

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 172**

[Docket No. 87F-0179]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Olestra

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of sucrose esterified with medium and long chain fatty acids (olestra) as a replacement for fats and oils. This action is in response to a petition filed by the Procter & Gamble Co.

DATES: The regulation is effective January 30, 1996. Submit written objections and requests for a hearing by February 29, 1996. Submit written comments on the labeling requirement (§ 172.867(c)) by April 1, 1996. The Director of the Office of the Federal Register approves the incorporations by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of certain publications at 21 CFR 172.867, effective January 30, 1996.

ADDRESSES: Submit written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Helen R. Thorsheim, Center for Food Safety and Applied Nutrition (HFS-216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3092.

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I. Introduction

Olestra, also called sucrose polyester, is the common name for a mixture of substances formed by chemical combination of sucrose with six, seven, or eight fatty acids. The fatty acids, bound to sucrose by ester bonds, are of the type commonly found in edible oils and fats. Olestra has physical properties similar to those of natural fats. Olestra's particular physical properties depend on the specific fatty acids used and the degree of esterification.

The Procter & Gamble Co., 6071 Center Hill Rd., Cincinnati, OH 45224-1703 (the petitioner), submitted a petition to FDA on April 15, 1987, for the use of olestra in shortenings and oils as a calorie-free replacement for fats and oils. The petition (FAP 7A3997) was filed on May 7, 1987. In a notice in the Federal Register of June 23, 1987 (52 FR 23606), FDA announced that the food additive petition had been filed by Procter & Gamble, proposing the issuance of a food additive regulation providing for the safe use of sucrose esterified with medium and long chain fatty acids as a replacement for fats and oils. On July 6, 1990, the petitioner amended the petition to limit the intended use of olestra to a 100 percent replacement for conventional fats in the preparation of savory snacks (i.e., snacks that are salty or piquant but not sweet, such as potato chips, cheese puffs and crackers). During the course of the petition evaluation, the petitioner also amended the proposed specifications that describe the additive.

In the Federal Register of October 17, 1995 (60 FR 53740), FDA announced that a public meeting of the agency's Food Advisory Committee (the FAC) and a working group of the FAC would

be held on November 14 through 17, 1995. The working group was asked to discuss and comment on whether all relevant issues associated with olestra had been addressed (Ref. 1). The discussion covered all aspects of the safety review of olestra, including nutrient effects and compensation, gastrointestinal effects, and labeling (Ref. 2¹).

In the Federal Register of November 16, 1995 (60 FR 57586), FDA announced that it would consider public comments on the petition, including comments on the proceedings before the FAC, only if filed on or before December 1, 1995. This action allowed the agency to identify precisely which data and information to consider in making its decision on the petition. This measure was necessary to facilitate the agency's decision making process and to come to closure on the petition. By letter dated December 8, 1995, FDA extended to December 21, 1995, the time by which such comments could be submitted. This extension was in response to a request of the Center for Science in the Public Interest (CSPI).²

A. Safety Testing-Background

1. Legal Context of the Safety Evaluation

Section 409 of the act (21 U.S.C. 348), sets forth the statutory requirements for approval of a food additive (21 U.S.C. 321(s)). With the enactment of the Food Additives Amendment of 1958 (the Amendment), Congress established a premarket approval system whereby the company seeking to market a food additive must first obtain approval from FDA. Through this mechanism, Congress sought to shield the public from unsafe or potentially unsafe products.

Under section 409(c)(3) of the act, 21 U.S.C. 348(c)(3), FDA is not to approve

¹ The transcript of the Olestra Working Group and full Food Advisory Committee meetings are provided as reference. Throughout the preamble to this final rule, reference is made to comments of Committee members and presenters to the Committee; footnotes indicate the transcript volume and page numbers of these. The affiliation and credentials of the commenter are also described.

² On October 25, 1995, CSPI submitted a comment to the olestra petition entitled "White Paper on Olestra" (the White Paper). (CSPI subsequently submitted revised versions of the White Paper on November 2 and 3, 1995.) The November 3, 1995, White Paper was provided to the Olestra Working Group and FAC members for consideration at the meetings of November 14-17, 1995 (Ref.3). In addition, the authors of the White Paper, Drs. Myra Karstadt and Michael Jacobson, presented data from the White Paper on all of the issues covered in the White Papers, namely, (1) consumption estimates, (2) effect of olestra on carotenoids, (3) effect of supplementation of olestra with vitamin K on coumadin therapy, (4) effect of olestra on GI symptoms, and (5) animal carcinogenicity studies.

a food additive petition " * * * if a fair evaluation of the data before the Secretary³ * * * fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe * * *. This provision is commonly referred to as the "general safety clause."

By requiring that the data concerning a food additive "establish" safety, Congress squarely placed the burden of proving safety on the sponsor of a food additive petition, in this case Procter & Gamble. FDA need not prove that the additive is unsafe in order to deny approval.

The term "safe" is not defined in the act itself. The legislative history of the Amendment makes clear, however, that a demonstration of absolute harmlessness is not required to sustain the approval of a food additive:

Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance. This was emphasized particularly by the scientific panel which testified before the subcommittee. The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance. H. Rept. No. 2284, 85th Cong., 2d sess. 4-5 (1958). *Accord*: S. Rept. No. 2422, 85th Cong., 2d sess. 2 (1958). FDA regulations incorporate the concept of safety articulated in the Amendment's legislative history. 21 CFR 170.3(i). ("Safe" means that " * * * there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.")

Although the concept of "harm" is central to the act's safety standard, neither the statute, nor regulations implementing the food additive provisions, define harm. Once again, however, congressional intent is clear from the legislative history of the amendment. Specifically, "harm" means the capacity to injure or otherwise damage the health of individuals consuming the additive. +

The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. H. Rept. No. 2284, 85th Cong., 2d sess. 4 (1958). *See also* Letter from Assistant Secretary of Health, Education, and Welfare Elliot L. Richardson to Congressman Lister Hill, Chairman,

³ This decision has been delegated to the Commissioner of Food and Drugs, 21 CFR 5.10(a)(1).

Senate Committee on Labor and Human Resources, dated July 29, 1958. (“* * * in our opinion the bill is aimed at preventing the addition to the food our people eat of any substances the ingestion of which would expect to produce not just cancer but any disease or disability.”)

The concept of harm was discussed during the Olestra Working Group and FAC meetings. One FAC member expressed the opinion that he would consider an effect that is undesirable as harmful or adverse⁴. However, the legislative history reflects that an effect is harmful if it affects health, not if it is simply an undesirable or unexpected effect that has no adverse health consequences.

The statute leaves the methods and criteria for interpreting data up to the discretion and expertise of the agency. Congress did, however, direct FDA to consider the following three factors:

(A) The probable consumption of the additive and of any substance formed in or on food because of the use of the additive;

(B) The cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet; and

(C) Safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data. (21 U.S.C. 348(c)(5).)

In the case of olestra, the product’s broad marketing potential and expected consumption by persons of all ages, including children, are aspects that have been considered in the safety evaluation.

Importantly, Procter & Gamble is not required to show, nor is FDA permitted to consider, that olestra has benefits, health or otherwise, for consumers of the additive. Again, the legislative history of the Amendment is clear on this point.

The question of whether an additive produces such [a technical] effect (or how much of an additive is required for such an effect) is a factual one, and does not involve any judgement on the part of the Secretary of whether such effect results in any added ‘value’ to the consumer of such food or enhances the marketability from a merchandising point of view.

S. Rept. No. 2422, 85th Cong., 2d sess. 7 (1958). *Accord*: H. Rept. No. 2284, 85th Cong., 2d sess. 6 (1958).

⁴ Statement of Dr. Dennis Hsieh. Dr. Hsieh is a professor of environmental toxicology at the University of California at Davis. Transcript of the November 14 to 17, 1995, meeting of FAC (hereinafter Transcript), vol. 3, p. 40.

In summary, the general safety clause places on Procter & Gamble the burden of proving that a fair evaluation of the data in the administrative record establishes that there is a reasonable certainty that olestra will not be harmful under the prescribed conditions of use. Only if Procter & Gamble meets this burden can the food additive be approved.

2. Dietary Context of Safety Evaluation

Olestra presents a different set of safety issues compared to most food additives. For example, most substances can induce toxic effects provided that the dose administered is sufficiently high. The primary purpose of most safety testing is to determine the toxic dose and to evaluate whether there is a sufficient margin of safety between the highest dose that is not toxic and the expected human exposure.

Because olestra is intended to substitute for fat, a substantial component of the diet, it is difficult, if not impossible, to feed olestra to laboratory animals in amounts sufficiently high to allow use of the 100-fold safety factor that is commonly used to ensure safety (21 CFR 170.22), when evaluating animal studies. The use of a safety factor is intended to account for the uncertainty of extrapolating from toxicity data from animals to humans. (See 21 U.S.C. 348(c)(5)(c).) FDA concludes that in the case of the olestra petition, the agency is justified in not using the 100-fold safety factor for the following reasons. First, no toxic effects from olestra consumption were observed when olestra was fed at levels up to 10 percent of the diet of laboratory animals (as discussed in section III. of this document). Second, olestra is not appreciably absorbed by the body and the minuscule amount of material that is absorbed is metabolized to substances (sucrose and fatty acids) that are further metabolized normally in the body. Thus, no major component of olestra is available to produce a toxic effect. Finally, a significant number of human studies have been performed to assess the safety of olestra, which assessment may be performed without the need for a safety factor.

The fact that olestra is not absorbed also means, however, that as food components are absorbed from the intestine, the amounts of olestra present in the intestine will become an increasingly larger fraction of the total intestinal contents. Thus, the safety issues for olestra are focused on effects in the intestine, including potential interference with absorption of nutrients.

The petitioner completed the standard toxicological testing program to demonstrate safety for a direct food additive, as outlined in FDA’s guidance on such testing (Ref. 4). However, to account for the possible variations in composition, effects on composition due to heating, and inherent difficulties in extrapolating from laboratory animals to humans, the initial animal tests have been supplemented with a variety of human and additional animal studies taking into account the properties of olestra. In fact, since the original petition was submitted in 1987, Procter & Gamble has submitted more than 50 additional safety studies for review. In 1992 and 1993, the pivotal safety studies with regard to nutritional effects from the petitioned use of olestra were submitted.

B. Toxicological Studies—Overview

The petition submitted to FDA consists of data and information from toxicity studies in several animal species, including the rat, mouse, dog, and rabbit. The toxicity data base includes a battery of three mutagenicity/genotoxicity tests; subchronic feeding studies in mice, rats, hamsters, and dogs; and reproduction/teratology testing in the rat and rabbit. To determine whether olestra affects the structure and function of the gastrointestinal (GI) tract, a series of absorption, distribution, metabolism, and elimination (ADME) studies were conducted in rats, mini-pigs, and guinea pigs.

C. Nutritional Impact Studies—Overview

The limited digestibility of olestra poses a number of nutrition issues, including olestra’s effect on fat-soluble vitamins and whether these effects could be compensated for by the addition of an appropriate amount of the affected vitamins. As a result, the petitioner conducted several studies, including those listed below, in both pigs and humans. Procter & Gamble conducted studies in swine because they have a digestive system similar to humans and can be evaluated for nutrient stores in the liver and bone. Five of the studies that were carried out in swine are: (1) a 12-week dose-response study (the 12-week DR study) of olestra on the status of vitamins A, D, E, and K, and on hard-to-absorb and limited-in-diet nutrients; (2) a 12-week vitamin restoration study (the 12-week VR study) to determine levels of vitamins A, D, and E needed to offset olestra effects; (3) a 26-week dose-response and vitamin restoration study (the 26-week DR/VR study) to extend

the findings of the 12-week DR and 12-week VR studies to longer times and lower olestra intake levels; (4) a 39-week study (the 39-week VR study) to confirm the effects of 0.25 percent olestra and added vitamin A and E measured in the 26-week DR/VR study over a longer exposure time; and (5) a 4-week dietary context study (the 4-week DC study) to compare olestra's effects on vitamins A and E when olestra is consumed either with the diet or between meals.

Procter & Gamble conducted studies of olestra in humans to eliminate any uncertainty related to extrapolating from pigs and to obtain subject reports on gastrointestinal effects. Those objectives were pursued in several human studies including: Two clinical studies, two studies in free-living subjects,⁵ and one short-term study designed to assess olestra's effect on vitamin A and fat absorption (the vitamin A/fat study). The two human clinical studies were an 8-week study to determine the dose response of olestra on the status of vitamins A, D, E, and K, and on hard-to-absorb and limited-in-diet nutrients (the 8-week DR study) and an 8-week study to confirm the compensation levels for vitamins A and E (the 8-week VR study). The free-living studies were a 16-week study to assess the status of vitamin E in subjects consuming 18 grams/day (g/d) olestra (the 16-week vitamin E study) and a 6-week study to determine the effect of 20 g/d olestra on vitamins D and K (the 6-week vitamin D/K study).

D. GI Effects—Overview

The petitioner performed several studies to evaluate olestra's effects on the gastrointestinal (GI) tract including the following. The two clinical studies (the 8-week DR and 8-week VR studies) were used to evaluate adverse gastrointestinal effects as reported by the test subjects. In addition, the effect of olestra on intestinal microflora was measured by conducting a breath gas expiration study. Several studies were also conducted to evaluate olestra's effects on bile acid metabolism and absorption. In order to determine olestra's effects, if any, in an at-risk population, studies were conducted in

inflammatory bowel disease patients. Because some drugs are lipophilic (fat-soluble) and may partition into (i.e., be partially absorbed by) olestra, olestra's potential to affect absorption of drugs was also investigated. In addition, because nonabsorbable liquid oil can separate from other fecal material in the colon and leak through the anal sphincter, a human clinical study was performed to determine the relationship between olestra's stiffness and passive oil loss.

E. FDA's Decision Process

In light of the novel issues raised by the review of the olestra data, FDA's Center for Food Safety and Applied Nutrition (CFSAN) determined that it would be valuable to obtain additional expertise in resolving certain issues that had been raised. A Regulatory Decision Team (RDT) composed of senior FDA managers was established for the purpose of recommending, to the Director of CFSAN, a decision on the olestra food additive petition. In addition, FDA retained the services of several scientific consultants from outside the agency to facilitate the agency's deliberations.

