestra can reduce the absorption of fat-soluble nutrients, including carotenoids. The less-sensitive, newer studies should certainly be considered, but they do not negate the significance of the more-sensitive, older studies. Those older studies demonstrate the effects of olestra on someone who eats olestra with each meal.

Clinical studies have considered the effects on fat-soluble nutrients of consuming olestra with one or several meals. Animal research considered the impact of consuming olestra between meals. In summary:

* Procter and Gamble’s 8-week clinical (“dose-response” and “vitamin restoration”) studies: Doses of 8 to 32 grams of olestra per day reduced serum levels of total carotenoids by 50% to 60%.

⁴ Petition, p. 61.

* A four-week clinical study supported by Unilever involved feeding 21 subjects 12.4 grams of olestra with the main meal each day.⁵ That study found substantial decreases of serum levels of carotenoids, with the greatest reductions in beta-carotene (34% decrease) and lycopene (52% decrease). The researchers noted:

It might be argued that the particular setup of our studies reflects a worst-case scenario.... We believe that a realistic consumption scenario of SPE [sucrose polyester] in typical consumer foods will never exclude the possibility of concurrent ingestion of dietary carotenoids and such low amounts of SPE as used by our low-dose study... In view of the evidence that carotenoids may have positive effects on health, decreases of the magnitude we observed are undesirable.”

B. Post-marketing studies

The petitioner reports the results of a post-market study of serum nutrient levels. The study purports to correlate olestra consumption with decreased calories from fat, decreased serum cholesterol (with no breakdown between LDL and HDL), and no change in carotenoid levels. This study provides little useful data. While it looked at “high” consumers (90th percentile), those people actually consumed no more than two grams per day. That’s equivalent to about one-fourth or one-fifth ounce of olestra-containing snack per day. The study says nothing about people who eat even moderate amounts of olestra-containing snacks, especially the sub-group that consumes those snacks with meals.

This study is limited by the small numbers of people who consumed substantial amounts of olestra. Indeed, only “about 15% of adults in the study ate at least one olestra snack per month.”⁶ That shortcoming, we speculate, was probably due to the high cost of the products, adverse gastrointestinal effects, and other factors. Whatever the reasons, the small number of people who ate substantial amounts of olestra limits the value of the study. Hence, the study provides little useful information about what the nutritional effects of high intakes of olestra would be. High intakes might occur more frequently if the label notice were removed, product prices were lower, consumer attitudes toward olestra-containing products changed, or more desirable or tastier products were developed and marketed. Labeling policy must be developed not on the basis of the unexpectedly low current consumption but on the basis that current and future high-olestra-intake consumers should be protected. Eliminating all references to decreased nutrient intakes is not the proper response. Instead, the FDA should base its notice on the potential nutritional effects of daily consumption of olestra, as documented by pre-market

⁵ JA Weststrate and KH van het Hof, *Sucrose polyester and plasma carotenoid concentrations in healthy subjects* 62 AM. J. CLIN. NUTR. 591 (1995).

⁶ Petition, p. 30.

clinical studies. Alternatively, the FDA should require fortification with the relevant fat-soluble carotenoids.

A clinical study not conducted by the petitioner (and apparently not cited in the petition) was conducted at Addenbrooke's Hospital in Cambridge, UK and funded by Unilever. In that study, in which subjects ate a mean of 27 grams of olestra per day for up to 12 weeks, "Profound falls were seen in all carotenoids measured."⁷ Plasma lipid concentrations of lutein, beta-cryptoxanthin, lycopene, alpha-carotene, and beta-carotene declined by 30% to 40%. The researchers stated: "Until further knowledge is available, it would seem prudent to avoid introducing foodstuffs into the diet which reduce the absorption of potentially beneficial substances from plants." In an invited commentary accompanying that paper, Clare Lawton, of the University of Leeds, concluded similarly: "For the time being, however, I would agree with Kelly and colleagues that the deleterious side effects of SPE consumption, as observed in their study, warrant further investigation before this product is made available for widespread long-term consumption in a broad range of foods."⁸ (Of course, in the United States, olestra is not yet approved for a "broad range" of foods.)

C. Current understanding of the possible health effects of carotenoid losses.

Please see the comment (filed April 26) by Professor Walter Willett, chairman of the nutrition department at the Harvard School of Public Health. Dr. Willett (as he and many others in the academic community) has long maintained that loss of fat-soluble carotenoids by heavy consumers of olestra is inconsistent with the FDA's standard of "reasonable certainty of no harm." In his recent comment, Dr. Willett also highlighted the worthlessness of the petitioner's study of carotenoid levels in a free-living population. He notes that he and a colleague had advised the petitioner before they commenced the study that it would have inadequate power to identify any effect of olestra on carotenoid losses.

D. The label notice should be revised.

The post-approval research demonstrates only that small amounts of olestra do not affect serum carotenoid levels. The older research demonstrates that frequent consumption of olestra snacks with meals drastically reduces serum carotenoid levels. The FDA should base its regulations on near-worst-case assumptions, namely; that more products will contain olestra and those products will be eaten more frequently, and that some people will be eating olestra-containing products within a couple of hours of eating carotenoid-rich foods. Either fat-soluble

⁷ SM Kelly *et al.* *A 3-month, double-blind, controlled trial of feeding with sucrose polyester in human volunteers*, 80, BRIT. J. NUTR. 41 (1998).

⁸ CL Lawton, *Regulation of energy and fat intakes and body weight: the role of fat substitutes*, 80, BRIT J NUTR. 3 (1998).

carotenoids should be added to foods made with olestra or a label notice should advise people of the possibility of losing carotenoids.

The current notice is confusing because it states that fat-soluble vitamins and other nutrients are lost and that vitamins A, D, E, and K are added back. The reference to "fat-soluble vitamins" serves little purpose for consumers. As we stated at the June 1998 FAC meeting, we concur with the petitioner that it would be appropriate to indicate in the ingredient listing that vitamins A, D, E, and K are "Not nutritionally significant."

The current notice indicates that nutrients *other* than vitamins A, D, E, and K are lost, but is silent about the import of that finding. Data in Procter and Gamble's earlier petition for approval of olestra demonstrate clearly that olestra can interfere with the absorption of fat-soluble carotenoids. There is growing evidence that certain fat-soluble carotenoids provide a health benefit.⁹

We recommend that the label notice include a sentence such as: "Frequent consumption of olestra may reduce your body's absorption of fat-soluble nutrients (carotenoids)."

II. Gastrointestinal symptoms

The June 1998 FAC was asked to consider whether any "unexpected" problems were observed in studies on olestra. Consequently, symptoms like diarrhea, cramps, and nausea could be downplayed because they were "expected," not "unexpected." Also, the committee was directed not to consider any evidence provided to the FDA *prior* to approval -- even when that evidence, such as from the petitioner's stool-composition study that was apparently provided to the FDA after the November 1995 FAC meeting (and, hence, not reviewed by that committee). Thus, the 1998 FAC's conclusions and recommendations must be understood in the context that it did not review or consider in any way whatsoever studies conducted prior to January 30, 1996, including those that *proved* that olestra can cause gastrointestinal symptoms and deplete serum levels of fat-soluble carotenoids.

A. The current petition ignores data demonstrating that olestra can cause gastrointestinal symptoms.

The current petition states that post-approval studies "provide a strong basis for concluding that there are no significant adverse gastrointestinal effects that can reasonably be

⁹ Studies indicating that carotenoids offer health benefits, other than beta-carotene's conversion to vitamin A, were reviewed by Dr. Graham Colditz, a professor at the Harvard School of Public Health, at the June 1998 FAC meeting. Several more recent studies were noted in Dr. Walter Willett's separate comment on the current petition.

attributed to the ingestion of olestra-containing foods.”¹⁰ The company, though, does acknowledge that olestra causes stool softening. The post-approval studies involved much lower or less frequent consumption of olestra than the controlled clinical studies submitted before olestra was approved. Those earlier studies demonstrated clearly that olestra can cause gastrointestinal symptoms, which are sometimes severe. The less-sensitive, newer studies should certainly be considered, but they should not supersede or override the more-sensitive, older studies.

Clinical studies have considered the gastrointestinal effects of consuming olestra with one or several meals. In summary:

- * Procter and Gamble’s 8-week (“dose-response” and “vitamin-restoration”) clinical studies showed a dose-response relationship between olestra consumption and such symptoms as diarrhea, loose stools, fecal urgency, abdominal cramps, and nausea. FDA’s analysis of those studies found that, compared to placebo, olestra caused increased rate and duration of severe symptoms.¹¹ It is important to note that the FDA recognized that olestra can cause not just mild symptoms, but severe ones.
- * A clinical study conducted at Addenbrooke’s Hospital in Cambridge, UK and funded by Unilever found that olestra (mean consumption of 27 g/day for up to 12 weeks) caused fecal urgency, looser and more frequent stools, flatulence, anal leakage, and abdominal pain (at eight weeks).¹² The researchers concluded: “This study has demonstrated important deleterious effects of SPE [sucrose polyester] which need to be carefully examined before this product is made available for widespread long-term consumption in a broad range of foods.”