As is the case with all food additive petitions, the olestra data were reviewed by staff scientists. Because of the large number of studies and the diverse nature of the information, each of these scientists reviewed a portion of the total body of data on the additive, focusing on his particular area of expertise. These staff-level reviews, including any questions or issues raised by such reviews, were subsequently considered by the RDT, assisted by the outside consultants. In the RDT deliberations, an overall Center position on olestra's safety was synthesized; in the process, issues raised by individual reviewers were resolved, were determined to be not significant, or were incorporated into the synthesized position. During this deliberative process, the members of the RDT weighed the various pieces of scientific information and applied their scientific judgement as they developed an overall Center position.

After the conclusion of the RDT deliberations and the meetings with consultants from outside the agency, FDA convened a public meeting of its FAC and a special Olestra Working

Group of the FAC on November 14 through 17, 1995, to undertake a scientific discussion of the agency's evaluation of the safety data in the petition. The membership of the standing Committee was supplemented with temporary members and consultants to the Committee, representing scientific disciplines appropriate to the evaluation of a macro-ingredient fat substitute.

At the Olestra Working Group meeting, Procter & Gamble presented a summary of the data it considered adequate to establish the safety of olestra, the experts with whom the agency had consulted presented their views on the sufficiency of the information to assess the safety of olestra, interested members of the public presented their opinions and evaluations of the data, and FDA presented its evaluation of the data. The Committee was asked to assess, in light of the state of the science relative to macro food ingredients, whether all critical safety issues with respect to the use of olestra in savory snack foods had been addressed.

As set out in detail below, having completed its evaluation of the data in the petition and having considered the deliberations of the Olestra Working Group and the FAC, including all presentations to the Committee, and the comments received on the petition, the agency is amending the food additive regulations to permit the use of olestra in place of fats and oils in prepackaged ready-to-eat savory snacks.

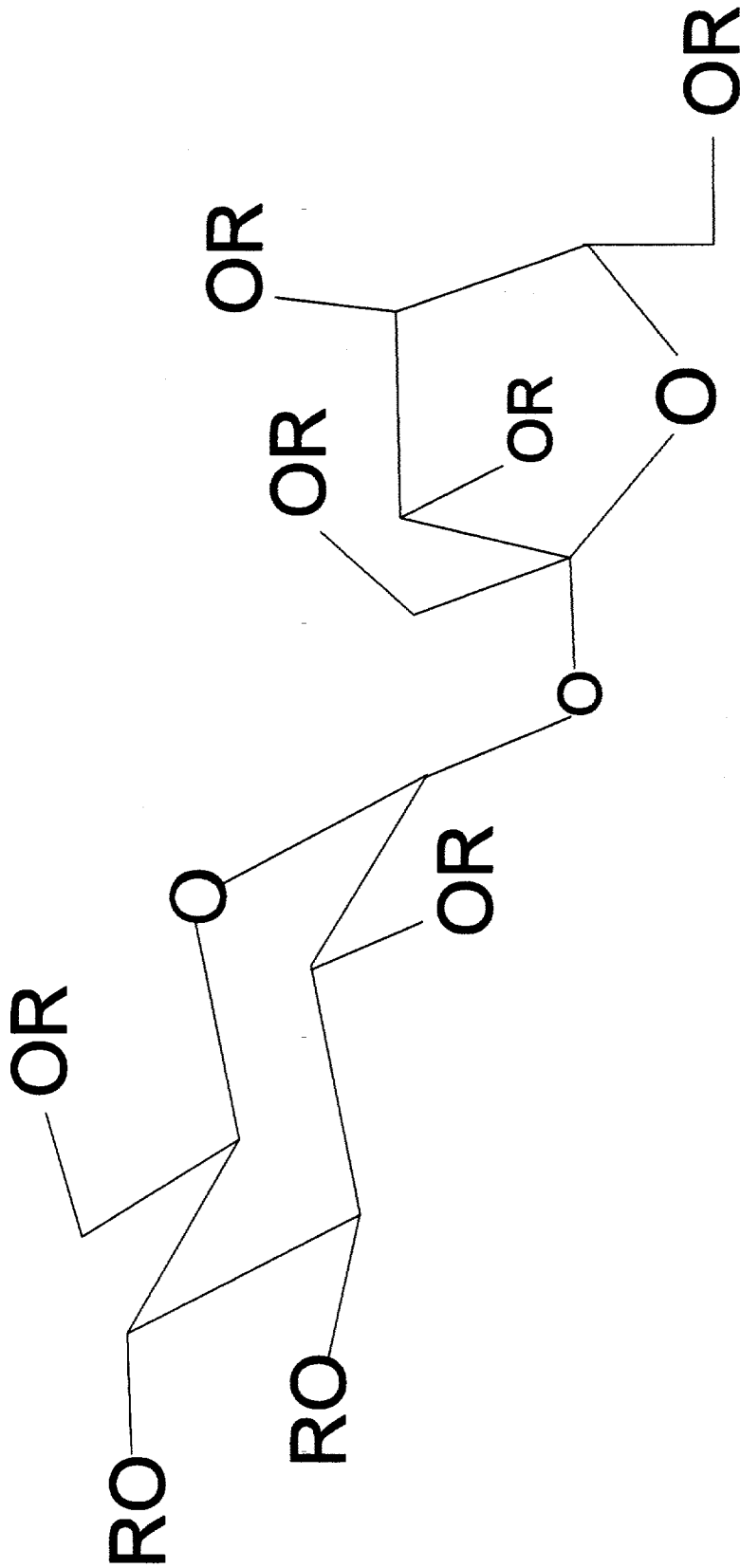
II. Identity and Use

Olestra is the common name for the mixture of sucrose esters formed from the addition of six, seven, or eight fatty acids to the available eight free hydroxyl moieties of sucrose. Saturated and unsaturated fatty acids of chain length C12 to C20 and higher can be used to manufacture olestra. The final product is defined by specifications which include the fatty acid composition.

The identity of sucrose octaester as the principal component of olestra has been verified by infrared, mass, and nuclear magnetic (proton and ¹³carbon) spectrometry (Ref. 5). The generalized structure for olestra is set forth below.

BILLING CODE 4160-01-F

⁵ Free-living subjects maintain their normal diets and eating patterns except for consumption of the test article as instructed.



R = Fatty Acids (C12 - C20)

A. Manufacturing Processes

Olestra is prepared by the addition of medium- and long-chain fatty acid methyl esters to sucrose in the presence of catalysts. The postsynthesis purification steps are the same as those generally practiced in the edible oils industry. These purification steps depend upon physical separations and do not involve chemical bond rearrangement or the use of solvents or catalysts.

The methyl esters used to prepare olestra can be obtained by procedures common in the food industry such as the reaction of refined triglyceride oils with methanol in the presence of sodium methoxide or from esterification of their fatty acids. The resulting esters are washed with water to remove residual methanol, dried under vacuum, and distilled. The fats and oils can be derived from a variety of edible sources such as, but not limited to, soybean, palm, coconut, fully hydrogenated rapeseed, and cottonseed.

Sucrose and the methyl esters are mixed with an alkali metal soap of a long-chain fatty acid. A small amount of transesterification catalyst such as an alkali metal (sodium or potassium) carbonate, bicarbonate, hydride, or alkoxide is added and the mixture heated under vacuum to withdraw the volatile methanol byproduct. Following the reaction, excess methyl esters and free methanol are removed by evaporation under vacuum. Standard steam deodorization removes free fatty acids and odors. Different lots of olestra may be mixed to achieve desired properties or to meet product specifications.

The manufacture of olestra can be well controlled, based upon the petitioner's analysis of representative lots (Ref. 5).

B. Constituents

The principal trace constituents of olestra are collectively identified as the unsaponifiable fraction, ranging in concentration from 0.08 percent to 0.3 percent. These constituents are primarily aliphatic hydrocarbons and plant sterols that naturally arise from the edible triglyceride sources of fatty acids used in the synthesis of olestra. In this respect, these trace constituents of olestra do not differ from those found in typical edible oils. Additionally, difatty ketones (DFK's), formed during its manufacture, are found as trace constituents in olestra as consumed.

DFK's form in olestra during the alkaline rearrangement manufacturing process. The DFK's that are present in olestra are a family of compounds with

a common general structure consisting of two fatty acid chains with a central keto group. They are formed from naturally occurring vegetable oil-derived fatty acids used to make olestra. The length and degree of unsaturation of the fatty acid chains are determined by the source oil used to make olestra.

Quantitative analysis of olestra by gas chromatography and mass spectrometry of 15 typical lots of olestra determined that olestra contains 36 to 416 parts per million (ppm) DFK's. The potential DFK range of olestra was altered to 100 to 300 ppm when the method of manufacture was updated. Qualitative analysis of soybean oil-based olestra showed that the DFK's ranged from 31 to 35 carbons in length, consistent with the predominance of C₁₆ and C₁₈ fatty acids in soybean oil.

Identical analytical techniques showed that similar types (C₂₉-C₃₅ fatty acid chain length), but lower levels, of DFK are found in vegetables (5 to 86 ppm), cooked meat fat (0.15 to 2.73 ppm), and food-approved emulsifiers (10 to 55 ppm). Historically, the once-common commercial practice of rearranging fats and oils by base-catalyzed methods produced levels of DFK that exceeded 300 ppm. These results show that olestra is an additional dietary source of those DFK's that are now, and have been, commonly consumed in the food supply (Ref. 6).

C. Specifications

Olestra comprises a range of possible compositions that can be identified by a three-dimensional matrix defined by: (1) Fatty acid chain length; (2) the degree of fatty acid unsaturation; and (3) the distribution of full and partial esters of olestra. The petitioner has proposed specifications that include ranges for fatty acid chain length and degree of unsaturation to ensure functional products for use in savory snacks. The specified range of esterification ensures the nonabsorbable and noncaloric nature of the product.

Traditional edible oil specifications that ensure purity and safety also are incorporated into the olestra specifications. These values include specifications for free fatty acid content, total methanol residues, water, residue on ignition, peroxide value, total heavy metal content, and lead.

D. Stability

Olestra is stable under ambient and high-temperature storage conditions. In all cases, olestra is at least as stable as triglycerides with similar fatty acid composition.

Polymers form in both olestra and triglycerides during cooking,

purification, or storage, when olestra or triglycerides are exposed to heat, moisture, and air. The polymers, comprised almost entirely of dimers and trimers, form by cross-linking at points of unsaturation on the fatty acid chains. This mechanism of cross-linking in olestra is the same as that which occurs in triglycerides. The amount of polymer found in olestra is less than that found in a conventional edible oil stored under identical, controlled conditions.

Typical bulk lots of olestra were demonstrated to be as stable as triglycerides of similar fatty acid composition when stored at room and elevated temperatures (120 F) for up to 1 month. These olestra batches were found to be stable based upon the lack of significant change in fatty acid composition, ester distribution, free fatty acid levels, polymer levels, and oxidative stability (Ref. 7).

Heating food fats in the presence of moisture and air results in the production of decomposition byproducts. Such byproducts are removed regularly from commercial cookers to maintain an effective frying system under good manufacturing practice. Use of olestra for frying savory snacks will similarly lead to production of byproducts. The petitioner conducted research to determine the extent of byproduct production from olestra compared to conventional frying fats, and to determine whether unique byproducts would be formed.

A variety of analytical techniques were employed to characterize the profile of byproducts formed during the heating of olestra and conventional frying fats. The gross identity of the heated products was determined by standard methods such as fatty acid composition, carbon number profile, and peroxide value. In addition, comprehensive analyses of changes to the fatty acid side chains were undertaken. Fatty acids were methylated by transesterification, isolated by silica gel column chromatography or solid phase extraction, and analyzed by a variety of techniques including gas chromatography (GC), GC/mass spectrometry (MS), two-dimensional GC/MS, and high performance liquid chromatography (HPLC). This battery of tests provided an analytical sensitivity to detect a component present in the heated oil at a level of 17 ppm (equivalent to 0.05 ppm in the diet of 90th percentile consumers of olestra) (Ref. 8).

For both olestra and conventional frying fats (triglycerides), the predominant chemical changes that occur under frying conditions are

oxidation reactions on the fatty acid side chains (Ref. 8). The principal byproducts of frying are polymers (dimers and trimers) which are joined primarily by bonds between unsaturated fatty acid components. Both olestra and conventional fats of similar fatty acid composition undergo a similar number of polymerization reactions under common heating conditions. For example, the amount of polymer increased 0.003 mole/100 g for olestra and 0.004 mole/100 g for a triglyceride of similar fatty acid composition.

Levels of olestra and triglyceride polymers absorbed into the cooked foods under worst-case conditions are similar and show that there is no selective concentration in food. For example, polymer levels in food fried in either olestra or triglyceride ranged from 4 to 6 percent of total lipid weight. These values correspond to the concentration of olestra and triglyceride polymer in the bulk heated oil phases (Ref. 8).

Baking conditions do not degrade olestra or triglyceride as readily as frying conditions, even though soda crackers commercially prepared with olestra may experience temperatures ranging from 250 to 350 °F. This is because crackers are exposed to such temperatures for only a few minutes (not hours), and the temperature within the body of the cracker can be expected to be substantially lower than the oven temperature.

This stability in baking assessment was confirmed when both olestra and a triglyceride of similar fatty acid composition were used to prepare soda crackers, and the crackers were baked for 6 minutes at the more common commercial temperature of about 250 °F. The neat (i.e., prior to baking) olestra and triglyceride were analytically characterized, and the profiles compared to those obtained from the fats extracted after the soda crackers were baked.

Unlike during frying, neither olestra nor the triglyceride formed any measurable polymer during the 250 F baking (Ref. 9.). Consistent with a lack of change in polymer content, results demonstrate that neither olestra nor the triglyceride experienced any significant change in primary structural composition (i.e., ester distribution for olestra; or the tri-, di-, or monoglyceride profile for the triglyceride).

The only notable change in both olestra and the triglyceride was a slight increase in free fatty acid content. This latter effect is expected because free fatty acids may be present in the cracker raw ingredients, and the alkaline chemical leavening agents used in soda

cracker production can promote ester hydrolysis. The similarity of changes in olestra and triglycerides during soda cracker baking is consistent with the fact that the chemical changes in both products take place on the fatty acids, and yield the same decomposition products.

To test stability during storage after baking, both olestra and a triglyceride of similar fatty acid composition were used to make soda crackers, unflavored plain crackers, and unflavored snack crackers. All products were packed in air to reflect current market practice, aged under controlled temperatures and time to reflect common and worst-case storage conditions, and analyzed for parent, polymer, and decomposition products. The results demonstrate that the stability of olestra and triglyceride were comparable under the conditions studied (Ref. 9).