B. Post-marketing studies

The petitioner provided the FDA with four published or unpublished studies that purport to demonstrate that olestra does not cause gastrointestinal symptoms. The petitioner argues that those studies supersede its pre-approval (and other) clinical studies and exonerate olestra of causing any significant gastrointestinal symptoms, as had been seen consistently in those earlier studies.

In general, the post-marketing studies are less sensitive than the pre-approval studies. They are not a reason to reject all the previous evidence that olestra can cause gastrointestinal

¹⁰ Petition, p. 61.

¹¹ 61 Fed. Reg. 3,118, 3,153 (1996).

¹² SM Kelly *supra*

symptoms, which are sometimes severe. We also note that there is not a single study referred to in the petition that was conducted by researchers independent from the petitioner. We do not allege that the studies were conducted improperly, but do note that problems or mistakes could occur, including giving the wrong chips to subjects, failure of the “olestra” chips to contain olestra (no assays were apparently done by the researchers), misreading of symptoms, errors in recording data, etc. That said, the four studies cited appear to provide some assurance that occasional consumption of olestra snacks does not cause consistent, frequent, or severe adverse effects. They do not, and cannot, disprove that olestra products cause adverse effects in smaller percentages of consumers.

1. Acute consumption study

The petitioner contends that this study,¹³ conducted in a movie theater, demonstrates “that there were no significant differences in GI effects between the group eating regular, full-fat chips and the group eating olestra chips.”¹⁴ The study indicates that olestra did not cause widespread gastrointestinal symptoms. However, failure to detect the true incidence of GI effects following a single olestra exposure may result from lack of statistical power or inadequate controls and provides inadequate assurance of safety.¹⁵ The statistical power of the movie-theater study apparently was inadequate to detect GI effects following a single average dose of 17.5g of olestra. With an incidence of “any GI event” of about 15%, 550 subjects in each group would have provided only about a 50% probability of detecting a 5% actual increase in the treatment group. The two end points of greatest concern to the FDA based on the clinical trials — diarrhea and loose stools — were increased less than 1% in the olestra group over baseline levels of 2.6% and 1.1%, respectively. Maintaining 80% power to detect a 1% increase over a 2% baseline requires about 4,000 subjects per group. If the true incidence of diarrhea and loose stools from one olestra exposure was 1% (Frito-Lay has acknowledged that “roughly 2%” of people eating olestra snacks experience GI effects¹⁶), then national marketing of olestra snacks would lead to hundreds of thousands of extra cases of those effects annually.

In addition, other methodological problems with this study (in a darkened movie theater) include potential exposure misclassification (some “olestra eaters” may have eaten few or none

¹³ LJ Cheskin, *et al.*, *Gastrointestinal symptoms following consumption of olestra or regular triglyceride potato chips: a controlled comparison*, 279, JAMA, 150 (1998).

¹⁴ Petition, p. 14.

¹⁵ MF Jacobson, MA Brown, EB Whorton, *Gastrointestinal symptoms following olestra consumption. (Letter)* 280, JAMA, 325 (1998). Attachment 1. A response from the petitioner’s consultants is included.

¹⁶ *Hoosiers have voted* (Frito-Lay advertisement), INDIANAPOLIS STAR, March 30, 1997:C8. Attachment 2.

of their chips; some “non-olestra eaters” may have eaten friends’ olestra chips) and delay of up to 10 days to assess symptoms while background rates increased. Also, non-olestra eaters ate one-third more chips than did the olestra eaters (27 grams versus 21 grams).

2. 6-week consumption study

The petitioner states that this study found that “The percentage of subjects reporting any or total GI symptoms was not different between the olestra and placebo groups.”¹⁷ The petitioner did acknowledge, however, that there was a significantly higher percentage of subjects reporting nausea in the placebo group and a significant increase for olestra eaters in days when more frequent bowel movements were reported.

In a published comment on this study, we noted that the researchers overlooked some of the data.¹⁸ Considering that most subjects ate relatively little olestra snacks, it is important to focus on the relatively small number of heavier consumers. The incidence of more frequent bowel movements and loose stools in the highest decile of olestra consumers was *twice* that of controls. Those olestra consumers had symptoms on 18% of person-days, compared with only 12% of days in the control group. Olestra consumers missed some or all of their activities on 0.4% of days, compared with 0.2% in the controls.

3. Rechallenge study

People who previously reported adverse effects attributed to olestra were challenged twice with olestra and twice with conventional chips over a four-week period.¹⁹ This is a classic example of a weaker study design being presented as evidence that no problem exists. We note that a previous rechallenge study was submitted by the petitioner in 1995. (That study was not reviewed by the first FAC, because it was submitted after its meeting, nor was it reviewed by the second FAC, which reviewed only those studies conducted after the January 30, 1996, approval.) Unlike the newer study, that previous study included a screening phase to weed out people who either did not react to olestra or who reacted inconsistently to it. That study, too, started with a pool of people (52) who felt they had been affected by olestra. In a screening phase, for each of 5 days, those people ate foods containing 0 or 20 grams of olestra. Only people who responded to olestra underwent the second “study” phase. In that phase, 18 people consumed 0, 10, or 20 grams of olestra for each of 7 days. The researchers concluded:

¹⁷ Petition, p. 17.

¹⁸ MF Jacobson, *Olestra snacks compared with regular snacks. (Letter)*, 131, ANN INT MED., 866 (Dec. 7, 1999) Attachment 3.

¹⁹ Petition, p. 19.

... reports of diarrhea, loose stool, and urgency increased dose-responsively with olestra intake. Response to diarrhea, being statistically significant. GI symptoms occur within 2-3 days after olestra consumption is started and occur most often when olestra is consumed in every meal. The diarrhea reported in this study was not pathological diarrhea...²⁰

According to a memo by an FDA medical officer:²¹

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 ... to have underlying medical conditions that could be exacerbated if they become dehydrated.

In contrast to the study provided to the FDA in 1995, the more recent rechallenge study did not pre-screen people who thought they might have been affected by olestra. Also, there is a strong likelihood of bias introduced by the fact that only about 10 percent of people contacted were willing to participate in the study. In addition, to reduce the sensitivity of the study, the petitioner had the subjects eat olestra on only two days, at least one week apart. The newer study assumes 100 percent reproducibility -- that an individual who thinks he or she is sensitive to olestra will experience adverse effects every time he or she consumes olestra. That assumption may be simplistic. Though research has not explored this area, the development of gastrointestinal symptoms may depend on a wide range of factors -- time of day, the nature of other recently consumed foods, emotional state, recency of exercise, etc. In other words, a person who is sensitive to olestra may only experience symptoms in certain circumstances.

4. Stool composition study

This study, which used sorbitol as a positive control, indicated that olestra does not cause diarrhea in healthy subjects (who had not reported being sensitive to olestra), while sorbitol does.²² The petitioner states that this study found that olestra did not meaningfully change either total-stool or stool-water output.

²⁰ Olestra docket, page 153626.

²¹ Memorandum from Karl C. Klontz, Medical Officer, Center for Food Safety and Nutrition, Office of Scientific Analysis and Support, Division of Market Studies (December 26, 1995).

²² Partly on the basis of that study, CSPI petitioned the FDA to require a better label notice on products that contain sorbitol and other sugar alcohols.

This study does not negate and should not supersede the previous eight-week clinical studies or the stool-composition study reported to the FDA in 1995. P&G states now that the previous study did not affect stool water or electrolytes in subjects reporting diarrhea.²³ However, according to an FDA medical officer, several people (who previously reported problems with olestra) had high rates of water loss.²⁴ In addition, we note that the highly technical, narrow definition of diarrhea preferred by the petitioner and the FDA is not one that is used by the Centers for Disease Control and Prevention (CDC). CDC defines diarrhea as “3 or more loose stools in a 24-hour period.”²⁵ Many subjects in the eight-week clinical studies and people who provided anecdotal reports believe that what they experienced was diarrhea. Self-reporting is usually considered sufficient to conclude that people experienced diarrhea, regardless of demonstrated loss of electrolytes.

C. Anecdotal reports

The petitioner was required by the FDA to conduct “passive” post-market surveillance to obtain information about possible adverse effects of olestra. The FDA has received approximately 18,000 such reports from Procter and Gamble and more than 2,000 such reports from CSPI. Those 20,000 reports are far more than have been collected for all other food additives in history *combined*. Most of those reports describe adverse effects similar to those predicted by studies provided by the petitioner and those published in medical journals: diarrhea, loose stools, abdominal cramps, bloating, and nausea. A small percentage of the reports describe other effects, including rectal bleeding, allergic reactions, and other symptoms not detected in clinical studies.

The 20,000 reports likely represent just a small percentage of all people who believed they experienced an adverse effect caused by olestra.²⁶ Many people don’t connect the innocent-looking snacks with subsequent gastrointestinal symptoms, don’t know who to contact, or don’t bother contacting the manufacturer or CSPI. And though the petitioner claims that its system is a “zero tolerance phone in system”²⁷ that “captures all ‘symptom’ related calls...” there is evidence

²³ Petition, p. 20.