FDA concludes that use of olestra in frying media for savory snacks results in neither more nor different byproducts of the frying process than currently experienced with conventional oils. Also, olestra is as stable as triglyceride in crackers during baking and in baked crackers stored under expected and worst-case conditions.

E. Use and Intended Technical Effect

Olestra is proposed for use as a calorie-free replacement for up to 100 percent of the conventional fats and oils used in the preparation of savory snacks such as flavored and unflavored chips and crisps, flavored and unflavored extruded snacks, and crackers. These uses include substitution for fat for frying as well as sources of fat in dough conditioners, oil sprays, and flavors. Olestra will function in savory snacks as a texturizer and as a formulation aid (21 CFR 170.3(o)) at levels not in excess of that reasonably required to produce its intended effect.

F. Estimated Daily Intake for Olestra (EDI)

When conducting a food additive safety evaluation, FDA typically uses estimated 90th percentile chronic intakes. The petitioner has provided a study of probable intake for olestra, completed by the Market Research Corporation of America (MRCA), that contains sufficient information to estimate both chronic and acute exposures to olestra.

The MRCA methodology estimates the daily consumption of olestra from savory snacks for individuals by combining: (1) The individual's frequency of consumption of savory snacks; (2) the average amount eaten per eating occasion of that savory snack;

and (3) the amount of olestra in that savory snack. Eating occasion frequencies were determined from 14-day dietary diaries that were kept by heads of household. The amount of food eaten per eating occasion was derived from the USDA's Nationwide Food Consumption Surveys. The amount of olestra in snacks was determined in the petitioner's laboratories.

The MRCA survey data show that at the 90th percentile, the probable lifetime-averaged intake of olestra is 6.4 g/p/d. FDA believes however, that it is appropriate to consider energy needs in estimating the daily intake of olestra. Based on the assumption that consumers of olestra will compensate for calories "lost" due to consumption of olestra by increasing their intake of food (including olestra-containing snacks), the agency has concluded that the lifetime-averaged EDI for olestra should be increased by 10 percent to 7.0 g/p/d (Ref. 10).

Any effects of olestra on nutrients or nutrient absorption could be exhibited during less than chronic exposure conditions. To evaluate sub-chronic conditions, FDA has estimated that a "high" acute consumer of olestra (every day for 12 weeks) would consume 20 g/p/d, equivalent to eating a 2-ounce (oz) bag of potato chips every day (Ref. 11). The MRCA survey information submitted by the petitioner shows that the 99th-percentile, 14-day average intake for olestra would be 14.8 g/p/d (corrected to 16.3 g/p/d for caloric compensation) in the 18 to 44 year old male group. The 99th-percentile single-day intake of olestra for the group consuming the highest level of savory snacks (13 to 17 year old male group) is 40.4 g/p/d (corrected to 45 g/p/d). It is not likely that this high single day intake would be repeated every day in the 12-week time frame previously mentioned.

In terms of consumption patterns, the MRCA data also show that approximately 9 percent of lunch and dinner meals include a snack food that could potentially contain olestra. The data also show that 63 percent of snack food eating occasions occur with a meal.

Consumption estimates of olestra-containing savory snacks were discussed at the Olestra Working Group and FAC meetings. In particular, CSPI raised three concerns about these estimates. First, CSPI presented several consumption scenarios to the Olestra Working Group⁶ that the organization

⁶ These CSPI comments were presented by Dr. Myra Karstadt, Ph.D. Transcript, vol. 2, p. 49. This information is also discussed in CSPI's White Paper (Ref. 3).

asserted better represented expected olestra consumption. These consumption estimates ranged from 4.2 g/p/d to 37.5 g/p/d. CSPI's higher consumption estimates included an increase in consumption of olestra-containing snacks over full-fat snacks; this increase was based on the results of a telephone survey, which survey indicated that people think they would eat 25 percent more snacks if the snacks contained lower fat. Based on these scenarios, CSPI asserted that there would likely be a substantial number of snack eaters consuming olestra in quantities similar to those fed in the 8-week human studies (8, 20, and 32 g/d).

Second, CSPI asserted that consumers usually eat an entire bag of chips at one sitting, and that bags marked "single-serving" typically contain from three-quarters of an ounce to 2 ounces. Therefore, CSPI claimed that in many cases, people would eat several ounces of chips at one sitting, and that, in evaluating olestra's for GI effects, it is important to consider single-sitting consumption levels.

Third, CSPI expressed concern that the MRCA survey population may not represent the most vulnerable high-volume consumers of snack products, such as minority teenagers resident in low socioeconomic areas, who may both consume large quantities of savory snacks and have poor nutritional status.

Dr. Gail Harrison, consultant to the petitioner,⁷ presented her analysis of the MRCA survey demographics to the Olestra Working Group, which responded to CSPI's third concern. Dr. Harrison stated that the MRCA survey population is very representative of the U.S. population in terms of regional census areas, census regions, and urbanization. Further, in terms of different population groups, she said that children of all ages are appropriately represented, while young homemakers are slightly underrepresented. In addition, there is a slight, though not statistically significant underrepresentation of minority households, and the income distribution slightly underrepresents highest-income and lowest-income households by about three to four percent. Also, information was provided to the Olestra Working Group by the petitioner from an analysis of USDA's 1990-1991 Continuing Survey of Food Intake that the average intake of salty snacks (crackers, popcorn, pretzels, and corn chips) by food-stamp recipients

was about 4 g/p/d while nonrecipients consumed about 7 g/p/d.⁸

After presentations by the petitioner, CSPI, FDA, and others, the members of the Olestra Working Group generally agreed that all issues with regard to the chemistry and consumption of olestra had been adequately addressed.

FDA agrees that it is appropriate to use conservative assumptions in the safety evaluation of olestra, the effect of which is likely to over-estimate consumption patterns. For this reason, FDA has assumed that 100 percent of all savory snacks will be replaced by olestra-containing snacks. That is, once olestra is approved, some consumers will eat only savory snacks containing olestra. FDA further believes that it is appropriate to rely on the MRCA survey data to estimate consumption because the survey is well designed, includes a large base of people, and a sound methodology in that the survey relies on food-intake diaries kept by participants rather than relying on participants' recall of what they ate sometime in the past. In light of the discussion before the Olestra Working Group, FDA further concludes that the MRCA survey data are sufficiently representative of the eating habits of the U.S. population and, in particular, that the eating patterns of low-income individuals are captured by the MRCA data and thus, such individuals are included in the agency's consumption estimates. In addition, FDA finds that a scenario-driven estimate of 20 g/p/d, based on consumption of 2 oz of chips per day, which is greater than the 99th percentile, 14-day average intake in the highest consuming group of snack eaters (18 to 44 year old males), is a reasonable estimate of a "short-term" high consumer. FDA has not used the largest amount reported to have been eaten in one sitting during the MRCA survey period because that amount represents an extreme that is unlikely to be repeated for more than a few days. FDA further concludes that there are no scientific data to justify increasing the estimated olestra exposure derived from the MRCA survey in order to account for the potential consumers' increase in consumption of snacks because the snacks are low-fat.

FDA has also evaluated the potential chronic exposure to DFK's formed from the manufacture of olestra. Mean DFK intake from olestra-prepared snacks is 0.4 mg/p/d (DFK level of 125 ppm). The 90th percentile for DFK's, based on an

olestra intake of 7 g/p/d, is 0.87 mg/p/d. For perspective, the mean level of DFK in foods (primarily beef, chicken, pork, and the brassica vegetables) is 9 mg/p/d and the 90th percentile background exposure (typically approximately twice the mean for commonly consumed foods such as meat and vegetables) would be 18 mg/p/d (Refs. 12 and 13).

Thus, FDA has determined that the available data and information support the use of 7 g/p/d olestra as an estimate of chronic consumption by the 90th percentile snack eater and 20 g/p/d olestra as an estimate of shorter term consumption.

III. Toxicity Data—Discussion and Evaluation

A. Absorption, Distribution, Metabolism, and Elimination

The petitioner conducted a series of preliminary studies to assess the absorption of olestra in rats. In order to identify which organs might accumulate intact olestra or metabolize olestra if absorbed, rats were intravenously (IV) injected with olestra radiolabelled with ¹⁴C on the sucrose portion of the molecule. The radiolabelled olestra initially deposited in the liver and, to a lesser extent, in the spleen. The data in these early studies show that, olestra was taken up rapidly by the reticuloendothelial system and deposited in the liver and spleen within 3 days following intravenous injection. There was a minor accumulation in the fatty tissues with only a trace amount detected in expired air. At 21 days, the concentration of olestra in the liver dropped to about 50 percent of the 3-day level. Olestra was excreted unchanged via the biliary and fecal routes.

These results demonstrate that the olestra that accumulated in the liver following intravenous injection was not metabolized because radiolabel was not accumulated in other tissues, which would have occurred if olestra had been hydrolyzed by hepatic enzymes. The absence of olestra's metabolism was confirmed by thin-layer chromatography, which showed intact olestra in the bile and feces. The half-life of olestra in the liver was about 5 days.

Examination by electron microscopy of liver tissue from rats injected intravenously with olestra showed that, at 56 days after dosing, lipid accumulation was greatest in the Kupffer cells. By 84 days post-dosing, the greatest accumulation was in the parenchymal cells, indicating that both kinds of cells handle olestra following

⁷Dr. Gail Harrison, Professor, School of Public Health, University of California-Los Angeles. Dr. Harrison presented at the petitioner's request. Transcript, vol. 2, p. 73.

⁸Information from testimony by Mr. Thomas Breaker from the Mathematica Policy Research Group before the Committee on Agriculture's Subcommittee on Department Operations and Nutrition (Transcript, vol. 2, p. 163).

iv administration. Tissue deposition studies were also conducted in rats fed one percent olestra for 30 days. Based on the data submitted, there was no significant radioactivity detected in the liver, spleen, lung, thymus, or adipose tissue from animals fed olestra.

Procter & Gamble conducted a series of studies in male and female rats to determine the fate of penta-, hexa-, hepta- and octa-ester preparations of olestra administered by gavage. The livers were removed and lipid extracts were analyzed for the various esters. No esters were detected by thin layer chromatography. However, the overall sensitivity of the method was only approximately 2 to 3 percent of the administered dose. Therefore, any olestra in rat liver extracts containing less than 3 percent of the administered olestra ester preparations could not be detected. Additional fat balance studies conducted in the rat demonstrated that enzymatic hydrolysis can convert mono-through penta-ester formulations of olestra to sucrose and fatty acids while hexa- through octa-ester formulations are not absorbed (Ref. 14).

To assess further the potential for olestra to be absorbed from the GI tract, the petitioner conducted a series of absorption studies in rats, guinea pigs, and mini-pigs. These studies used uniformly-labeled olestra with high specific activity and sensitive analytical methods to analyze tissues, especially

liver, for intact olestra and urine for ¹⁴C-sucrose, a metabolic product that would result from the metabolism of any absorbed olestra.

1. Rat Studies

In the rat studies, in order to detect the absorption of a very small amount of the administered dose, olestra of high chemical and radiochemical purity and high specific activity (1 millicurie/g) was dosed at high levels (0.1 millicurie/rat). Tissues were collected, combusted, and analyzed for radiolabelled CO₂, or the lipid fraction was extracted and analyzed for intact olestra by HPLC. Urine, feces, expired CO₂, and the carcass were analyzed for ¹⁴C. The urine was analyzed for ¹⁴C-sucrose to assess whether olestra had been absorbed and metabolized (Refs. 15 through 19).

Five samples which represented the extremes, and beyond, of the olestra specification range, as well as a typical mid-range composition, were tested. This set of samples included the following: (1) a sample in which the fatty acid chains were 100 percent saturated; (2) a sample in which the fatty acid chains were highly (85 percent) unsaturated; (3) a sample rich in short-chain length fatty acids (59 percent) and penta- and hexa-esters (84 percent); (4) a sample which represented the unheated mid-range of the olestra specification; and (5) a mid-range olestra sample which was subjected to conditions of repeated

thermal stress as would occur in the commercial preparation of savory snacks. Although the short-chain length fatty acids (59 percent) and penta- and hexaesters (84 percent) sample falls outside the olestra specifications proposed in the petition, the sample was tested to determine the absorption of these components that might occur in olestra in trace amounts.

The mean recovery of unabsorbed radiolabel from the rat feces, GI tract and contents, animal wipes and animal rinse solutions, and cage wipes and cage rinse solutions was greater than 98.5 percent of the administered dose regardless of the radiolabeled olestra formulation studied (Ref. 19). This recovered amount represents olestra that is not absorbed. The recovery of absorbed radiolabel carbon from olestra ranged from 0.02 percent of the administered dose of the high saturated olestra formulation to 1.5 percent of the administered dose of the short chain length and low ester formulation. The majority of the absorbed radioactivity was found in the expired CO₂ and urine. Analysis of liver lipids for intact olestra and urine for ¹⁴C-sucrose did not show any radiolabelled carbon. These data demonstrate that most of the ingested olestra remains intact and is not absorbed, but is excreted intact in the feces. The percent absorption of these olestra formulations are shown in Table 1 below.

TABLE 1.—PERCENT ABSORPTION OF OLESTRA FORMULATIONS IN RAT ABSORPTION STUDIES

Olestra Composition	Percent Absorbed
Low Chain/Low Ester	1.50
Mid-Range	0.16
Heated Mid-Range	0.14
High Unsaturates	0.05
High Saturates	0.02

The absorption measured for the sample rich in short-chain fatty acids and penta and lower esters was 1.5 percent of the administered dose. This higher value, compared to the other olestra formulations tested, resulted from the hydrolysis of the penta and lower esters to sucrose and free fatty acids in the GI tract. Sucrose molecules released by hydrolysis of the lower esters in the GI tract were further hydrolyzed by intracellular mucosal sucrase and passed into the portal system as the monosaccharides glucose and fructose. These molecules were metabolized normally and the radiolabel was excreted rapidly in expired air and urine. The only variable that significantly affected absorption was the

lower chain length and lower degree of esterification. Restriction of these lower chain length and lower esters in olestra through specifications for the additive limits the absorption to less than 0.16 percent of the administered dose. Of the five radiolabelled olestra formulations studied in the rat, the heated mid-range formulation with 0.14 percent recovery of absorbed radiolabel represents the olestra formulation proposed to be marketed for human consumption. FDA concludes that the low level (0.14 percent) of absorbed radiolabelled carbon from penta- and lower esters contained in the heated olestra is biologically insignificant because the only components shown to be absorbed are metabolized to sucrose and fatty

acids which are metabolized normally (Ref. 19).

2. Guinea Pig Studies

The petitioner conducted studies in male and female poligeenan-fed guinea pigs to assess the potential for increased absorption of olestra across a damaged intestinal mucosa. (Poligeenan is known to cause intestinal damage.) Male and female guinea pigs were given 3 percent poligeenan in tap water, or tap water alone (controls), for 5 weeks until GI lesions similar to those seen in acute and chronic human GI diseases (such as ulcerative colitis and Crohn's disease) were induced. The guinea pigs were then dosed with 200 microcuries of a heated olestra and the absorption of

olestra was compared between animals with normal GI tracts and those with compromised GI tracts.

The total recovery of radiolabelled olestra was greater than 97 percent of the administered dose for female guinea pigs in both the normal and compromised groups.⁹ The majority of radiolabel, 87 percent to 95 percent, was found in feces and GI contents. Guinea pigs in the compromised group had comparable amounts of radiolabel in the GI tract and contents compared to the normal group. In addition, there were no consistent differences between the normal and compromised groups in the distribution of the absorbed radiolabel among various tissues, blood, urine, or expired CO₂. These findings show that the absorption of intact olestra is no greater in guinea pigs with compromised GI tracts than in guinea pigs with normal GI tracts (Refs. 20 and 21).

3. Mini-Pig Studies

The absorption of a typical, mid-range heated olestra was determined in weanling mini-pigs. The weanling mini-pig was chosen because its GI tract is physiologically and anatomically similar to humans and, like man, the mini-pig can tolerate a high fat diet. The design for the mini-pig study was similar to the design in the rat absorption studies except that expired CO₂ was not collected from the mini-pigs because metabolic cages large enough to house mini-pigs were not available at the contract laboratory. In addition, the dose of radiolabelled olestra was increased to 0.35 millicuries per mini-pig so that the detection limit was comparable to that in the rat studies.

For both male and female mini-pigs, 98.9 percent of the recovered radiolabel was found unabsorbed in the feces, GI tract plus contents, and animal rinse solutions. No radiolabelled olestra was found in the lipid fraction that would have contained olestra, if present, in the lipids extracted from livers of the mini-pigs (Ref. 22).

Overall, the results from these studies in rats, guinea pigs, and mini-pigs demonstrate that while a small percentage of the olestra formulation consisting of penta- and lower esters is absorbed and metabolized to fatty acids and sucrose, nearly all of the ingested olestra remains intact and is not absorbed (Refs. 19, 21, and 22). Heating does not significantly increase olestra

absorption and absorption is no greater when the GI tract is compromised than when it is intact.

B. Genetic Toxicity Studies

The petitioner conducted a battery of genetic toxicity studies with the unheated mid-range olestra formulation. Olestra was not genotoxic in any of the following test systems: An Ames Salmonella test with or without metabolic activation, a mouse lymphoma cell mutagenicity assay with or without activation, an unscheduled DNA synthesis test, and a Chinese hamster ovary cell in vitro cytogenetics test with or without activation.

Because of solubility problems with olestra in these early genetic toxicity studies, the petitioner conducted an additional battery of in vitro assays and in vivo cytogenetic studies on heated mid-range olestra with Pluronic F-68, a nontoxic, nonionic surfactant to ensure cell contact with olestra. No evidence of mutagenicity or genetic toxicity from heated olestra was observed in the following test systems: The Salmonella/mammalian microsome mutagenesis assay; the L5178Y TK +/- mouse lymphoma assay; the test for chemical induction of unscheduled DNA synthesis in rat hepatocytes; and the cytogenicity study in Chinese hamster ovary (CHO) cells. These tests were conducted in the presence and absence of liver enzyme (S-9) activation at concentrations of up to 5 mg/mL. In addition, there was no evidence of chromosomal aberrations from heated mid-range olestra observed following examination of the bone marrow in the in vivo cytogenicity assays (using both acute and chronic dosing protocols) conducted on Sprague-Dawley rats (Ref. 23). Based upon the foregoing result, FDA concludes that olestra is not genotoxic.

C. Animal Toxicity Studies

1. Teratogenicity Studies

The teratogenic potential of olestra was evaluated in studies conducted in the rat and rabbit. These studies establish that olestra was not teratogenic when fed during organogenesis in either species. Olestra was also not teratogenic nor did it affect reproduction in a multi-generation rat reproduction/teratology study.

Olestra was fed to rats (10/group) at 3.2 percent, 6.4 percent, or 12 percent of the diet beginning on the 6th day of pregnancy. Dams were sacrificed on days 13 and 20 of pregnancy, and the fetuses examined for abnormalities. The uterine contents of rats killed on day 13 of pregnancy were evaluated for

implantation, resorption sites, and the number of corpora lutea. The fetuses of the dams sacrificed on day 20 were removed and corpora lutea counted; the pups were sacrificed and evaluated for anomalies. One-third of the fetuses were cleared and stained for study of the skeleton, and two-thirds were sectioned for study of the soft tissues. This study provided no evidence that olestra is teratogenic or embryotoxic (Ref. 24).

In a rabbit teratology study, heated olestra was administered via gavage at doses representing 1 percent, 5 percent, and 10 percent of the diet during the critical stages of gestation (days 6 to 19); control animals were dosed with distilled water. Dams were sacrificed on day 30 of pregnancy and the fetuses examined for abnormalities. This study provided no evidence that olestra was teratogenic (Ref. 25).

For the multi-generation study, weanling rats were maintained on diets containing 0 percent, 1 percent, 5 percent, or 10 percent olestra for a 91-day growth period. The mid- and high-dose diets were supplemented with vitamin A (2.5 times the National Research Council (NRC) requirements¹⁰) and vitamin E (five times the NRC requirements), in order to compensate for the reduced absorption of these nutrients in the presence of olestra. At the end of 91 days, F₀ dams were mated for a reproduction (F_{1A}) phase and then were mated again for a teratology (F_{1B}) phase. After the growth period, the F_{1A} offspring were mated for the F_{2A} and F_{2B} generations. Olestra had no effect on mating, conception, embryonic development, fetal and postnatal viability, or postnatal growth in either generation (Ref. 24).

2. Subchronic and Chronic Feeding Studies

Early feeding studies in rats with unheated olestra at levels of 4 percent, 8 percent, or 15 percent of the diet for 28 or 91 days resulted in no deaths, no decrease in the absorption of triglycerides or protein, no differences in urine or blood chemistry, hematology, or gross or microscopic histopathology. These studies are not addressed further.

a. *Ninety-Day subchronic feeding study in rats.* The petitioner conducted two subchronic toxicity studies in rats. The first subchronic olestra feeding study in rats showed no adverse effects but used unheated olestra. Therefore, the petitioner, conducted a second 90-day toxicity study in rats using olestra

⁹Incomplete collection of fecal material from support screens, sides and bottoms of cages, and fur of animals for male guinea pigs resulted in lower radiolabel recovery (88.1 percent) and greater variability in results than for female guinea pigs.

¹⁰NRC requirements are actually recommendations set at levels close to the amount required for good health in the subject animals.

that had been heat abused to a degree exceeding that likely to occur during the preparation of savory snacks.

Specifically, olestra that had been heated for 7 days at 190 °C (representing an extreme heating condition) was fed to 6 groups of 40 rats each (20 rats per sex) at 0 percent, 0 percent, 1 percent, 5 percent, 10 percent, and 0 percent in rodent chow ad libitum for 90 days. Groups I and II were chow controls while Group VI control rats were maintained on a diet that contained 10 percent previously heated triglyceride. Diets for groups II-V were supplemented with vitamins A, D, and K (five times the NRC requirement); vitamin E was added to these four diets at 8.0 times, 0.8 times, 4.0 times, and 8.0 times the NRC recommended levels, respectively.

The study included twice-daily observations and weekly physical examinations. Body weight, body weight changes, food consumption, and olestra intake were determined weekly. Ophthalmoscopic examinations were performed pretest and at study termination. Clinical chemistry, hematology, and urinalysis parameters were measured at study termination on 10 animals/sex/group.

Complete gross postmortem examinations were performed on all animals at study termination. The brain, adrenals, ovaries, testes (with epididymides), kidneys, and liver were removed, weighed, and organ-to-body-weight and organ-to-brain-weight ratios were calculated. A full complement of tissues was examined histopathologically from all animals in Groups I, II, V, and VI surviving to study termination, and any animals in Groups III and IV dying unscheduled deaths. Lungs, liver, kidneys, and gross lesions were evaluated from Group III and IV animals surviving to study termination.

Survival, physical condition, body weight, food consumption, feed efficiency, organ weight, organ-to-body weight ratios, hematologic parameters, and histomorphology were evaluated. Olestra fed rats compensated for the decrease in caloric intake due to olestra having zero calories by consuming more food than control rats. No adverse treatment-related effects were observed. These results establish that heated olestra is not-toxic when fed to rats at levels as high as 10 percent of their diet for a period of 90 days (Ref. 26).

b. *Two-year carcinogenicity studies in rats.* Two 2-year carcinogenicity studies of olestra were conducted in rats. In the first study, Fischer 344 rats, 70 per sex per group, were fed olestra at levels of 0 percent, 1 percent, 5 percent, or 9 percent of the diet for 2 years with interim sacrifices at 12 and 18 months.

In the second study, Fischer 344 rats, 50 males and 73 females per group, were fed olestra at 0 percent or 9 percent of the diet for 2 years with an interim sacrifice at 12 months. In both studies, diets were supplemented with five times the NRC recommended levels of vitamins A, D, E, and K, to offset the reduced absorption of fat-soluble vitamins in the presence of olestra. The diets in both studies also contained 2 percent fully hydrogenated palm oil to control passive oil loss (anal leakage). The studies included twice-daily observations, and weekly physical examinations. Body weight, body weight changes, food consumption, and olestra intake were determined weekly for the first 12 weeks and monthly thereafter. Feed efficiency was determined during the first 12 weeks. Ophthalmoscopic examinations were conducted pretest, and at scheduled sacrifice. Clinical chemistry, hematology, and urinalysis parameters were measured at 12 and 24 months. Complete gross postmortem examinations were performed on all animals. Selected organs were removed, weighed, and organ-to-body-weight and organ-to-brain-weight ratios were calculated for all rats surviving to scheduled sacrifice periods. Liver samples were taken from rats in the 9 percent olestra groups from both studies for analysis of olestra.

Histopathological evaluations were conducted on a full complement of tissues from animals in the control and 9 percent olestra groups from both studies. Liver, pituitary gland, gross lesions, and tissue masses were evaluated for all animals on study. The duodenum, jejunum, ileum, cecum, and colon were examined for all animals sacrificed at 12, 18, and 24 months.

Rats compensated for the caloric dilution of olestra by consuming more food than was consumed by the controls. Olestra had no effect on ophthalmology, organ weight, organ-to-body- and organ-to-brain-weight ratios, clinical chemistry, hematology, or urinalysis parameters. There was no evidence that intact olestra accumulated in the liver tissue of rats fed 9 percent olestra for 2 years.

There were no treatment-related adverse effects on growth, longevity, or general health, and there were no treatment-related neoplastic responses or evidence of chronic toxicity in either study. In the first study, there were four instances in which differences between treated groups and controls required FDA pathologists to assess whether the effect was treatment-related: male survival, incidence of pituitary adenoma (males and females), mononuclear cell

leukemia (males), and basophilic liver foci (females). FDA pathologists also evaluated the following differences in incidence in the second chronic rat study: Incidence of pituitary cysts (males), mineralization of the renal cortex and bile duct hyperplasia, and basophilic liver foci in females. The differences observed between treated groups and controls in both chronic studies are marginal.

Pituitary adenomas are very common spontaneous tumors in Fischer-344 rats with a tendency for highly variable background incidences (Ref. 27). The increased incidence of pituitary adenoma in both sexes in the first chronic rat study represent expected variations in spontaneous background incidences. Thus, FDA concluded that there was no association of the pituitary adenomas with olestra treatment.

Likewise, FDA concludes that there was no association between the incidence of leukemia in male rats and treatment with olestra for several reasons. First, the possible association is not supported by the results of the second study in which there was no comparable development of leukemia. Second, the incidences in the first study, particularly the control group, are unusually low compared to historical data from the National Toxicology Program (NTP) data base and compared to the results of the second study (Ref. 27). Third, mononuclear cell leukemia in Fischer-344 rats is a common spontaneous disease in old age with considerable tendency for background variation (Ref. 27). Therefore, such differences in incidence are not unusual but rather are expected from the normal variation of spontaneous tumor incidences.

In the first rat study, there was an increase in the number of olestra-treated female rats with basophilic liver foci at the 1 year interim sacrifice without any clear increase in the severity of this lesion at the end of 2 years. However, female groups including the terminal sacrificed animals as well as the unscheduled deaths, demonstrated no clear increase in the incidence of basophilic liver foci with olestra treatment. The same phenomenon of early occurrence of basophilic liver foci in olestra-fed female rats was observed in the second study. In both studies, the basophilic foci in the control and treated rats were similar morphologically.

In presentations to the Olestra Working Group and the FAC, and in its White Paper, CSPI expressed concern about the significantly higher incidence of basophilic liver foci at the end of 12 months, although CSPI acknowledged

that the difference between control and treatment groups disappeared by 24 months. CSPI asserted that, although 24 months is the majority of a rat's lifetime, the study should have been carried out for the rats' entire lifetime because it is possible that the foci might have progressed to cancer. CSPI also recommended that an expert Committee (such as NTP review) the findings.¹¹

Based upon an examination of all of the data in both studies, FDA pathologists concluded that these findings represented normal biological variability in 24-month-old rats and were not related to olestra ingestion for the following reasons. First, the findings lacked a dose-response effect and were not observed in both male and female rats in both chronic studies (Refs. 28 and 29). Second, the spontaneous occurrence of basophilic liver foci is frequent and variable in aging Fischer-344 rats (Refs. 30 and 31) and the incidence can reach 100 percent at 2 years (Refs. 32 and 33). Further, the majority of foci do not become neoplasms. Third, the most recent studies indicate that hepatocarcinogens induce more morphologically variable foci than those observed spontaneously (Refs. 30, 34, and 35). Thus, the early occurrence and morphological similarity of the basophilic liver foci in the control and the olestra-treated female rats are not indicative of hepatocarcinogenic potential for olestra in the rat.