²⁴ Klontz K. Memo, *supra*

²⁵ Personal communication, Fred Angulo, Foodborne and Diarrheal Diseases Branch, National Center for Infectious Diseases, May 22, 1998.

²⁶ We recognize that some of the adverse reactions attributed to olestra were likely due to some other cause.

²⁷ Minutes, post-marketing surveillance committee, Jan. 6, 1997 (page 154598 of docket).

that its system is not quite that effective. In fact, as we have pointed out to the FDA in the past,²⁸ many people have told us that when they called the 800 numbers on packages they got a recorded message to call back later, or a telephone clerk argued with them and said that olestra could not have caused their gastrointestinal symptoms, or there was no answer. Other people sent letters or e-mails to Procter and Gamble or Frito-Lay describing adverse gastrointestinal symptoms attributed to olestra, but the petitioner's quarterly reports to the FDA have not included a single such report. Clearly, the petitioner has not provided the FDA with all symptom-related reports. We urge the FDA to investigate the missing data.

The petitioner claims that:

The post-marketing surveillance data provide reliable evidence upon which to conclude that no serious reactions are likely to be caused by olestra. Simply stated, post-market surveillance data and a thorough, professional review of those data, reveal nothing that calls into question FDA's original decision that olestra can be safely marketed in snack foods.²⁹

However, the petitioner ignores several salient facts. In some cases the patients' own physicians attributed symptoms to olestra. While such diagnosis does not constitute proof, the views of those professionals should be given considerable credence. Also, the petitioner ignores the fact that it has reached out-of-court settlements with an unknown number of people who attributed severe symptoms to olestra or that it has reimbursed, or offered to reimburse, people for some or all of their medical expenses attributed to olestra. While we are aware of some of those individuals, we do not pretend to know how many people Procter and Gamble paid, and we urge the FDA to obtain that information, disclose it to the public (without identifying any particular individuals), and consider its import for its current rulemaking. Third, the petitioner claims that its expert panel of consultants reviewed all the anecdotal reports received by the company (we suspect it did not examine the reports submitted by CSPI) and found that "none was probably related" to olestra.³⁰ That is, the committee concluded that not one out of some 16,000 adverse reactions was due to olestra. It appears that the committee of paid consultants was preoccupied with finding a reason *not* to believe that olestra was the cause — and *not* that olestra was a cause (such as by giving credence to the views of a complainant's physician). We wonder how it interpreted cases in which the petitioner paid money to the complainant.

²⁸ Letter from Michael F. Jacobson, Executive Director, *CSPI*, to Mary Ditto, *Center for Food Safety and Nutrition, Office of Premarket Approval, Division of Product Policy*, July 27, 1998. Letter from Michael F. Jacobson to Fred Shank, Director, *Center for Food safety and Nutrition*, Nov. 27, 1996.

²⁹ Petition, p. 24.

³⁰ Petition, p. 44.

An FDA medical officer who reviewed some of the anecdotal reports has acknowledged that olestra may have been responsible for some of them:

...three lines of evidence suggest to me that there may be a subset of the population that experiences olestra-associated adverse GI effects after a short latency period. First, several subjects in the two eight-week clinical trials previously conducted by P&G reported experiencing diarrhea and/or abdominal cramps on the first day of the studies.... Second, a possible role for olestra in the etiology of short-latency abdominal cramps and diarrhea is supported by reports from consumers in post-marketing surveillance who indicate they had diarrhea and/or abdominal cramps on multiple eating occasions separated by disease-free intervals.... Finally, two consumers reported abdominal cramps and diarrhea or loose stools within three hours after eating olestra-containing snacks on days that they had not eaten any other food. Thus, the symptoms could most likely be attributed to the olestra-containing snack, and not another food item.³¹

Subsequently, FDA medical officers stated in another review:

The significant number of consumers who reported Olean-associated adverse gastrointestinal effects to P&G's postmarketing surveillance system during this reporting period, and the consistency of these reports in terms of time to onset of illness and duration of symptoms, suggest, in our opinion, that a subgroup of the population may indeed be sensitive to Olean; as a result of eating Olean-containing snack products, these individuals may experience abdominal cramps and/or diarrhea sufficiently severe to lead them to seek medical care.... three of the 59 subjects in the two 8-week clinical trials who reported diarrhea had diarrhea on the first day of the studies; these three subjects may represent individuals who responded to olestra ingestion with an acute onset of symptoms similar in a fashion to the consumers described in the present review.³²

Those FDA officers also expressed concern about

the severity of some of these illnesses, leading several consumers to go to emergency rooms, to be hospitalized for diagnostic evaluation, to be referred to surgeons or gastroenterologists, or to undergo outpatient colonoscopy.

³¹ Memorandum from Karl C. Klontz to Helen Thorsheim, *Center for Food Safety and Nutrition*, Aug. 8, 1996.

³² Memorandum from Karl Klontz and Eileen F. Barker, memo to Helen Thorsheim (date after 3/13/97; exact date not available due to FDA failure to provide CSPI with first page of memo; page 154373 of olestra docket).

Additionally, some consumers were advised by their physicians to discontinue eating Pringles or that their symptoms were caused by Olean.

To our knowledge the FDA has never conducted in-depth investigations (beyond reviewing medical records of a few individuals) of *any* of the anecdotal reports, even those for serious symptoms, including rectal bleeding, hospitalization, and death. On December 15, 1999, CSPI submitted to the FDA reports of three serious reactions that were attributed by the victims to olestra. Two involved surgical removal of the colon (and, in one case, rectum); the third involved the death of a middle-aged woman. The FDA's failure to investigate such cases, while it considers the petitioner's request to eliminate the interim label notice, is outrageous. Certainly, it is premature to rescind the requirement for a label notice without fully investigating, if not all reports of adverse reactions, all adverse reactions that entailed medical attention.

Up to several percent of the adverse reactions submitted to the FDA reported allergic reactions (hives, urticaria, difficulty breathing, etc.). While there is no reason to think that olestra itself causes such reactions, it is possible that a contaminant or other ingredient in olestra-containing chips causes such reactions. We have urged the FDA to conduct (or require the petitioner to conduct) simple challenge studies.³³ To our knowledge the FDA has failed to take either course of action. The FDA cannot design an accurate label notice until such studies have been conducted.

Heretofore, the FDA has ignored all the anecdotal reports, saying that there is no proof that any of the reports was due to olestra. Of course, there *is* no way to prove in a given situation that olestra was the cause of the symptoms. Considering that the nature and timing of the symptoms is consistent with what clinical studies have demonstrated, failure to give any credence to those reports (and the positive clinical studies) imperils the public's health and the public's confidence in the FDA.

D. Other considerations

We note that a recent study from Baylor University found that consumption of olestra results in increased excretion of fecal fat.³⁴ Consumption of 40g of olestra per day resulted in levels of fecal fat observed in patients with steatorrhea caused by the malabsorption syndrome. The researchers noted: "... physicians may suspect the malabsorption syndrome in patients who consume olestra and may subject them to unnecessary diagnostic tests....some of which are expensive or can be associated with serious complications."

While the results of that study may not, by itself, warrant label notices or revocation of

³³ Letter to Mary Ditto, *supra*.

³⁴ R. Balasekaran, *et al.*, 132, ANN. INT. MED., 279 (2000).

olestra's approval, it should be factored in with the studies demonstrating olestra's adverse effects on nutrient levels and gastrointestinal symptoms. It does not make sense to add to commonly eaten foods an additive that could result in an incorrect medical diagnosis and the undertaking of expensive and possibly dangerous procedures.

III. Legal issues

A. FDA may require disclosure of facts that are material to the consequences of olestra consumption.

Contrary to the petitioner's assertions, the FDA certainly has ample legal authority to require that all olestra-containing foods disclose the material effects of olestra consumption. Section 403(a)(1) of the Food Drug and Cosmetic Act ("Act")³⁵ provides that a food is misbranded if its labeling is false or misleading in any particular and section 701(a) authorizes the FDA to issue regulations for the efficient enforcement of the Act.³⁶ Thus, the FDA may require specific information to appear on the food label if that information is necessary to prevent consumers from being misled. Under Section 201(n), the FDA determines whether the food label is misleading by examining, among other things, the extent to which the labeling fails to reveal material consequences that may result from the use of the product under "conditions of use prescribed in the labeling" or "under such conditions of use as are customary or usual."³⁷

The petitioner claims that the gastrointestinal effects of olestra consumption are not material because four "real life" post-approval studies show that "eating olestra snacks causes no meaningful GI effects different from those associated with eating regular full-fat chips"³⁸ and that they "provide a strong basis for concluding that there are no significant adverse gastrointestinal effects that can reasonably be attributed to the ingestion of olestra-containing foods."³⁹

As discussed above, while those studies provide some reassurance that no more than a small percentage of consumers experience such symptoms, they certainly do not negate the more sensitive older studies that demonstrated clearly that olestra can cause gastrointestinal symptoms, which are sometimes severe. In fact, the petitioner's more sensitive pre-approval clinical studies of the effects of olestra consumption demonstrate that a statistically significant increase of incidence of gastrointestinal disturbances occurred at consumption levels of 20g/day and 32g/day

³⁵ 21 U.S.C. § 343(a)(1).