Dr. John Doull, a clinical toxicologist and temporary member of the FAC, agreed with the FDA evaluation that the basophilic liver foci findings are not significant and that basophilic liver foci are not predictors of carcinogenicity.¹² Dr. Eugene McConnell,¹³ a presenter to the Olestra Working Group, agreed with Dr. Doull, and noted that the control groups in both chronic rat studies exhibited abnormally low incidences of foci compared to the foci rate historically observed in rats at these ages; he postulated that the addition of vitamins to the feed in both chronic rat studies may have caused this low foci occurrence rate in the control groups. The rate of foci in the treatment groups was compared to historical control rates

and was slightly lower than historical controls.

Dr. McConnell also noted that the slides were reviewed by (1) Board-certified pathologists in the contractor lab performing the study (2) board-certified pathologists employed by the petitioner, (3) an independent pathology laboratory, (4) a group of internationally known pathologists, and (5) FDA pathologists. All of the reviewers came to the same conclusion that none of the data suggests evidence of carcinogenic activity in either species.

Therefore, in light of the discussion of the Olestra Working Group and the presentations of CSPI and Dr. McConnell, FDA confirms its conclusion that there was no olestra-related toxicity or carcinogenicity in these studies.

c. Two-year chronic toxicity and carcinogenicity studies in mice. Two 2-year mouse studies were conducted to evaluate the chronic toxicity and carcinogenicity potential of olestra. The first mouse study compared three levels of olestra (2.5 percent, 5.0 percent, and 10.0 percent of the daily diet) to two control groups. Olestra was supplemented with vitamins A, D, E, and K to account for amounts which potentially would be lost due to the high levels of olestra fed. One of the two control groups provided basal levels of fat-soluble vitamins; the second control group was fed supplemental vitamins A, D, E, and K. To confirm the findings, a second mouse study was conducted with a chow-fed control group and a 10 percent olestra group supplemented with vitamins A, D, E, and K.

One hundred mice of each sex were placed in a total of seven groups in the two studies. (The first mouse study had five groups and the second mouse study had two groups.) Fifty animals/sex/group were allocated to the carcinogenicity portions of each study, and all survivors sacrificed at 24 months. Fifteen animals/sex/group were allocated to the toxicity portion of each study, and all were sacrificed at 12 months. Finally, sentinel animals (35/sex/group) were included, and seven/sex/group were sacrificed at one, two, three, six, and nine months for assessment of hepatic vitamin A and E status.

The studies included daily observations and weekly examinations. Body weights and food consumption were determined weekly. Ophthalmoscopic examinations were conducted pretest, and at scheduled sacrifice. Clinical chemistry and hematology data, gross necropsy observations, and organ weights were collected on animals sacrificed at 12

and 24 months in both studies.

Complete gross postmortem examinations were performed on all animals. Selected organs were removed, weighed, and organ-to-body-weight and organ-to-brain-weight ratios were calculated for all mice surviving to scheduled necropsy. Histopathological evaluations were conducted on a full complement of tissues from all control and treated animals assigned to the carcinogenicity portion of both chronic studies.

At the end of 24 months, there were no treatment-related effects in either study as determined by mortality, body weights, clinical pathology, gross necropsy findings, organ weights, hematology, clinical chemistries, or histopathology of a comprehensive collection of tissues.

In the first study, there was an increase in the incidence of lung carcinomas and combined lung carcinomas and adenomas in mid-dose olestra-fed male mice but not in any other group. This association of olestra consumption with lung tumors in male mice in the first mouse study was not confirmed by the results of the second mouse study. Lung adenomas and carcinomas are common lesions in Swiss CD-1 mice and tend to have a high and variable background rate (Refs. 36 and 37). The increased combined incidence of lung adenomas or carcinomas in male mice in the first mouse study (Ref. 38) cannot credibly be associated with olestra consumption, and represents expected variation in spontaneous incidence of lung tumors in Swiss CD-1 mice (Ref. 37). Thus, upon review, FDA pathologists concluded that this was not an olestra-related effect because there was no other lung pathology, there was no relation between olestra exposure and time-to-onset of the tumors, the incidence of the tumors was typical for mice of this age and sex based on historical data, and there was no association between olestra exposure and lung tumors in other chronic rodent studies (Ref. 39).

At the Olestra Working Group meeting, CSPI expressed concern about the increase in the incidence of combined lung carcinomas and adenomas in the mid-dose male mice.¹⁴ Dr. Doull noted that an analysis of the data for CSPI by Dr. Renata Kimbrough (Ref. 3) essentially agreed with FDA's conclusions. Specifically, although the mid-dose male mice in the first chronic study had an increased incidence in lung tumors, there was no dose response, the increased incidence of

¹⁴ Transcript, vol. 2, p. 136. Discussion of this concern also appears in the White Paper (Ref. 3)

¹¹ Transcript, vol. 2, p. 135.

¹² Dr. John Doull, Kansas University Medical Center Transcript vol. 2, p. 113.

¹³ Dr. Eugene McConnell, D.V.M., D.V.B.T was chief of the Pathology Branch and Director of the Division of Toxicology Research and Testing for the NTP. Dr. McConnell is a diplomate of the American College of Veterinary Pathologists and the American Board of Toxicology. Dr. McConnell consulted for the petitioner and presented at its request. Transcript, vol. 2, p. 147.

lung tumors was not repeated in the second study, and the lung tumor incidence rate was within the range of that observed in the NTP program in lung tumors.¹⁵ Dr. Doull further stated his view that this data leads to the conclusion that olestra is not carcinogenic.¹⁶

Therefore, in light of the discussion before the Olestra Working Group, FDA confirms its conclusion that the lung tumors in this study were not an olestra-related effect.

d. *Dog feeding studies.* The petitioner conducted two short-term feeding studies of olestra in beagle dogs. Olestra was fed at a level of 4 percent of the diet for 28 days or 15 percent of the diet for 30 days. Histological examination of several tissues, including the liver, revealed no abnormalities. The olestra-fed animals consumed more food because of the caloric dilution of the diet by olestra, but there was no difference in body weight gain. In a third study, olestra was fed to dogs at 10 percent of the diet for 91 days. No adverse effects were noted among the treated animals in terms of histopathology, hematology, or blood chemistries.

The petitioner also conducted a 20 month chronic feeding study in five male and five female beagle dogs. The animals were fed a chow diet with 0 percent, 5 percent, or 10 percent olestra. Olestra diets were supplemented by adding 1.5 times the NRC recommended dietary level of vitamin A and 2.5 times the NRC recommended dietary level of vitamin E to the low-dose (5 percent) diet. The high-dose (10 percent) diet received 3.0 times the NRC recommended dietary level of vitamin A and 5.0 times the NRC recommended dietary level of vitamin E. The study included twice-daily observations, as well as weekly physical examinations, and determination of growth and food intake. Hematology, clinical chemistry, serum vitamin A and E concentrations, and ophthalmoscopic status were evaluated after 12 and 20 months of treatment.

At the end of the study, all dogs were sacrificed and their tissues subjected to complete gross and microscopic examination. Organ weights and organ-to-body-weight ratios were determined for brain, adrenals, kidney, liver, ovary, testes, and thyroid/parathyroid. A complete set of tissues from all animals was examined by light microscopy.

No evidence of toxicity was observed, and all animals survived the entire length of the study. Growth, as

measured by body weight gain, was not affected by olestra ingestion. Food consumption was increased to offset the caloric dilution of the diet by olestra. No biologically significant changes were seen in any of the hematological or biochemical parameters measured. Histopathology revealed no olestra-related effects (Ref. 40).

D. Toxicology Summary

In summary, the results of the toxicological tests submitted by the petitioner support the conclusion that olestra is not toxic or carcinogenic, not genotoxic, and not teratogenic. Heating olestra, as would occur in the commercial preparation of savory snacks made using olestra, does not increase the absorption of the additive or affect its toxicity.

IV. Effect of Olestra on Absorption of Drugs

Because olestra is a fat-like material that has been shown to alter the absorption of some lipophilic nutrients, FDA considered whether the bioavailability of lipophilic drugs might also be affected by consumption of olestra. To address this question, the petitioner carried out a series of studies in both animals and humans. The petitioner established the following criteria to use in deciding which drugs to study:

- (1) The drugs should have wide spread use by the general population.
- (2) The absorption, metabolism and elimination of the drugs should be similar in rats and humans.
- (3) The drugs should cover a wide range of solubilities, from water-soluble to fat-soluble.
- (4) The drugs should include representatives of those used to prevent life-threatening situations.
- (5) Most of the drugs should have partition coefficient data already available.
- (6) The drugs must be commercially available in radiolabeled form.

Using these criteria, the petitioner selected the following drugs for use in two rat studies: aspirin, diazepam, propranolol, and the oral contraceptives ethinyl estradiol and norethindrone. Because results of studies in rats are not definitive predictors of human conditions (Ref. 41), the petitioner also sponsored two human clinical trials to study the olestra/drug issue. In the first of these clinical trials, propranolol, diazepam, norethindrone, and ethinyl estradiol were included; in the second clinical study, the oral contraceptive Lo/Ovral-28, containing norgestrel and ethinyl estradiol, was evaluated.

A. Effect of Olestra on the Absorption of Selected Lipophilic Drugs (EC-40)

The primary objective of this study was to determine whether olestra affects absorption of drugs relative to corn oil. This study was conducted in Sprague-Dawley derived male and female rats and had three separate experimental components. The olestra used was prepared from safflower oil, while corn oil served as the triglyceride control. Hydrogenated palm oil was added to both the olestra and control diets, to mimic the earlier proposed use of olestra in combination with convention oils.

In the first experiment, 20 male rats were fed either a control diet with 6 percent added corn oil or a similar diet but with 6 percent added olestra for 13 days; the test animals were then fasted, weighed, subdivided into four groups (five rats per group), and gavaged with slurries of either the control or olestra diets to which tritiated diazepam or tritiated propranolol had been added. In the second and third experiments, no initial acclimation period was used. In the second experiment, 20 female rats were fasted, weighed, divided into four groups (five rats per group), and gavaged with slurries of either control or olestra diets to which tritiated ethinyl estradiol or tritiated norethindrone had been added. In the third experiment, 10 male rats were fasted, weighed, divided into 2 groups (5 rats per group), and gavaged with slurries of either control or olestra diets to which C14-labeled acetylsalicylic acid (aspirin) had been added.

In all three experiments, serial blood and urine samples were taken over a 48-hour period after dosing. Fecal samples were also collected at 24-hour intervals. All samples collected were assayed for drug associated radioactivity, and the results evaluated for treatment related effects on drug absorption.

The five drugs studied in these experiments cover a range of lipophilicity, from nonlipophilic (aspirin) to strongly lipophilic (ethinyl estradiol and norethindrone). The petitioner concluded that co-administration of the drugs with olestra did not affect the absorption of any of the drugs tested when compared with corn oil.

FDA concludes that the petitioner's choice of drugs, which were selected based on physico-chemical properties, was reasonable. Further, the study correctly focused on rate and extent of absorption, both of which are important factors in the overall evaluation of human drug absorption. Although the use of total radioactivity measurements,

¹⁵ Transcript, vol. 2, p. 111.

¹⁶ Transcript, vol. 4, p. 113.

as was done in this study, is not a comprehensive evaluation taken alone, the study design is adequate as a first exploration of olestra/drug interactions (Ref. 41).

B. Effect of Olestra on the Absorption of Selected Lipophilic Drugs (EC-41)

The objective of this study was to determine whether a single dose of olestra caused an alteration of the absorption or excretion profiles of lipophilic drugs that were orally administered prior to the olestra. This study was conducted with Sprague-Dawley derived male rats. After a 4 day acclimation period all rats were fasted, weighed, divided into treatment groups (four/group), and gavaged with either tritiated diazepam, tritiated propranolol, or C¹⁴-labeled aspirin (acetylsalicylic acid). Following each drug dosing, rats were gavaged with one ml of either water, corn oil, or olestra. Additional rats dosed with propranolol and aspirin received an olestra emulsion (one of the

projected final forms for initial marketing of olestra).

Serial blood and urine samples were collected over a 48-hour period, postdosing, while fecal samples were obtained at 24-hour intervals. Forty-eight hours after dosing all rats were sacrificed, their gastrointestinal tracts removed and the contents collected, selected organs excised, and carcasses frozen in liquid nitrogen and ground. All samples were assayed for drug-associated radioactivity. Results of the radioactivity assays were evaluated for treatment-related effects.

The petitioner concluded that there were no differences in rate or extent of absorption of diazepam, propranolol, or acetylsalicylic acid when administered before olestra consumption compared with administration prior to water consumption. Drug excretion profiles were also not affected by olestra. Corn oil (a control substance) reduced the rate of absorption of all drugs studied. The petitioner concludes that these results demonstrate that olestra would

not be expected to affect the acute absorption of drugs such as diazepam, propranolol or aspirin, and thus are consistent with EC-40. FDA concludes that, as with EC-40, the design and conduct of this investigation are adequate as a further exploratory study of the potential for olestra/drug interactions (Ref. 41).

C. Effect of Olestra on Drug Bioavailability (EC-42)

The objective of this clinical trial, consisting of 3 experiments, was to determine whether olestra consumption alters drug bioavailability in humans when used as a substitute for absorbable dietary fat. Subjects were assigned to test one drug in a crossover design so that bioavailability of the drug was evaluated with single doses of olestra, water, or a triglyceride (partially hydrogenated soybean oil) placebo treatment. Table 2 provides basic information on subject and treatment assignment.

TABLE 2.—SUBJECT AND TREATMENT ASSIGNMENT IN EC-42

Exp. No.	Subject No. male/female	Age Range (years)	Drug and treatment amount
1	5/3	27 to 47	Propranolol, 20 mg
2	4/4	20 to 40	Diazepam, 5 mg
3	0/10	not available	Norethindrone, 1 mg and Ethinyl estradiol, 0.07 mg

In each experiment, 18 g of olestra, 18 g of triglyceride, or six ounces of water were consumed following ingestion of the respective drug under study. Serial blood samples collected from all subjects were processed and the resulting serums frozen for subsequent drug analyses. The data on peak serum concentrations, times to peak, and areas under the concentration curves (AUC) were analyzed statistically for treatment effects.

Based on its analyses of the results from the three experiments, the petitioner concluded that there were no statistically significant differences in the absorption of the drugs administered with olestra, triglyceride placebo, or water as assessed by total area under the curve (AUC) and time to peak concentration data. The time to peak concentration values for diazepam were slightly longer with the triglyceride placebo than with olestra. There was wide, although not unexpected, between-patient variability. The petitioner concluded that a single dose of 18 g of olestra did not alter the bioavailability characteristics of orally administered propranolol, diazepam, or norethindrone/ethinyl estradiol when

compared to water or a triglyceride such as partially hydrogenated soybean oil.

FDA concludes that the design of this clinical study was excellent, and that the study may be used by itself, without any reliance on the two studies in rats, to assess olestra's potential for affecting absorption of lipophilic drugs. The results from EC-42 demonstrate that olestra does not interfere with the absorption of drugs when administered at the 18 g dose (Ref. 41).

D. Effect of Olestra on the Systemic Levels of Steroidal Hormones in Women Taking Oral Contraceptives (EC-51)

The objective of this clinical trial was to determine the effect, if any, of chronic olestra consumption (targeted at 20 g/d) on the absorption and efficacy of a low-dose oral contraceptive in normal women.

Thirty healthy, menstruating female subjects aged 20 to 38 years were assigned to two groups. A double-blind, placebo-controlled, crossover study design was used which covered two complete ovarian cycles. Subjects were instructed to begin taking the oral contraceptive Lo/Ovral-28 (0.30 mg norgestrel and 0.03 mg ethinyl

estradiol), 5 days before the onset of menstruation. One group of subjects received food items with triglyceride placebo, while the other group received similar food items containing a "mid-range" olestra formulation.

Daily intake of olestra was set at 18 g with one-third (6 g) of the daily dose being consumed at each meal. At the conclusion of the first 28-day cycle, the treatments were crossed over (placebo to olestra, olestra to placebo). All subjects were asked to take their oral contraceptive only in the morning and before the morning meal. Serum progesterone levels were determined at a baseline visit, 5 to 7 days after menstruation and twice weekly for the remainder of the ovarian cycles.

Serial blood samples were collected during each of the two ovarian cycles. These samples were then processed and the serums frozen for subsequent drug analysis. Results were evaluated for treatment effects by comparing AUC, maximum drug concentration, and time to maximum concentration data.

The petitioner concluded that there were no significant effects of consuming 18 g of olestra on the absorption of either norgestrel or ethinyl estradiol, the

two steroid components of Lo/Ovral-28. Serum progesterone levels in subjects in both the olestra and triglyceride placebo groups were found to remain in a range that would prevent ovulation, thereby providing evidence that oral contraceptive efficacy was not affected by olestra. The petitioner also stated that because the oral contraceptive used in this study contains the lowest amounts of two of the most lipophilic steroid hormones (norgestrel and ethinyl estradiol), the results from this study should prove valid for "all high-dose oral contraceptives having less lipophilic constituents." In addition, the petitioner believes that the data from EC-51 provide further support generally for the conclusion from other studies in animals and humans that olestra consumption does not alter the absorption of lipophilic drugs, and therefore, will not affect the efficacy of orally administered drugs.

FDA believes that this study is an excellent extension from single-dose olestra to chronic dosing, at least for the once-a-day situation. Further, in this study, there was no evidence that olestra would affect the efficacy of orally administered drugs (Ref. 41).

E. Summary

The petitioner has submitted two animal studies and two clinical studies assessing olestra's potential to alter drug absorption. Procter & Gamble believes that these studies demonstrate that olestra does not alter the absorption nor affect the efficacy of orally administered drugs.

Members of the Olestra Working Group were unanimous that, with respect to drugs, all the issues had been identified and there were sufficient data to address each issue.¹⁷ There was also nearly unanimous agreement that, with respect to drug interactions, there was no obstacle to approval and reasonable certainty of no harm from olestra consumption.¹⁸

During the Olestra Working Group and FAC meetings and in numerous comments to FDA, individuals have expressed concern about the effects of olestra on coumarin drugs (e.g., Coumadin or warfarin, Dicumarol, etc.) as well as other drugs. Dr. Ian Greaves, a specialist in environmental and occupational medicine,¹⁹ expressed concern about persons taking

anticoagulants such as coumarin drugs that antagonize Vitamin K. He asked how olestra would bind to coumarin and whether there would be difficulty in maintaining an anticoagulant status in people receiving coumarin who intermittently eat olestra-containing products. He stated that his experience with managing patients on anticoagulants is that some of them are very variable for no good reason, and he could easily foresee a patient becoming either overly anticoagulated or under-anticoagulated, depending on whether Vitamin K was being bound or whether the coumarin was being bound. Also, if a person taking coumarin happened to have an intra-cerebral bleed or bleed from his gastrointestinal tract and was also consuming olestra, he felt it would be difficult to know whether olestra had a role in the bleeding. Finally, he stated he was concerned about other fat-soluble drugs, particularly those that cross the blood-brain barrier such as anticonvulsants, psychotropic drugs, and antidepressants. Dr. Greaves's questions covered the concerns that were raised by other individuals.

FDA notes that the results concerning the hormonal preparations are extremely useful because these drugs represent extremely lipophilic substances and are substances that have a narrow therapeutic index in which a lowering of the absorbed concentration would be a concern. In addition, the drug, propranolol, is a compound that has very similar physical/chemical properties to Coumadin or sodium warfarin,²⁰ a drug about which FDA has received comments concerning olestra's effects. In response to a question by an FAC member, FDA noted that in the previous 5 years, there has been only one drug that FDA has reviewed that is more lipophilic than the hormone drugs tested in the human drug-interaction studies. That drug is a very specialized drug (Atovaquone), which is an anti-pneumocystis drug used in AIDS patients.²¹ Therefore, FDA expects that the results observed in the reviewed studies would be representative of nearly any drug on the market.

Regarding coumarin drugs specifically, FDA notes that the effects of a variety of meals (e.g., high-protein, high-carbohydrate, and high-fat) on absorption of sodium warfarin (Coumadin), the most commonly prescribed form of coumarin, were studied and no effect was seen in the total amount of sodium warfarin absorbed. Also, there was no effect on absorption when Coumadin was

consumed with high-fat or high-protein meals. When consumed with a high-carbohydrate meal, Coumadin was more slowly absorbed, but only for the first hour after ingestion of the drug²² (Ref. 42). Therefore, FDA would not expect significant effects on Coumadin absorption from olestra consumption.

Olestra's effects on vitamin K are discussed in the Nutritional Studies section below.

FDA concludes that the test compounds studied adequately represent the range of physical properties of drugs marketed for human use, and that the magnitude of olestra's effects on drug absorption were minimal, when compared to the effects normally encountered in drug-food interaction studies. FDA further concludes, considering the results of all four studies, the discussions during the Olestra Working Group and FAC meetings, comments received, and information in the literature, that there is no evidence that consumption of olestra would significantly influence the rate or extent of absorption of drugs (including Coumadin drugs).

V. Nutritional Studies

A. Issues Associated with Olestra

The petitioner has hypothesized that olestra interferes with the absorption of fat-soluble nutrients when the nutrients partition into olestra in the GI tract. When this happens, the portion of the nutrients that is present in the olestra phase is unavailable to the micelle-mediated transport system and, rather than being absorbed by the body, is excreted in the feces along with the olestra.

Neither existing olestra data nor the partitioning mechanism suggest that water-soluble nutrients would be affected by olestra. However, certain water-soluble nutrients such as folate and vitamin B12 (hard-to-absorb nutrients) are absorbed in multi-step processes. The multi-step nature of the processes might allow the opportunity for olestra to interfere with key steps in the processes, such as binding or cleavage reactions. Calcium, zinc, and iron are limited in the U.S. diet; thus, any effect on their absorption might increase the risk of nutritional inadequacy. In addition, the nutrients would be present in the diet at levels that are small, on a mass basis, relative to the amount of olestra. Thus, if olestra has an effect on water-soluble nutrients, these five nutrients (folate, vitamin B₁₂, calcium, zinc, and iron) would be the most important water-soluble nutrients

¹⁷ Transcript, vol. 4, p. 50.

¹⁸ Transcript, vol. 4, p. 50.

¹⁹ Dr. Ian Greaves is an Associate Professor and Deputy Director, Minnesota Center for Environmental and Health Policy, University of Minnesota School of Public Health. Dr. Greaves presented at the request of CSPI. Transcript, vol. 2, p. 265.

²⁰ Transcript, vol. p. 124.

²¹ Transcript, vol. p. 124.

²² Transcript, vol. p. 119.

to monitor and the most likely to reflect adverse nutritional effects. Therefore, folate, vitamin B₁₂, calcium, zinc, and iron were chosen as representative markers for olestra's effects on the nutritional status of water-soluble nutrients.

The potential nutritional effects of olestra consumption were studied in both humans and animals. The pig was chosen as the appropriate animal model because it has a gastrointestinal tract similar to that of man; it is able to ingest, tolerate, and metabolize fat at a level comparable to that found in the human diet; and its vitamin stores and nutritional indices are responsive to dietary changes. Where possible, FDA has relied upon the results of human consumption studies as the primary determinants of olestra's safety, thereby avoiding the uncertainties raised by extrapolating from the pig to humans. Thus, FDA is relying primarily on the human studies to assess olestra's effects

on vitamins E, D, K, and B₁₂, and on folate and iron. There are certain nutrients, such as vitamin A, for which no noninvasive procedure can be used to assess status in humans. Therefore, FDA has relied upon the results of the pig studies for determining olestra's effects on vitamin A. In addition, there are certain advantages to studying olestra's nutritional status in pigs. The studies can be conducted over the major developmental and growth periods of the pig's life, dose levels higher than those in man can be studied, and invasive techniques can be used to measure nutrient stores in tissues (such as bone and liver). Therefore, results from the pig studies are valuable supportive information that expand upon the knowledge gained in the human studies.

To apply the results of the pig studies to humans, it is necessary to correlate the percent olestra fed in the pig diet to g/p/d olestra. Olestra's effects on

nutrients are caused by its physical presence in the gut. If nutrients dissolve into olestra, they will be carried out of the body with the olestra rather than being absorbed. The amount of olestra's effect depends on the amount of olestra present in the GI tract compared to other fats (as well as on the solubility of the vitamins in olestra). Thus, FDA has concluded that the most appropriate means for correlating olestra's effects in animals to humans is the percentage by weight of olestra in the diet. For a person eating about 2,000 calories/d, 10 g of olestra would be about 2.4 percent of the diet (Ref. 43).

B. Effects of Olestra on Fat-Soluble Vitamins

The effect of olestra on fat-soluble vitamins was assessed in five nutritional studies with humans and five studies with pigs, as summarized in Table 3.

TABLE 3.—SUMMARY OF STUDIES DESIGNED TO ASSESS NUTRITIONAL EFFECTS OF OLESTRA CONSUMPTION

Human Studies	Pig Studies
8-week clinical dose response (8-week DR)	26-week dose response and vitamin restoration (26-week DR/VR)
8-week clinical vitamin restoration (8-week VR)	39-week vitamin restoration (39-week VR)
6-week vitamin D/K status in free-living subjects (6-week vitamin D/K)	12-week dose response (12-week DR)
16-week vitamin E status in free-living subjects (16-week vitamin E)	12-week vitamin restoration (12-week VR)
14-day vitamin A/fat absorption (14-day vitamin A/fat)	4-week dietary context (4-week DC)

In evaluating olestra's nutritional effects, FDA believes that it is appropriate to rely primarily on the two 8-week clinical studies because in these studies, there was complete control of nutrient intake, they were well designed, and most nutritional parameters were monitored. Also, these two studies were performed recently using state-of-the-art analytical techniques and were designed taking into consideration findings from previous studies.

FDA believes that the 16-week vitamin E study, the 6-week vitamin D/K study, and the 14-day vitamin A/fat study are appropriately used to support the findings in the two 8-week studies. The results of these latter three studies do not weigh as heavily in the safety evaluation because of their limitations: the 16-week vitamin E and 6-week vitamin D/K studies were conducted in free-living subjects so that it was not possible to control completely or have more than imprecise knowledge of nutrient intake; the vitamin A/fat study investigated only olestra's effects on preformed vitamin A absorption and provides less information than the pig studies for assessing olestra's long-term

effects on vitamin A stores (which are derived from both preformed vitamin A and carotenoids).

Of the studies performed in the pig, FDA believes that it is appropriate to rely primarily on the results of the 26-week DR/VR and 39-week VR studies to assess olestra's nutritional effects because these studies were the longest term and were designed to confirm the results of the 12-week DR and 12-week VR studies. The 4-week DC study was more limited in scope and duration, and was intended to demonstrate how olestra's effects are modified by changes in dietary patterns.

1. Primary Human Studies

The petitioner performed two 8-week human studies, in both of which the entire diet of the subjects was controlled during the study. The first study was the 8-week DR study which was intended to determine the dose-response effect of olestra on the status of folate, zinc, iron, and vitamins A, E, D, K; on the absorption of vitamin B₁₂; and on the bioavailability of β -carotene and total carotenoids. The 8-week VR study was intended to determine the efficacy and safety of compensation with vitamins A,

E, and D, and to confirm the conclusions drawn in the 8-week DR study about the effects of olestra on vitamin K, zinc, and iron status, serum 25-hydroxyvitamin D₂ (25-OHD₂) concentration, carotenoid bioavailability, and vitamin B₁₂ absorption. These two studies are of similar design and the results are complementary.

a. Eight-week DR study design. The 8-week DR study was a parallel, double-blind, placebo-controlled study with controlled diets fed for 8 weeks. Subjects were normal, healthy, 18 to 44 year-old males and females. The study had four groups of 21 to 24 subjects per group (88 subjects total). Subjects were randomly assigned to treatment groups that were balanced with respect to age, sex, body mass index (BMI), serum α -tocopherol, and total serum carotenoid concentrations. Subjects were provided with all meals for 56 days.

The diets were formulated to provide about 15 percent of calories from protein, about 55 percent of calories from carbohydrate, and about 30 percent of calories from fat. The total digestible fat content was kept the same across the four treatment groups by adding

triglyceride, in the form of butter, margarine, or vegetable oil, into the diets to compensate for the amount of fat replaced by olestra in the olestra-containing foods. Therefore, the total amount of lipid (digestible fat plus olestra) increased with increasing olestra dose.

Olestra was added to food items (potato chips, muffins, biscuits, and cookies) by substituting olestra for triglyceride in recipes or in cooking oils. Because each meal contained olestra, or the corresponding placebo (triglyceride), this study design provided maximum opportunity for olestra to interfere with nutrient absorption.