³⁶ 21 U.S.C. § 371(a).

³⁷ 21 U.S.C. § 321(n).

³⁸ Petition, p. 13.

³⁹ Petition, p. 61.

in an eight-week period. If the studies had included larger subject groups, statistical significance would have appeared at 8g/day.⁴⁰ The symptoms that occurred were diarrhea, loose stools, fecal urgency, nausea, abdominal cramps, gas, and bloating. Results of other clinical studies confirm the nature of the symptoms, their high incidence, and their persistence.⁴¹ The less-sensitive newer studies should be considered when revising the current label requirement, but they certainly should not supersede the more sensitive older studies nor diminish the need to inform consumers of the potential gastrointestinal effects of olestra consumption.

The petitioner also argues, on the basis of results from its active surveillance program, that “there was not an association (as observed within the current power of the study) between olestra intake and the serum levels of other fat-soluble vitamins or carotenoids.”⁴² However, the petitioner’s pre-approval clinical studies found that total carotenoid concentrations fell markedly with consumption of 8g of olestra per day⁴³ -- equivalent to about one ounce of potato chips. As discussed previously,⁴⁴ data from *in vitro*, animal, and epidemiological studies all point to a role for carotenoids in protection of health. Carotenoids may reduce the risks of macular degeneration (the most common cause of age-related blindness), cancer, cardiovascular disease, and other health problems.

Information concerning the possible gastrointestinal and carotenoid-depleting effects of olestra consumption is not simply a matter of “general interest,” as the petitioner has characterized it,⁴⁵ but is absolutely essential. Those facts are necessary for consumers to make informed decisions about whether to purchase and consume olestra-containing foods and restrict

⁴⁰ During the meeting of the Special Working Group (SWG) in November, a member of the FAC and a consultant to the SWG/FAC both noted that increases in incidence of gastrointestinal effects would likely be seen at 8 g/day if larger subject groups than in the two eight-week clinical studies were used. Transcript of hearings of the SWG/FAC, Nov. 16, 1995, p. 52. In addition, Dr. Marvin Schneiderman, a noted statistician, performed a trend test on the incidence data and concluded that there was an increase in incidence of gastrointestinal disturbances above placebo level at 8 g/day.

⁴¹ Gastrointestinal disturbances were also reported by subjects in, among others, the anal-leakage (passive oil loss) study, 16-week study of vitamin E status, and study of fecal water content.

⁴² Petition, p. 30.

⁴³ 61 Fed. Reg. 3,118, 3,136 (1996).

⁴⁴ See CSPI’s previous submissions and testimony; testimony by Dr. Graham Colditz; submissions by Drs. Walter Willett and Meir Stampfer.

⁴⁵ Petition, p. 69.

consumption to minimize possible side effects. Consumers need information on gastrointestinal effects so that they learn to associate olestra with possible symptoms and therefore could avoid olestra in the future in the event that such symptoms occur. Consumers need information concerning carotenoid absorption since they cannot themselves monitor depletion of their carotenoids and detection of health changes caused by this depletion may occur only after irreversible damage has taken place. Thus, both the gastrointestinal and nutrient-depleting effects are certainly material consequences that may result from the customary consumption of olestra-containing foods, and the FDA has ample legal authority to require their disclosure.

B. Although parts of the current label statement are misleading, the label statement should be revised, not rescinded.

The petitioner submits post-marketing consumer research data that suggest that the current label requirement misleads consumers and should therefore be rescinded. We agree that the language about vitamins being added serves little purpose for consumers and support the petitioner's proposal to indicate in the ingredient listing that vitamins A, D, E, and K are "not significant." With regard to the other aspects of the label requirement -- the loss of other nutrients and the gastrointestinal effects -- we agree that the current label notice is confusing, but we strongly disagree with the petitioner's request to eliminate it. Indeed, the label would be misleading *without* a statement concerning carotenoid loss and gastrointestinal effects.

The petitioner states that the label notice's reference to gastrointestinal symptoms leads a substantial number of consumers to believe that the product is not safe.⁴⁶ While the petitioner argues that evidence supports removal of any reference to gastrointestinal symptoms at all on the label, it really indicates that the FDA must determine how to be sure that consumers are informed that some people are adversely affected by olestra without alarming other people who may not be affected. The premarket clinical studies demonstrate clearly that olestra can cause gastrointestinal symptoms, which is supported by the unprecedented flood of anecdotal reports submitted by consumers of olestra chips. On the other hand, the petitioner's post-marketing studies provide some reassurance that no more than a small percentage of consumers experiences such symptoms. Therefore, we propose that the notice be revised to indicate that gastrointestinal symptoms occur in only a "small percentage of consumers."

The label notice is confusing with respect to carotenoids because it merely indicates that nutrients other than vitamins A, D, E, and K are lost, but is silent about the importance of that fact. Given the evidence from the petitioner's own pre-approval studies, as well as other research, that olestra can interfere with the absorption of carotenoids, information concerning olestra's interference with carotenoid absorption and the health implications of that interference should be clearly stated on the label.

⁴⁶ Petition, p. 38.

We also urge that the label notice be revised to provide additional information. First, it is important that the notice include a telephone number that consumers can call to report and ask questions about adverse effects. The FDA suggested that companies provide a number in the label notice⁴⁷ but no company has done so, forcing consumers to locate the number elsewhere on packages. The notice should also advise consumers to contact a health professional if the symptoms persist or are severe because symptoms could reflect a more serious problem than the transient problems caused by olestra (indeed, the petitioner asserts that all symptoms blamed on olestra, including symptoms requiring hospitalization, were caused by something else).

In view of those concerns, we recommend the following revised label notice:

This product contains olestra.

Olestra may cause abdominal cramping and loose stools in a small percentage of consumers. If you experience adverse effects that may be caused by olestra, call 1-800-OLESTRA. If your symptoms persist or are severe, contact a health professional.

Frequent consumption of olestra may reduce your body's absorption of fat-soluble nutrients (carotenoids). Carotenoids, found in fruits and vegetables, may protect you against certain chronic illnesses.

In addition, we urge that the label notice be repositioned to increase its prominence. The purpose of the statement is to inform consumers of the possible side effects of olestra consumption, thereby allowing consumers to make better decisions about the purchase and consumption of such products. This goal can only be achieved to the extent that consumers read and process the statement. Accordingly, it is essential that the notice be placed in such a manner as will most likely cause consumers to read it.⁴⁸ The current placement, on the bottom of the back label, insures minimum visibility. Indeed, many people who filed adverse-reaction reports with CSPI indicated that they had not seen the notice before they purchased or consumed olestra-containing products. Therefore, the notice should be required near the top of the principal display panel of packages.

It is worth noting that Joanne Lupton, who was a special consultant to the FDA at the

⁴⁷ 61 Fed. Reg. 3,118, 3,162 (1996).

⁴⁸ See, e.g., 63 Fed. Reg. 37,030, 37,044 (1998) (Final Rule on Food Labeling: Warning and Notice Statement; Labeling of Juice Products).

1995 FAC meeting stated that “Olestra will modify stool and cause stool softening which may be perceived as ‘loose stool’ or ‘diarrhea.’ Olestra containing products should carry a label mentioning potential changes in GI function.”⁴⁹ Dr. Lupton later became a member of the petitioner’s “expert committee.”

C. Requiring the disclosure of the material effects of olestra consumption is not inconsistent with agency precedent.

The petitioner contends that requiring a label notice for olestra-containing foods is “inconsistent with agency precedent and unfairly singles out olestra for unique, unwarranted regulatory treatment.”⁵⁰ For example, the petitioner argues that FDA does not require a similar notice for psyllium-containing foods, even though psyllium also poses digestive effects. Despite the petitioner’s argument, FDA’s treatment of psyllium certainly does not preclude the agency from requiring a label notice for olestra.

First, the gastrointestinal effects of psyllium consumption and olestra consumption are entirely different. Although the petitioner argues that the digestive effects of psyllium consumption are similar to those that occur after eating significant amounts of olestra,⁵¹ the petitioner’s own premarket approval studies show otherwise. FDA concluded on the basis of those studies “that consumption of olestra causes gastrointestinal symptoms, such as bloating, loose stools, abdominal cramping, and diarrhea-like symptoms”⁵² and therefore found it necessary to inform consumers of those side effects to preclude unnecessary concerns and prevent unnecessary medical treatment.⁵³ In contrast, the FDA found that ingestion of psyllium seed husk as a component of food would have no effect on the bowel “other than to promote normal functioning by softening fecal contents and increasing fecal volume.”⁵⁴ Unlike olestra, those mild effects would not cause consumers significant discomfort, undue concern, or cause them to seek unnecessary medical treatment and were therefore not deemed material. However, if studies ever show that psyllium does increase the incidence of significant gastrointestinal effects, we would certainly urge the FDA to add a similar notice to the label of psyllium-containing foods.

⁴⁹ Nov. 15, 1995, slide (page 145136 of olestra docket).

⁵⁰ Petition, p. 74.

⁵¹ Petition, p. 70.