The diets provided each subject with 80 percent to 120 percent of the RDA of folate, zinc, and vitamins A, D, E, and K. Calcium and iron intakes were not targeted to be within the 80 percent–120 percent RDA range, although they were controlled and kept consistent among the diets. Vitamin B₁₂ levels were allowed to exceed the 80 to 120 percent RDA range in order to maintain zinc and protein consumption at the target levels. In addition to the vitamin D in the diet, subjects were given 20 µg/day (two RDA) of vitamin D₂ as a supplement, one third of which was consumed with each meal.

The dosages of olestra were 0 (placebo), 8, 20, and 32 g/d. Body

weights were measured every week and the subjects were questioned daily about changes in their health, including GI symptoms. If a GI symptom was experienced, the subject completed a detailed questionnaire that asked about the type, severity, and duration of symptoms they experienced. (The monitoring and reporting methods for adverse experiences is discussed in section VI.B. of this document.) Table 4 summarizes the measurements that were made to assess the status of the various nutrients. Most parameters were measured at baseline (week 0) and at 2-week intervals throughout the 56-day study period.

TABLE 4.—MEASUREMENTS OF MICRONUTRIENT STATUS IN THE EIGHT WEEK DR STUDY

Nutrient	Measurements
Vitamin A	Serum retinol concentration ²³ , serum carotenoid concentration
Vitamin E	
Vitamin D	
Vitamin K	Serum concentration of 25-OHD ₂ , 25-hydroxyvitamin D ₃ (25-OHD ₃), and 1,25-dihydroxyvitamin D (1,25-(OH) ₂ D)
Folate	Serum phylloquinone concentration, urinary excretion of γ-carboxy glutamic acid, plasma concentration of des-carboxy prothrombin (PIVKA-II), plasma prothrombin concentration, and prothrombin time, and partial thromboplastin time
Vitamin B ₁₂	
Zinc	
	Serum and red blood cell folate concentration
	Schilling test, serum vitamin B ₁₂ , serum vitamin B ₁₂ metabolites
	Serum and urinary zinc concentrations

²³ Serum retinol concentration is the only practical measure of preformed vitamin A status that can be made in humans who have adequate liver stores. (Other measures require invasive tissue sampling, such as measurements of liver stores.)

b. Eight-week VR study design. The study design for the 8-week VR study was the same as that of the 8-week DR study, except for the following elements. The 8-week VR study had 6 groups, each containing 16 or 17 subjects (100 subjects total). The

measurements of micronutrient status in the 8-week VR study differed from those in Table 4 in that folate and zinc were not monitored while iron status was monitored by measuring serum ferritin and iron concentrations and total iron binding capacity. Unlike the 8-week DR

study, no vitamin D₂ supplement was consumed by the test subjects. Finally, in addition to the vitamins provided in the diet, graded levels of vitamins A, E, and D were provided, as described in Table 5.

TABLE 5.—VITAMIN DOSES EXPRESSED AS PER GRAM OF OLESTRA (µG) AND PER DAY (/D) FOR THE SIX TREATMENT GROUPS IN 8-WEEK VR STUDY

Treatment Group Olestra (g/d)	Vitamin A		Vitamin E		Vitamin D ₂	
	µg/g	µg/d	mg/g	mg/d	µg/g	µg/d
0 (placebo)	0	0	0	0	0	0
8	83	664	2.5	20	0	0
20	33	660	1.5	30	0.20	4
20	83	1660	2.5	50	0	0
20	132	2640	3.5	70	0.80	16
32	83	2656	2.5	80	0	0

c. Results and conclusions from primary human studies.—i. Vitamin A. In the human diet, there are two sources of dietary vitamin A, preformed vitamin A (retinyl esters) and carotenoids such as β-carotene that are converted in the body into vitamin A (provitamin A carotenoids). Partitioning of either of these sources of vitamin A into olestra

could affect vitamin A levels in the body.

The petitioner concluded that there was no effect of olestra in either of the two 8-week studies on the serum concentration of retinol. This result was not unexpected because serum retinol concentrations are relatively stable and not subject to significant change except under conditions of prolonged and

inadequate vitamin A intake. Only under such extreme conditions would changes in liver vitamin A storage be reflected by changes in serum retinol. Thus, the petitioner concluded, and FDA agrees, that to establish the effect of olestra on vitamin A status in humans, data on vitamin A liver stores collected in the pig studies and data on the postprandial absorption of vitamin

A in man must be considered. Those data are discussed in sections V.B.3.c.i. and V.B.2.c. of this document.

ii. Vitamin E. The petitioner evaluated the effect of olestra on vitamin E status and found that there was a highly significant trend in decreased serum levels of vitamin E with increasing olestra dose in the 8-week DR study, an effect evident by day 14 of the study. Serum vitamin E was reduced by 6 percent, 17 percent, and 20 percent compared to control levels when olestra was consumed at 8, 20, and 32 g/d respectively in every meal. The maximum effect was obtained between 2 and 4 weeks.

The petitioner calculated, based on the results of the 8-week VR study, that the effects on tissue concentrations of vitamin E were offset by the addition of 2.07 mg of vitamin E (d- α -tocopheryl acetate) per g olestra. This level is equivalent to 1.9 mg α -tocopherol equivalents/g olestra and 0.94 RDA of vitamin E per 1 oz serving of savory snacks containing 10 g of olestra.

FDA agrees that 1.9 mg of α -tocopherol equivalents/g olestra adequately restored serum vitamin E levels in this study, as indicated in the data adjusted for baseline serum vitamin E levels²⁴ (Ref. 44). FDA finds that this study adequately controlled vitamin E consumption, analyzed appropriately for vitamin E levels, and was of sufficient duration to observe olestra's effect, because the effect had reached a plateau after a few weeks into the study (Ref. 43). Therefore, FDA agrees that compensation for olestra's effects on vitamin E can be calculated from the results of this study, and further agrees that 1.9 mg of α -tocopherol equivalents per g of olestra is the appropriate compensation level.

iii. Vitamin D. In the human diet, there are two sources of vitamin D, dietary (vitamin D₂) and endogenous (vitamin D₃) produced in the body via sunlight-catalyzed dermal synthesis. The nature of the dose-response effect of olestra on dietary vitamin D₂ was determined by measuring serum levels of 25-OHD₂, which is derived only from dietary vitamin D. Serum levels of 25-OHD₃ (from dermally synthesized vitamin D₃), 1,25-(OH)₂D, and 25-OHD were also measured to assess olestra's effects on total vitamin D status. The serum concentration of 25-OHD reflects total vitamin D status.

The petitioner found that there was an olestra treatment effect in the 8-week DR study on the serum concentration of 25-OHD₂. At the end of the study, the reductions in 25-OHD₂ were 23 percent, 13 percent, and 27 percent for 8, 20, and 32 g olestra/d, respectively, relative to control. The effect had levelled off within 4 weeks. There was no effect on serum 25-OHD₃ or 1,25-(OH)₂D. In this study, the diet contributed 55 to 68 percent to total vitamin D status (the remainder coming from sunlight). The amount supplied by the diet was relatively high because of excess vitamin D₂ supplied by the dietary supplement.

Although the subjects in the 8-week VR study did not receive supplements (the diet contributed 12 to 20 percent of total vitamin D), the reductions in 25-OHD₂ in the 8-week VR study were similar to those observed in the 8-week DR study: 22 percent, 29 percent, and 22 percent for 8, 20, and 32 g olestra/day, respectively, relative to control. The reductions in serum total 25-OHD were less compared to the reductions in the 8-week DR study because a larger fraction of the total vitamin D was endogenous. The petitioner concluded that olestra's effect on serum vitamin D₂ in the 8-week VR study could be offset by adding 0.07 times the RDA of vitamin D₂ per 1 oz serving of savory snack containing 10 g olestra (equivalent to .07 μ g/g olestra or 2.7 IU). The petitioner further concluded that olestra's effect on vitamin D status is not nutritionally significant because the effect is relatively small (on the order of a few percent in the 18-week VR study) and sunlight synthesis is a more important contributor to total vitamin D levels.

FDA agrees with the petitioner that olestra reduced serum vitamin D in both studies. Because the effect of olestra on serum vitamin D₂ levels had levelled off within the first 4 weeks of the study, FDA considers the studies of sufficient length to assess olestra's effects (Ref. 43). However, it is difficult to quantify olestra's effect because of confounding factors, such as the lack of a strong relationship between dose and reductions in 25-OHD₂ in both studies. In addition, the effect of olestra on serum total 25-OHD levels is difficult to quantify in the 8-week VR study because total serum 25-OHD levels were falling in the control group as well as the treated group during the study. (For example, total serum 25-OHD levels in the group not consuming olestra decreased 30 percent over the course of the study.) Compensation of two of the 20 g/d olestra groups with 0.2 and 0.8 μ g vitamin D₂/g olestra reduced the

decrease in total serum 25-OHD (which was due to both olestra and test diet effects). At the 0.2 μ g/g olestra supplementation level, the decrease in total 25-OHD was slightly less than in the group not consuming olestra (26.8 percent vs. 30 percent respectively). With the higher level of compensation (0.8 μ g/g olestra) the decrease in 25-OHD was about one-half that of the group not consuming olestra (15.6 vs. 30) (Ref. 45).

Although FDA believes that the variability of the data and the "on diet" effects on vitamin D status make quantitation of the magnitude of olestra's effects difficult, the agency concludes that the 8-week VR study can be used to estimate olestra's effects on vitamin D because dietary vitamin D₂ consumption was not excessive and the effect of olestra had levelled off within 4 weeks. FDA concludes that these results show that 0.2 μ g vitamin D₂/g olestra adequately compensated for olestra's effects on vitamin D status in the 8-week VR study (Ref. 45).

iv. Vitamin K. The petitioner found that in the 8-week DR study, olestra caused a dose-response decrease in serum phylloquinone (vitamin K₁) concentration that levelled out within 2 weeks. Eight, 20, and 32 g/d olestra reduced serum phylloquinone by 36 percent, 40 percent, and 47 percent, respectively. There was no effect of olestra on the status of vitamin K as measured by the plasma concentration of des-carboxylated prothrombin (PIVKA-II), urinary excretion of γ -carboxyglutamic acid (urinary Gla), and plasma prothrombin concentration, which are all measures of functional activity of vitamin K. Prothrombin time (PT) and partial thromboplastin time (PTT), the normal measures of clinical vitamin K status, were also not affected by olestra intake. The 8-week VR study showed similar results. FDA agrees with the petitioner's findings in both studies.

The petitioner concluded that the lack of any change in vitamin K functional activity indicates that the decrease in serum phylloquinone concentration does not represent a significant reduction in vitamin K status. FDA notes that, although olestra did not demonstrate any effect on the vitamin K-related functional parameters (i.e., urinary excretion of γ -carboxy glutamic acid, plasma concentration of des-carboxy prothrombin (PIVKA-II), plasma prothrombin concentration, and clotting times), the length of the study was insufficient to rule out possible effects on these vitamin K-related functional parameters after longer term consumption of olestra. Also, while serum levels in the studies after 56 days

²⁴ In controlled diet studies such as this, the controlled diet is often better in many respects than the free-living diet of the subjects, thus it is not unusual that the baseline vitamin E levels were lower than controlled-diet levels. Therefore, adjustment for baseline levels is appropriate.

can be considered to be only marginally reduced, when compared to true deficiency levels, the potential remains for continued decrease with long-term olestra consumption.

To calculate the level of vitamin K that would compensate for the reduction of serum vitamin K levels caused by olestra consumption, the petitioner relied upon the fact that serum vitamin K levels closely reflect the most recent (within 24 hours) intake of vitamin K. (Vitamin K has a half-life in serum of approximately 2 hours.) In the 8-week DR study, a 6 day rotating menu provided different vitamin K intakes for each day. As a result, the level of vitamin K on the days before each biweekly blood draw varied.²⁵ The serum level of vitamin K that would result from consumption of 1 RDA (80 µg) of vitamin K in the absence of olestra was obtained from the control group measurements. The compensation level was calculated as the amount of vitamin K needed in the presence of olestra to maintain the serum vitamin K concentration at the control level. This calculation yields compensation levels of 31 µg vitamin K in the 8 g/d group (4 µg/g olestra), 68 µg vitamin K in the 20 g/d group (3.2 µg/g olestra), and 82 µg vitamin K in the 32 g/d group (2.6 µg/g olestra). The petitioner averaged these three results to yield an estimated compensation level of 3.3 µg/g olestra.

FDA concludes that the response of serum vitamin K to the previous day's dietary intake is a reasonable, though imprecise, indicator of olestra's effects on serum vitamin K levels. Thus, FDA concludes that the petitioner's calculation provides only an estimate of appropriate compensation levels. FDA's conclusion regarding the appropriate compensation level for vitamin K is addressed in section V.B.4.e. of this document.

v. Carotenoids. In the 8-week DR study, the petitioner found that carotenoid bioavailability as measured by serum β-carotene and total carotenoid concentrations fell markedly with eight g/d olestra consumption although higher levels of olestra consumption did not cause a much larger decrease. At an olestra intake of 8 or 20 g/d, there was about a 60 percent reduction in serum β-carotene within the first 4 weeks and there was essentially no further decline for the remainder of the study. Olestra's effect on total serum carotenoids was of a similar magnitude. These results were

confirmed in the 8-week VR study. FDA's conclusions regarding olestra's effects on carotenoids are addressed in section V.B.4.f. of this document.

2. Other Human Studies

a. Six-week vitamin D/K study. The 6-week vitamin D/K study was a double-blind, placebo-controlled, parallel design using 221 normal, healthy, free-living subjects. The objective of this study was to assess the status of vitamins D and K in subjects consuming 20 g/d olestra. Subjects were randomly assigned to treatment groups and balanced with respect to age, sex, and body mass index (BMI). Subjects consumed a total of 20 g olestra or the corresponding triglyceride placebo per day in cookies eaten at each meal. Subjects consumed self-selected diets with an upper limit of 7 glasses of milk per day. Daily food frequency records were used to estimate phyloquinone intake. The diet was supplemented with 20 µg (800 IU) ergocalciferol (vitamin D₂), taken in capsule form with the morning meal. The study was conducted from February through April to lessen sunlight effects on vitamin D status. Vitamin K status was assessed by monitoring serum phyloquinone (vitamin K₁), serum Simplastin®/Ecarin® assay (S/E) (a measure of functional prothrombin in blood), and prothrombin (PT) and partial thromboplastin times (PTT). Vitamin D status was assessed by monitoring serum concentrations of 25-OHD₂, 25-OHD₃, and 1,25-(OH)₂D. All serum parameters were measured every 2 weeks, while PT and PTT were measured only at the beginning and end of the study.