⁵² 61 Fed. Reg. 3,118, 3,159 (1996).

⁵³ 61 Fed. Reg. 3,118, 3,161 (1996).

⁵⁴ 63 Fed. Reg. 8,103, 8,115 (1998) (considering daily ingestion of ten grams of psyllium seed husk).

Second, the FDA does require the disclosure of the *material* effects of psyllium consumption: the potential for esophageal blockage from not consuming adequate amounts of fluids. Specifically, the agency requires that when dry or incompletely hydrated psyllium husk is present in a food and the food bears a health claim,⁵⁵ the label must include a statement such as “The food should be eaten with at least a full glass of liquid. Eating this product without enough liquid may cause choking. Do not eat this product if you have difficulty swallowing.”⁵⁶ Thus, the fact that FDA does not require the disclosure of psyllium’s *non-material* mild bowel-normalizing effects, but does require the disclosure of psyllium’s *material* effects -- the potential to cause choking -- is entirely consistent with requiring the disclosure of olestra’s material gastrointestinal and carotenoid effects.

The petitioner also argues that “agency consideration of a graphic ‘box’ warning requirement like that now mandated for olestra is extremely rare in the context of food” and that “[o]nly in the unique case where death or very serious illness is a possible, but remote, outcome of some customary and usual use, could such a box warning be considered appropriate.”⁵⁷

We disagree with petitioner’s characterization of FDA’s box labeling requirements. First, the FDA stated explicitly that the olestra labeling requirement is not a warning label, but a notice statement. Second, there are no regulations that reserve the use of box labeling only for cases involving death or serious illness. In fact, box labels are used to provide consumers with noncontroversial information, such as the nutrition information provided in the Nutrition Facts panel. Box labeling is necessary to increase the likelihood that consumers will actually read the olestra statement, and does not imply the severity of the side effects that the food may cause.

The petitioner also argues that since box labels are not required to alert consumers to the potential of the sweetener sorbitol to create watery stools -- an effect the petitioner asserts is more pronounced than olestra’s gastrointestinal effects -- then olestra-containing foods should not be required to disclose such prominent notices either.⁵⁸ While we agree that FDA’s failure to require a similar label notice for sorbitol is inconsistent with requiring a notice for olestra, we do not agree that this indicates that the olestra labeling requirement should be *eliminated*; rather, we believe that the sorbitol label requirement should be *improved*. We have in fact already

⁵⁵ The FDA has not yet extended this required statement to psyllium husk-containing foods that do not bear a health claim because this was not a matter discussed in its proposed rule. Instead, the agency plans to propose in a separate rulemaking that the required label statement be extended to other psyllium-husk containing foods that do not bear a health claim. 63 Fed. Reg. 8,103, 8,114 (1998).

⁵⁶ 21 C.F.R. § 101.17(f)(1)(1999).

⁵⁷ Petition, p. 68.

⁵⁸ Petition, p. 68.

petitioned FDA to require a more prominent label notice for sorbitol that is proposed to read: “NOTICE: This product contains sorbitol, which may cause diarrhea, bloating, and abdominal pain. Not suitable for consumption by children. To protect yourself, start by eating no more than one serving at a time.”⁵⁹ We have also requested similar notice requirements for other foods that contain diarrhea-inducing sugar alcohols, including mannitol, maltitol, isomalt, and hydrogenated starch hydrolysate.⁶⁰

As an additional point, even if FDA’s required label statement for olestra were inconsistent with agency precedent, this does not, in and of itself, establish whether or not FDA has the authority to require such a statement. As the FDA stated in its rulemaking for 4-MMPD labeling:

[A] government agency is not estopped from taking warranted action against a particular hazard because of the existence of other hazards on which it has not taken action. Such a principle of estoppel could prevent the government from fulfilling its statutory responsibilities. As the Supreme Court stated in *Dandridge v. Williams*, 397 U.S. 471, 486-487 (1968), the government is not required to “choose between attacking every aspect of a problem or not attacking the problem at all.”⁶¹

D. The declaration of olestra in the ingredient statement is insufficient to inform consumers of the material effects of olestra consumption.

The petitioner argues that “every food that contains olestra will bear a labeling representation to that effect” and that “[f]or decades FDA has relied upon the ingredient statement not only as a source of fundamental information to consumers but also as a means of ensuring the consumer’s ability to identify or avoid specific ingredients in food.”⁶² Therefore, the petitioner concludes that consumers who “are interested in knowing whether olestra is in the foods they eat, will by virtue of the ingredient statement, always have access to that information in a clear, usable, and efficient label declaration.” However, a nondescriptive declaration of the word “olestra” in the ingredient listing does not inform consumers of the side effects of consuming olestra -- and unless consumers have already learned of the potential side effects, they would have no reason to consult the ingredient list to determine whether olestra is present in a

⁵⁹ Center for Science in the Public Interest, *Petition to the Food and Drug Administration for Regulatory Action to Revise the Labeling Requirements for Foods Containing Sorbitol*, Sept. 27, 1999.

⁶⁰ *Id.* at 4.

⁶¹ 44 Fed. Reg. 59,509, 59,512 (1979).

⁶² *Petition*, pp. 75-76.

particular food.

This concern is similar to the issue raised in the preamble to the FDA's final rule to require warning labels for unpasteurized juices. Several comments expressed the opinion that use of the term "pasteurized" or "unpasteurized" alone is sufficient to inform consumers of potential risks associated with consumption of juice products. However, the agency expressed concern "that some consumers do not know the significance of pasteurization and therefore, would not be able to make an informed decision on whether to purchase and consume the products" and that the use of the term "pasteurized" or "unpasteurized" alone "would not give consumers information about the risks presented by untreated juices."⁶³

The agency also noted an additional consideration:

Juice products historically have been consumed by individuals without treatment to control pathogenic microorganisms. In addition, the presence of some pathogens...that have been responsible for recent outbreaks of food borne illnesses associated with untreated juice products is a relatively new phenomenon. Therefore, consumers do not associate such pathogens, and the risk that they present, with the consumption of untreated juice. Accordingly... a juice warning statement is needed to protect the public health because consumers are unaware of the nature and magnitude of the health hazard.⁶⁴

Similarly, label statements for olestra are necessary to inform consumers of the unexpected potential consequences of consuming seemingly ordinary foods, such as potato chips and crackers, that have long been consumed by millions of people with no adverse effects. Simply disclosing the presence of olestra in the ingredient statement does not inform consumers of olestra's potential side effects and is therefore no substitute for a prominent, informative label notice.

E. Providing information about the consequences of olestra consumption would not crowd out other important information or confuse consumers.

The petitioner asserts that FDA "has even declined to require disclosure of material information when to do so would crowd out other more important information or confuse consumers."⁶⁵ To support this contention, the petitioner relies on FDA's rulemaking to require a label warning on hair dyes containing 4-MMPD, an animal carcinogen. The petitioner points out

⁶³ 63 Fed. Reg. 37,030, 37,034 (1998).

⁶⁴ 63 Fed. Reg. 37, 030, 37,032-33 (1998).

⁶⁵ Petition, p. 71.

that the agency was challenged by a comment contending that its proposal was inconsistent with its failure to require warnings about the possible presence of carcinogenic aflatoxins on milk, corn, and peanuts. The petitioner states that “FDA decided not to require labeling about the carcinogenic constituents reasoning that to do so would result in ‘warnings...so numerous they would confuse the public, would not promote informed consumer decisionmaking and would not advance the public health.’”⁶⁶

However, the petitioner’s out-of-context quote from the FDA’s explanation is misleading and does not accurately represent the agency’s policy concerning aflatoxin labeling. When the FDA’s entire discussion of aflatoxins is examined, it is clear that other factors were relevant to the agency’s decision not to require warning labels:

In regulating aflatoxins, FDA has been primarily concerned with the aflatoxin level above which foods with aflatoxin should be prohibited. FDA has not considered requiring a label warning. Aflatoxins are unintentional contaminants, and they do not appear in every unit of peanuts, corn, and milk, or the foods containing these ingredients. Thus, any warning on these products would have to be considered in light of the fact that no detectable levels of aflatoxin may be present in some foods affected by the warning....Moreover, given the prevalence of foods containing milk, corn and peanuts in some form, it may be impractical and confusing to require a warning on all the foods that may be affected. Indeed, a requirement for warnings on all foods that may contain an inherent carcinogenic ingredient or a carcinogenic contaminant (in contrast to a deliberately added carcinogenic substance) would apply to many, perhaps most, foods in a supermarket. Such warnings would be so numerous they would confuse the public, would not promote informed consumer decisionmaking, and would not advance the public health. Warnings concerning deliberately added, unbannable carcinogens do not present this difficulty.⁶⁷

Thus, FDA’s reluctance to require warning labels for milk, corn, and peanuts does not support the petitioner’s assertion that the agency has declined to require the disclosure of material information when to do so would crowd out other important information or confuse consumers. We also note that snack food packages are certainly large enough to provide information about olestra without crowding out any other information. Moreover, a revised label statement, as we have proposed, would not confuse consumers. Although certain portions of the current label requirement are confusing, this only means that the label statement should be revised for clarity, not abandoned altogether.

⁶⁶ Petition, p. 71 (quoting 44 Fed. Reg. 59,509, 59,513 (1979)).

⁶⁷ 44 Fed. Reg. 59,509, 59,513 (1979).

F. Requiring the disclosure of the material effects of olestra consumption does not violate the First Amendment.

The petitioner asserts that the “First Amendment could stand as a bar to agency efforts to compel other than material information or information otherwise deemed as essential under the Act to appear on the food label.”⁶⁸ This assertion is fundamentally flawed because it assumes that the information required on labels of olestra-containing food is not material and is not otherwise essential under the Act. Of course, as discussed previously, the label disclosure requirements and modifications that we have proposed are certainly material and essential.

The petitioner also asserts that *International Dairy Foods Association v. Amestoy*⁶⁹ “is instructive in the context of olestra.”⁷⁰ However, the petitioner’s reliance on *Amestoy* is misplaced. The facts of *Amestoy* are significantly different from the issue of olestra labeling. Moreover, *Amestoy* represents a sharp departure from established Supreme Court precedent that governs this area.

First, olestra labeling is significantly different from the facts of *Amestoy*. In *Amestoy*, the Second Circuit struck down the state of Vermont’s law that required labeling of products from cows treated with the growth hormone recombinant Bovine Somatotropin (rBST). The court found that the state failed to establish the second prong of the *Central Hudson* test -- that the government’s interest in compelling rBST labeling is substantial. The state merely defended its law on the basis of a “strong consumer interest and the public’s ‘right to know’...”⁷¹ -- interests that the court determined were insufficient. The court noted that FDA itself had “concluded that rBST has no appreciable effect on the composition of milk produced by treated cows, and that there are no human safety or health concerns associated with food products derived from cows treated with rBST.” The court also noted that it was undisputed that neither consumers nor scientists can distinguish rBST-derived milk from milk products by an untreated cow and the court found that the record contained no scientific evidence from which an objective observer could conclude that rBST had any impact at all on dairy products.⁷²

In contrast, the disclosure of the effects of olestra consumption is not merely a reflection of strong consumer interest or the public’s right to know. Rather, those who consume olestra-containing products *must* be informed of possible side effects so that they can avoid needless

⁶⁸ Petition, p. 72.

⁶⁹ 898 F.Supp. 246 (D.Vt. 1995), 92 F.3d 67 (2d Cir. 1996).

⁷⁰ Petition, p. 72.

⁷¹ 898 F.Supp. at 249.

⁷² *Id.* at 248.

medical treatment and decide whether to avoid the possibility of suffering those side effects in the first place. Moreover, unlike rBST milk products, olestra-containing products can indeed be distinguished from their traditional counterpart due to the presence of large amounts of a synthetic chemical.

Second, *Amestoy* constitutes a sharp departure from established Supreme Court precedent. The Second Circuit failed to recognize the unique status afforded disclosure requirements in commercial speech doctrine, as well as the distinctions between noncommercial and commercial compelled speech. In fact, the *Amestoy* decision was the first time that a federal appellate court had invalidated a statute requiring disclosure of truthful, nonmisleading commercial speech as violative of the First Amendment.⁷³

The majority in *Amestoy* stated that “the right not to speak inheres in political and commercial speech alike” and relied on political compelled speech cases to support its contention that the commercial speaker has a First Amendment right not to speak.⁷⁴ The court, however, failed to distinguish the interests implicated by a right not to speak in a commercial context from those implicated by the right not to speak in a political forum. Unlike the statutes at issue in political-right-not-to-speak cases, the Vermont law in *Amestoy* did not attempt to “prescribe what shall be orthodox in politics, nationalism, religion, or other matters of opinion”⁷⁵ or force an individual to foster “an ideological point of view he finds unacceptable.”⁷⁶ In contrast, the right not to speak in a commercial context involves whether material information relevant to consumer decision-making should be disclosed.

Indeed, the *Amestoy* court ignored Supreme Court precedent, which has distinguished commercial disclosure requirements from outright prohibitions on commercial speech. The Court has stated that the government may in fact require a commercial message to “appear in such a form, or include such additional information, warnings, and disclaimers, as are necessary to prevent its being deceptive.”⁷⁷ The Court reiterated this position in *44 Liquormart, Inc. v. Rhode Island* when it asserted that all commercial speech regulations are not subject to the same form of constitutional review. As the Court explained:

⁷³ Caren Schmulen Sweetland, *The Demise of a Workable Commercial Speech Doctrine: Dangers of Extending First Amendment Protection to Commercial Disclosure Requirements*, 76 TEX. L. REV. 471, 476-77 (1997).

⁷⁴ 92 F.3d at 71-72.

⁷⁵ *West Virginia State Board of Education v. Barnette*, 319 U.S. 624, 642 (1943).

⁷⁶ *Wooley v. Maynard*, 430 U.S. 705, 715 (1977).

⁷⁷ *Virginia Pharmacy Board v. Virginia Citizens Consumers Council, Inc.*, 425 U.S. 748, 772, n.24 (1976).

When a State regulates commercial messages to protect consumers from misleading, deceptive, or aggressive sales practices, or requires the disclosure of beneficial consumer information, the purpose of its regulation is consistent with the reasons for according constitutional protection to commercial speech and therefore justifies less than strict review.⁷⁸

For example, in *Zauderer v. Office of Disciplinary Counsel*, the Supreme Court reviewed a state law which required attorneys who advertised their services on a contingency fee basis to disclose that clients would be liable for costs even if their claims proved unsuccessful.⁷⁹ The Court reasoned that “because the First Amendment interests implicated by disclosure requirements are substantially weaker than those at stake when speech is actually suppressed, we do not think it is appropriate to strike down such requirements because other possible means by which the state might achieve its purposes can be hypothesized.”⁸⁰ The Court therefore held that First Amendment rights are adequately protected as long as disclosure requirements are “reasonably related to the State’s interest in preventing deception of consumers.”⁸¹

In explaining why commercial disclosure requirements are subject to less constitutional scrutiny, the Court noted that “all our decisions of restraints on commercial speech have recommended disclosure requirements as one of the acceptable less restrictive alternatives to actual suppression of speech”⁸² and that the state’s disclosure requirements were not an attempt to prevent attorneys from conveying information to the public, but to require them “to provide somewhat more information than they might otherwise be inclined to present.”⁸³ The Court also recognized that the interest of the government in requiring disclosure is consistent with the original purpose behind extending First Amendment protection to commercial speech -- the need to encourage the free flow of information⁸⁴ and acknowledged that “because the extension of First Amendment protection to commercial speech is justified principally by the value to consumers of the information such speech provides,” a constitutionally protected interest in not

⁷⁸ 517 U.S. 484, 501 (1996).

⁷⁹ 471 U.S. 626, 650 (1985).

⁸⁰ 471 U.S. at 652, n. 14.

⁸¹ *Id.* at 651.

⁸² *Id.* at 652, n. 14.

⁸³ *Id.* at 650.

⁸⁴ *Id.* at 651.

providing information is minimal.⁸⁵ The Court also noted that “in virtually all of our commercial speech decisions to date, we have emphasized that because disclosure requirements trench much more narrowly on an advertiser’s interests than do flat prohibitions on speech, ‘warning[s] or disclaimer[s] might be appropriately required...in order to dissipate the possibility of consumer confusion or deception.’”⁸⁶ Even prior to *Zauderer*, other courts had recognized the special status conferred to commercial disclosure requirements.⁸⁷

In sum, requiring olestra-containing products to disclose potential side effects provides important, content-neutral, material information to consumers, and any constitutional interest that petitioner may have in refusing to disclose such information is minimal. Since the FDA olestra-labeling requirement is “reasonably related” to the agency’s interest in preventing misleading food labels, the requirement does not violate the First Amendment.

IV. Other labeling issues related to olestra

CSPI has urged the FDA to make other changes in the labeling of olestra-containing products.⁸⁸ Certain olestra-containing products are labeled fat-free (other olestra-containing products contain small amounts of fat). Many other baked snacks are also labeled fat-free. We pointed out to the FDA that those two types of products are very different and that the fat-free labeling of olestra snacks is false and misleading. An ounce of a baked chips provides a full ounce of carbohydrate and protein, whereas an ounce of olestra chips provides only two-thirds to three-fourths of an ounce of carbohydrate and protein. Olestra is a fat, and products that contain it should not be allowed to state “fat-free.” The seven to ten grams of olestra in an ounce of product is chemically “something” -- and, if not a fat, what? In contrast, baked chips do not contain that “something.” We recommended that products that contain olestra not be allowed to state “fat-free.” Instead they could state: “No calories from fat. Contains x grams of olestra.” (Several makers of baked chips have filed complaints with the FDA on this point.)

⁸⁵ *Id.* (citing *Virginia Pharmacy Board v. Virginia Citizens Consumers Council, Inc.*, 425 U.S. 748, (1976)).

⁸⁶ *Id.* (quoting *In re R.M.J.*, 455 U.S.191, 201 (1982)). Accord, *Central Hudson Gas & Electric Corp. v. Public Service Comm’n of New York*, 447 U.S. 557, 565 (1980); *Bates v. State Bar of Arizona*, 433 U.S. 350 (1977); *Virginia Pharmacy Board v. Virginia Citizens Consumers Council, Inc.*, 425 U.S. 748, 772, n.24 (1976).

⁸⁷ See, e.g., *National Comm’n on Egg Nutrition v. FTC*, 570 F.2d 157, 164 (7th Cir.) (1977) (choosing to modify rather than invalidate the challenged FTC disclosure requirement despite a finding that the requirement was overbroad).

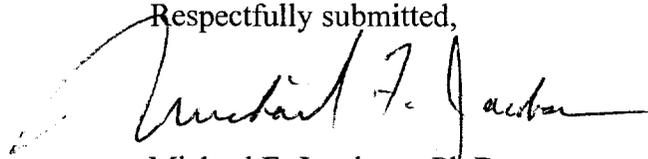
⁸⁸ Letter to Joe Levitt, Feb. 5, 1999. Comment on Docket Nos. 96N-0421 and 94-0453/CP1, June 10, 1998.

We also recommended that the Nutrition Facts label indicate that a serving contains x grams of total fat, with an asterisk pointing consumers to a note stating: "This product contains x grams of olestra, which is not digested by the body. The figures shown have been adjusted to reflect that reduced availability."⁸⁹ The amounts of available fat, saturated fat and polyunsaturated fat would be listed. Alternatively, if the Nutrition Facts label states "Fat 0 g," an asterisk should advise consumers: "Contains x grams of olestra, which is not absorbed by the body."

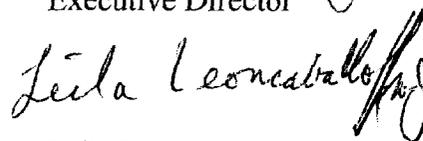
V. International considerations

It is worth noting that while the FDA is considering removing a label notice advising consumers of possible adverse effects of consuming olestra, other nations are not approving olestra. Procter and Gamble has petitioned the United Kingdom and Canada (and possibly other nations) to approve olestra. Apparently, none of those nations has concluded that there is a reasonable certainty that olestra does not cause harm (even with a label notice). Those independent decisions should provide some guidance as to how a novel chemical like olestra should be regulated. Though the FDA, at this time, apparently is not considering rescinding approval of olestra, a strong label notice is the *minimum* protection that the FDA should provide.

Respectfully submitted,



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Executive Director



Leila Leoncavallo
Senior Staff Attorney

⁸⁹ Comment on Docket Nos. 96N-0421 and 94-0453/CP1, June 10, 1998.

To the Editor.—The article by Dr Hanzlick and Ms Combs¹ is focused too heavily on the name of a death investigation system rather than on how that system actually works. The authors' assumption that "most heads of death investigation systems are adequately familiar with the history and statutory basis of their system to provide accurate information," at least as it applies to Iowa and Minnesota, was incorrect.

The Iowa state medical examiner is an employee of the Iowa Department of Public Safety (ie, the attorney general), has no investigatory staff or authority independent of law enforcement, and serves as the "autopsy referral service."² There are autonomous medical examiners in each Iowa county who are physicians, although not necessarily pathologists, and are responsible for investigating all sudden or unexpected deaths and for completing the death certificates for investigated cases.³ The county medical examiner may (but is not required to) "refer" a death to the state medical examiner for a post-mortem examination and may consider the state medical examiner's conclusions when completing the death certificate.

The medical examiner in Hennepin County, Minnesota, must be a pathologist, and the appointment is made by the Hennepin County Board of Commissioners on recommendation from specified community physicians.⁴ The coroner in the other 86 Minnesota counties is required to be a physician.⁵ However, 15 Minnesota counties have been unable to find a physician willing to perform the investigatory responsibilities for the Office of the Coroners. In 1972 the Minnesota legislature enacted legislation that allowed these counties to abolish the Office of the Coroners, to designate the sheriff as the investigating officer for all sudden or unexpected deaths, to assign ultimate responsibility for the investigation to the county attorney, and to hire a person (unfortunately called the "medical examiner") to complete the death certificate as directed by the county attorney.⁵ These counties are referred to by the authors as Minnesota's examples of county medical examiner systems. We are board-certified forensic pathologists and are the coroners for 6 Minnesota counties with a total population of approximately 600 000. Four additional Minnesota counties with a total population of 1.1 million have a coroner's office directed by a board-certified forensic pathologist. In Minnesota, forensic pathologists direct death investigations in 11 counties with a total population of 2.8 million, 61% of the state.

The article by Hanzlick and Combs fails to distinguish between death investigation systems directed by qualified personnel and those directed by unqualified people, regardless of their titles. Funding and statutory authority for trained medical professionals to investigate deaths independent of law enforcement are important; the name of the office (coroner or medical examiner) is irrelevant.

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2. Iowa Code ch 691.1-691.9 (State Criminalistics Laboratory and Medical Examiner).
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4. Minn Stat ch 383B.225 (Hennepin County).
5. Minn Stat ch 390.005-390.26 (Coroner), ch 390.31-390.36 ("Simplified Method of Death Investigation," so-called Medical Examiner's System).

In Reply.—We agree that the checks and balances for governmental control are not the same for medical examiners and coroners. However, we believe that most competent medical examiners are permitted by the government that hired them to retain their jobs, whereas most medical examiners who are fired by the government are probably fired for valid reasons. Indeed, the electoral process blurs how coroner competence relates to the number of terms in office, and impeachment

undoubtedly is rare. Also, some coroners do not fit the mold described by Dr Neiburger—some coroners are appointed, some are not state constitutional officers, some cannot arrest the sheriff, some are the sheriff, some can hold office for only 2 terms, and some can be removed or have their authority nullified if they do not meet certain requirements.^{1,2}

The systems in Iowa and Minnesota reinforce our point that idiosyncrasies among systems make them difficult to classify and compare in general. The name of an office may be irrelevant in some areas, but the fact remains that coroners must be physicians in only 4 of 28 states with coroners, while with few exceptions medical examiners are required to be physicians. We believe these facts and the elected nature of most coroners lend credence to a general classification scheme that distinguishes coroner systems from medical examiner systems. We are not sure how we could clearly distinguish between death investigation systems directed by qualified and unqualified people as Drs Plunkett and Thomas suggest. However, reasonable conclusions can be drawn by reviewing the results of our study along with information in other publications.^{2,4} For example, 25% of the US population live in areas that have no specific educational or training requirements for the person managing the death investigation system; the publications referenced in our article contain the necessary information to determine those areas.

Our reading of the Minnesota statute indicates that qualifications for coroners include academic courses in pharmacology, surgery, pathology, toxicology, and physiology. Granted, most qualifying people probably would be physicians (as are most Minnesota coroners), but Minnesota law does not specifically require an individual to have a doctor of medicine degree to be a coroner.

We favor death investigation statutes that require medical examiners or coroners to be adequately qualified. Statutory qualifications should be explicit and require demonstrated competence through successful completion of relevant education and other credentials, such as passage of professional certification or licensure examinations. No examination or certification currently allows a fair comparison of the qualifications of the diverse group of people who direct the nearly 2200 death investigation systems nationwide.

It was not our intent to advocate one system type over the other. In fact, one of us (R.H.) has written,³ "Arguments concerning the relative merits and deficiencies of coroners and medical examiners would become moot if measures were taken to ensure that medical examiners and coroners were adequately trained, funded, and staffed for the jobs they are expected to do."

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Gastrointestinal Symptoms Following Olestra Consumption

To the Editor.—Procter & Gamble's movie theater study¹ does a good job of answering the wrong questions. It fails to demonstrate a significantly increased incidence of gastrointestinal (GI) effects from a one-time, variable olestra exposure. But it sheds little light on what will happen when large numbers of Americans consume olestra over prolonged periods. Also, *JAMA's*

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.

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Will Future Physicians Learn to Treat the Individual or the Population?

To the Editor.—I was delighted with Dr Greenberg's¹ erudite and clever observations concerning the transition of medical care in the United States, but I became alarmed at his stumbling block, "One major ethical debate yet unresolved." He went on to explain that currently practicing physicians have not yet capitulated and become public health physicians, ie, community driven, not individual patient driven. Rather than "American Medicine Is on the Right Track," the article's title should have been "American Medicine Is on This Track." Accurate as his reporting is, it is not necessarily the right track, by any stretch.

Physicians are and should continue to be trained to be the partner of each individual patient, the patient's advocate in regaining health. Physicians are free to choose further training to become effective public health physicians, a long-standing and valued position, precisely for community, population-based medicine.

The people of the community, through the political system, are responsible for the health of the community, eg, violence, crime, clean water, immunization, safe food, traffic flow, communicable disease, mental disease manifested in homelessness, smoking, alcohol and other drug use—the list goes on.

The practicing physician has his or her plate full caring for those who present themselves as sick. Physicians simply do not have and should not take enough time to bear the "added obligations" of resource allocation, epidemiology, and the unmet needs of the community as Greenlick prescribes.² The physician can choose to spend a portion of time in public health matters and most do so, but to transfer all the physical and mental ills of America to practicing physicians is patently ridiculous. A physician is like a barber, trained to cut 1 head of hair at a time and do it very well. To force the physician through capitalistic or social engineering into overtreatment or undertreatment exploits everyone.

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1. Greenberg HM. American medicine is on the right track. *JAMA.* 1998;279:426-428.
2. Greenlick MR. Educating physicians for population-based clinical practice. *JAMA.* 1992;267:1645-1648.

In Reply.—Dr Dixon raises an issue I believe will emerge as an important ethical debate as the transformation in health care delivery goes forward. However, the thrust of my concern is not that individual practitioners will be coerced into practicing some brand of public health for which they are unqualified and that is inappropriate for their patient-oriented practice. On the other hand, I do believe all physicians in the future will get much more "public health" in their education.

Population-based medicine, as outlined by Greenlick,¹ is a pattern of physician obligation that expands the current perceived worldview of 1 to 1 (physician to patient) to 1 to N

because he or she sees the responsibility of the individual-physician in managed care organizations, the paradigm of the 21st century, to be centered on the population for which it assumes responsibility. I, too, envision a future in which most practitioner activity will occur within large organizations in which a fixed pool of monies from a finite pool of patients will place fiscal limits on the activities of individual practitioners. Without the cost-plus well of Medicare funds or the deep (or, rather, invisible) pockets of the hospital, the physician has another participant joining his or her private relationship with the patient. In the future, this partnership must be acknowledged.

Unlike Greenlick, however, I do not believe that the construct of population-based medicine is Hippocratic in nature, nor do I believe we have arrived at our present 1-to-1 relationship solely because of our fee-for-service design. As a non-philosopher, I view it as being most compatible with the ethics of the commons, an ethical construct that has served well in many settings for a long time, but not one usually associated with the practice of medicine. To his credit, Greenlick is asking that we educate tomorrow's physician to deal with this ethical problem. My point in the article is that resolving this dilemma will take time and will frustrate the generation of physicians who believed (if incorrectly) that we had few limitations on our management options. I am optimistic that we will wrestle this issue to the ground, but it will take time. How we will resolve this dilemma is unclear, but being aware of it and confronting its reality and impact are essential if we are to emerge with a health care system that we will value.

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Detection of Corticosteroid in an Over-the-counter Product

To the Editor.—Psoriasis is a chronic and often disabling skin condition that has stimulated the marketing and use of many approved and unapproved topical over-the-counter medications. Since the early 1990s, one of these over-the-counter medications, SKIN-CAP in spray, shampoo, or cream formulation (manufactured by Cheminova Laboratories International, SA, Madrid, Spain), has been sold in the United States by several distributors. The sole active ingredient in this product has been reported to be pyrithione zinc, which also is found in dandruff shampoos and is approved for the treatment of seborrheic dermatitis. SKIN-CAP is not approved by the US Food and Drug Administration (FDA) for the treatment of psoriasis or other dermatoses. Nonetheless, the use of SKIN-CAP for psoriasis has been widespread, and preliminary findings from a blinded clinical study of psoriasis have shown efficacy (C. Crutchfield, MD, E. Lewis, MD, B. Zelickson, MD, oral communication, May 13, 1997). To determine if other active ingredients were present, we examined SKIN-CAP spray formulation by several analytical methods, including capillary electrophoresis (CE) and tandem mass spectrometry (MS/MS).

A Beckman P/ACE CE instrument (Beckman, Fullerton, Calif) interfaced via an electrospray ion source to a Finnigan MAT 95Q tandem mass spectrometer (Finnigan MAT, Bremen, Germany) was used for the analysis of SKIN-CAP products. Structural characterization of detected species was conducted by online CE-MS/MS. SKIN-CAP spray was prepared for analysis by shaking the product and sampling 500 μ L into a microcentrifuge tube (1.5 mL) that was centrifuged for 1 minute to remove the suspended pyrithione zinc. The re-

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(AND COUNTING)



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finding that 71% of initial symptoms were brought to clinicians in internal medicine probably reflects a culture wherein the first contact is with an identified primary care provider; this is also seen in countries other than the United States (1). As we noted in our article, rates of presentation of breast symptoms did not differ by ethnic group, although presenting with a breast symptom was more likely in patients with a family history of breast cancer.

We agree that it would be interesting to know how clinicians document information on breast cancer risk factors. However, although the clinical factors (obesity, breast density, and estrogen replacement therapy) mentioned are known to be correlated with breast cancer risk in the general population, no data suggest that the presence or absence of these risk factors would modify the probability that a woman presenting with a symptom has breast cancer. Our study showed that any symptom significantly increased the likelihood that a woman had cancer over the baseline risk in the population; this suggests that all breast symptoms should be taken seriously.

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Reference

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Olestra Snacks Compared with Regular Snacks

To the Editor: Sandler and colleagues (1) state that anecdotal reports of severe diarrhea and abdominal pain associated with ingestion of olestra have not been substantiated by controlled testing. In fact, several clinical trials have shown such effects.

Procter & Gamble (the maker of olestra) conducted two 8-week studies indicating that daily consumption of 20 g of olestra (equivalent to 2.5 ounces of potato chips) increased rates of loose stools and diarrhea, fecal urgency, and flatulence. The Food and Drug Administration (FDA) concluded that those studies showed that olestra causes increased rates of severe symptoms (2). On the basis of those and other studies, the FDA requires a notice—"Olestra may cause abdominal cramping and loose stools"—on products containing olestra. Another Procter & Gamble study tested persons who thought they had previously reacted to olestra. That study confirmed that eating 20 g of olestra daily for several days can cause severe diarrhea (Klontz K. Personal communication to Thorsheim H. Food and Drug Administration, 26 December 1995). A study (underwritten by Unilever) found that daily consumption of olestra (mean, 24 g/d) increased "urgent calls to stool" and other symptoms (3).

Sandler and colleagues state that "clinically meaningful" symptoms are not associated with unregulated consumption of olestra. Still, in the highest decile of consumers, olestra doubled the incidence of more frequent bowel movements and loose stools. These persons had symptoms on 18% of person-days, compared with only 12% of days in the control group (the authors' Table 4). Olestra consumers missed some or all of their activities on 0.4% of days, compared with 0.2% in the controls.

The FDA has received more than 20 000 reports of gastrointestinal symptoms attributed to olestra, including hundreds from people who went to emergency departments or physicians' offices. Clinicians should be aware that olestra may cause severe gastrointestinal symptoms and should question patients about their consumption of foods containing olestra.

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Plasma Exchange for Hemolytic Crisis in Wilson Disease

To the Editor: Half of patients with Wilson disease, a disorder of copper metabolism with two mutant ATP7B genes (1), present with hepatic disturbance (2). Acute hepatic failure tends to be fulminant when it is associated with hemolysis (3); patients can survive for only days or weeks unless transplantation is performed (2). We describe a patient with Wilson disease whose hemolysis was treated with plasma exchange.

A 17-year-old boy was hospitalized because of fatigue. He was alert and slightly jaundiced. Laboratory findings included a hemoglobin level of 11.9 g/dL, an albumin level of 3.1 g/dL, an aspartate aminotransferase level of 135 U/L, an alanine aminotransferase level of 119 U/L, an alkaline phosphatase level of 212 U/L, a total bilirubin level of 60 $\mu\text{mol/L}$ (3.5 mg/dL), and a prothrombin time of 32%. Results of tests for viral hepatitis were negative. Ultrasonography showed a coarse echogenic texture of the liver and slight ascites. Acute hepatic failure with less pronounced elevations of aminotransferase levels prompted us to consider Wilson disease. Kayser-Fleischer rings were detected on slit-lamp examination. The serum copper level was 72 $\mu\text{g/dL}$ (normal range, 78 to 131 $\mu\text{g/dL}$), and the ceruloplasmin level was 8 mg/dL (normal range, 18 to 37 mg/dL). Free serum copper level, a reliable indicator of Wilson disease (4), was elevated at 61 $\mu\text{g/dL}$ (normal range, 4 to 7 $\mu\text{g/dL}$). On the sixth day of hospitalization, the hemoglobin level and prothrombin time decreased to 8.8 g/dL and 22%, respectively, and unconjugated hyperbilirubinemia was seen (total bilirubin level, 154 $\mu\text{mol/L}$ [9.0 mg/dL]; unconjugated bilirubin level, 82 $\mu\text{mol/L}$ [4.8 mg/dL]). Plasma exchange was started on 3 consecutive days. Copper elimination was 2300 μg at the first plasma exchange, which resulted in a reduction in total bilirubin level (21 $\mu\text{mol/L}$ [1.2 mg/dL]) at the completion of plasma exchange. One year later, prothrombin time returned to 70% and results of other laboratory tests were normal; D-penicillamine therapy was continued.

We treated acute hepatic failure related to Wilson disease at the beginning of hemolysis (caused by a flux of copper from hepatocytes); plasma exchange removed copper (5). Our report suggests that after rapid diagnosis of Wilson disease, liver transplantation can be avoided when hemolysis is controlled first with plasma exchange and thereafter with chelation therapy.

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