The petitioner found that mean serum concentrations of 25-OHD₂ rose in both placebo and olestra-fed groups, although serum concentrations rose more slowly in the olestra-fed group. At week two and beyond, the olestra group showed serum vitamin 25-OHD₂ levels that were about 19 percent below placebo, which persisted to the end of the study. No statistically significant changes in the measurements used to assess vitamin K status (S/E, clotting times, and serum phyloquinone concentration) were observed in the study, except that at week two, serum phyloquinone levels were lower in the olestra-fed subjects. The petitioner concludes from these results that 20 g/d olestra does not affect vitamin K status or vitamin D nutritional status.

FDA disagrees with the petitioner's conclusions regarding olestra's effects on vitamins D and K. First, the 19 percent decrease in serum 25-OHD₂ is indicative of an olestra effect on

nutritional status and specifically, on vitamin D status. Second, the study is of limited usefulness in assessing vitamin K status because the sensitivity of the tests used to evaluate the impact of low serum vitamin K₁ on vitamin K-dependent clotting protein function is either poor (PT and PTT) or not fully validated (S/E). Furthermore, the quantitative precision of the study is diminished because the subjects were eating diets that were not controlled. Thus, FDA disagrees with the petitioner's conclusion that olestra does not affect vitamin D nutritional status and further concludes that this study does not provide sufficient information for a conclusion regarding olestra's impact on vitamin K₁ nutritional status (Ref. 46).

b. Sixteen-week vitamin E study. The 16-week vitamin E study was also a double-blind, placebo-controlled, parallel design with 194 subjects. The purpose of the study was to assess the adequacy of 1.1 mg of d-α-tocopherol acetate/g olestra in maintaining vitamin E status in persons chronically consuming olestra and to determine the potential effects of 18 g/d olestra on the status of vitamins K and D, absorption of carotenoids, and concentrations of serum retinol. Test subjects were normal, healthy, male and female free-living persons between the ages of 18 to 65 who consumed 18 g/d olestra, with or without 1.1 mg tocopheryl acetate/g olestra, or triglyceride placebo for 16 weeks. The daily dose of olestra (contained in cookies and ice cream) was to be consumed with meals; meal content was not controlled and they were permitted to eat between meals foods of their own choosing. Subjects were not specifically requested to evenly divide the daily allocation of cookies and ice cream among the meals. Serum concentrations of cholesterol, α-tocopherol, β-carotene, and total carotenoids were measured biweekly. Serum 25-OHD concentration, clotting times (PT and PTT), and serum levels of functional prothrombin (S/E) were measured at weeks 0, 8, and 16.

The petitioner found that serum α-tocopherol concentration was reduced by 6 percent, relative to control, in the olestra group and by 4 percent in olestra with added α-tocopheryl acetate group. Serum concentrations of β-carotene and total carotenoids were reduced by 21 to 29 percent in both olestra groups. Serum 25-OHD, retinol concentrations, and vitamin K status were unaffected by olestra consumption.

The petitioner concludes that 1.1 mg α-tocopheryl acetate/g olestra was not sufficient to compensate for olestra's effect in this study and that olestra did

²⁵ In the 8-week VR study a 7-day rotating menu was used to ensure that the subjects received equivalent levels of phyloquinone on the days prior to blood draws.

not affect vitamin D or K status. FDA agrees that compensation for olestra's reduction of vitamin E status was not adequate and that there was no evidence of an olestra effect on vitamin D and K status in this study. However, the value of this study is limited because the subjects were free-living, which limits the quantitative precision of the study in predicting olestra's nutritional effects (Ref. 47).

c. *Vitamin A/fat study.* The vitamin A/fat absorption study was a parallel, double-blind, placebo-controlled study of 70 healthy males. The subjects consumed 0 or 10 g/d olestra in potato chips for a 30-day, free-living adaptation period. The adaptation period was followed by a 14-day in-house period in which the subjects received 0, 8, 20, or 32 g/d olestra in potato chips and cookies. One-third of this daily dose was eaten with each meal except on the days when vitamin A and fat absorption was measured; on those days, the entire dose of olestra was consumed in potato chips at breakfast along with the radiolabeled marker. The dose response of olestra on the absorption of preformed vitamin A was measured using radiolabeled retinyl palmitate.

The petitioner evaluated the results of the vitamin A aspects of this study and concluded that neither 8 nor 20 g of olestra in a single meal had any effect on the absorption of ³H-labeled retinyl palmitate contained in the meal, and further that 32 g of olestra in the test meal reduced vitamin A absorption from that meal by 19 percent relative to controls. The petitioner also calculated that when high responders (the group of subjects showing high triglyceride levels after fat ingestion) were removed from the calculation, olestra's effect on vitamin A absorption was reduced to 13 percent.

FDA finds no justification for removing a part of the subject population from the calculation and thus believes that the 13 percent reduction figure is of no value in assessing olestra's effects on vitamin A. FDA agrees, however, that the study supports the conclusion that olestra induced a 19 percent reduction, and considers this amount to be the most accurate measurement of olestra's effect on preformed vitamin A absorption in this study (Ref. 48).

The petitioner concluded that the lack of an effect at the lower olestra doses (8 and 20 g) indicates that chronic consumption of olestra at the 90th percentile estimated intake by the total population (7 g/d) or the 90th percentile estimated acute intake for the heaviest consumers of savory snacks (18 to 44

year old males, 20 g/d²⁶) will have no effect on preformed vitamin A absorption. While this interpretation of the data appears to be reasonable, FDA notes that this study only addresses olestra's effects on preformed vitamin A absorption. The study cannot, by design, address the decrease in vitamin A stores that would be caused by olestra's effects on carotenoid absorption.

3. Pig Studies

The petitioner conducted five nutritional studies of varying lengths (12, 12, 26, 39, and 4 weeks) in pigs. The objective of the 12-week DR study was to confirm the hypothesized dose-response effect of olestra on fat-soluble vitamins A, D, E, and K, and to determine whether there were any effects on specific marker nutrients that are difficult to absorb or are limited in the American diet (folate, vitamin B₁₂, calcium, iron, and zinc). The purpose of the 12-week VR study was to determine whether the effects of olestra on the status of vitamins A and E that were observed in the 12-week DR study could adequately be compensated for by the addition of vitamins to the diet.

The 26-week DR/VR and the 39-week VR studies were undertaken after the 12-week studies to evaluate olestra's effects on nutrient status in the period beyond the maximum growth phase. The purpose of the 26-week DR/VR study was three-fold: (1) To confirm the dose-response effect of olestra observed in the 12-week DR study; (2) to evaluate the effect of olestra on fat-soluble vitamins, folate, vitamin B₁₂, calcium, zinc, and iron, with longer exposure times and lower olestra levels than had been tested in the 12-week DR study; and (3) to determine the amounts of fat-soluble vitamins that would need to be added to the diet to compensate for olestra's effects. The 39-week VR study was designed to evaluate over a longer exposure period the effects of 0.25 percent olestra and added vitamins A and E that were measured in the 26-week DR/VR study. The 4-week DC study was designed to determine whether olestra's effects on vitamins A and E were dependent on the timing of olestra consumption (with meals or temporally separated from meals) or the means by which olestra enters the diet (as chips or admixed with feed).

a. *Study design of 12-, 26-, and 39-week studies.* The 12-week DR, 12-week VR, 26-week DR/VR, and 39-week VR pig studies used similar materials and methods. The 12-week DR study is

described in depth. For the three other pig studies, only the differences from the 12-week DR study are described.

i. *Twelve-week DR study.* The test animals were a domestic, cross-bred strain of pigs, and were 5 to 7 weeks of age when received. All treatment groups contained equal proportions of females and castrated males. The pigs were acclimated for 14 to 16 days before being placed on experimental diets: During the first 7 to 9 days of the acclimation period, the animals were fed a 20 percent protein swine chow (University of Wisconsin-Madison) *ad libitum*; during the last 7 days they were fed the purified basal diet that was fed throughout the remainder of the study.

The basal diet was a purified diet consisting of about 25 percent casein, 24 percent starch, 24 percent sucrose, 5 percent Alphacel, 14 percent lard, and 8 percent of a vitamin/mineral premix. The diet delivered about 30 percent of calories from fat, a level equivalent to the target fat consumption level recommended for the U. S. population, but lower than current actual fat consumption. The ratio of calories from saturated:monounsaturated:polyunsaturated fats was targeted at 1:1:1.

The basal diet provided the National Research Council (NRC) requirements of micronutrients for 5 to 10 kilogram (kg) pigs. The NRC requirements, as a percentage of the feed, decline for many nutrients as a function of increasing body weight. Therefore, as the pigs grew, most nutrients were actually fed in excess of the body-weight-specific NRC requirements.

In the basal diet, vitamin A was provided as a 3:1 ratio of retinol equivalents from retinyl palmitate and β -carotene, respectively. This targeted ratio simulated the average dietary sources of vitamin A for the U. S. population. Vitamin E was provided in the form of d,l- α -tocopheryl acetate. Dietary vitamin D was supplied as ergocalciferol (vitamin D₂). In addition to dietary vitamin D, pigs in this study were exposed to 2 minutes of ultraviolet (UV) light each day. Vitamin K was provided as phylloquinone, the major source of vitamin K in the human diet, rather than as menadione, the form typically added to swine chow.²⁷ Folate was provided as folic acid, vitamin B₁₂ was provided as cyanocobalamin, calcium as a mixture of CaHPO₄•2H₂O

²⁶ A dose of 20 g is equivalent to the consumption of two 1-oz servings of savory snacks at a single meal.

²⁷ The swine NRC nutrient requirement table gives the vitamin K requirement as menadione; there is no value listed for phylloquinone. Therefore, the petitioner calculated the added amount of phylloquinone based on the assumption that phylloquinone is equivalent to menadione on a weight basis.

and CaCO₃, iron as FeSO₄•7H₂O, and zinc as ZnSO₄•7H₂O. The micronutrients were added directly to the diet, separate from the olestra, during diet preparation.

The 12-week DR study consisted of 7 groups of pigs, containing 12 pigs each (except the control group of 20 pigs). Olestra was added to the diets at levels

of 0 percent (control), 1.1 percent, 2.2 percent, 3.3 percent, 4.4 percent, 5.5 percent, and 7.7 percent (by weight). The olestra was heated before incorporating into the diet by frying potato chips.

Growth, feed intake, hematology, and clinical chemistry measures and the status of vitamins A, B12, D, E, and K,

and folate, calcium, zinc, and iron were measured at regular intervals. Stores of vitamins A, E, B12, calcium, phosphorus, zinc, and iron were measured in the liver or bone at the termination of the study. The measurements used to assess the status of the various nutrients are summarized in Table 6.

TABLE 6.—MEASUREMENTS OF NUTRIENT STATUS IN THE 12-WEEK DR PIG STUDY

Nutrient	Measurements
Vitamin A	Liver and serum concentration
Vitamin E	Liver, serum, and adipose tissue concentration
Vitamin D	Serum concentration of 25-OHD ₂ , 25-OHD ₃ , and 1,25-(OH) ₂ D
Vitamin K	Prothrombin time
Folate	Plasma concentration
Vitamin B ₁₂	Liver concentration
Calcium	Bone, serum calcium, and bone ash concentration
Phosphorus	Bone and serum concentration
Iron	Liver iron concentration and serum concentrations of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)
Zinc	Liver, bone, and serum concentration

ii. Twelve-week VR study. The 12-week VR study consisted of 11 groups of pigs (one baseline, one control, and nine treatment groups), each containing

10 pigs (5 castrated males and 5 females). Pigs were exposed to 2 minutes of UV light each day. The amount of olestra and total amounts of

vitamins A, D, and E targeted to be in the diet for the nine treatment groups is summarized in Table 7.

TABLE 7.—STUDY DESIGN FOR 12-WEEK VR PIG STUDY

Percent Olestra	Vitamin A (x NRC) ¹	Vitamin D (x NRC) ¹	Vitamin E (x NRC) ¹
0 (control)	1.00	1.00	1.00
1.1	1.05	1.20	1.20
1.1	1.35	1.80	1.90
1.1	1.65	2.40	2.60
4.4	1.65	2.40	2.60
4.4	2.40	4.20	4.60
4.4	3.15	6.00	6.60
7.7	2.05	3.80	4.15
7.7	3.45	6.60	7.30
7.7	4.85	9.40	10.45

¹ Expressed as multiples of the NRC requirements of pigs.

A premix was prepared to provide additional amounts of vitamin A as well as vitamin D for each level of olestra fed. Vitamin D was added as vitamin D₂ (ergocalciferol), while vitamin A was in the form of retinyl palmitate. Above-basal levels of vitamin E, in the form of d- α -tocopheryl acetate, were combined with the olestra instead of adding it

directly to the diet because this procedure mimics that which would be used to add vitamin E to olestra for savory snack use, i.e., the vitamin would be added directly to the frying oil.

iii. Twenty-six week DR/VR study. The 26-week DR/VR study had 11 groups, each containing 10 pigs (5

castrated males and 5 females). Olestra was fed at five levels (0.25, 0.5, 1.1, 3.3, and 5.5 percent). Seven of the groups (baseline, control, 0.25, 0.5, 1.1, 3.3, and 5.5 percent olestra) did not have any additional vitamins above those present in the basal diet. The other four groups consumed added vitamins as described in Table 8.

TABLE 8.—VITAMIN DOSES FOR THE FOUR TREATMENT GROUPS IN THE 26-WEEK DR/VR PIG STUDY THAT HAD VITAMIN COMPENSATION

Percent olestra	Vitamin A (IU/kg diet)	Vitamin E (mg d- α -tocopherol acetate/g olestra)
5.5	3,300	1.71
0.25	150	1.71
0.25	300	3.42
0.25	600	5.13

Additional vitamins were added in the same manner as described for the 12-week VR study. The pigs in the vitamin-compensated 5.5 percent olestra group were exposed to 2 minutes of UV light each day. UV exposure was eliminated in the remainder of the groups in order to eliminate the possibility that the UV light might affect the magnitude of olestra's effect on dietary vitamin D₂. Instead, the diet was modified by increasing the vitamin D level to two times the NRC requirement to produce more readily measurable levels of vitamin D₂ in the serum.

In addition to the measurements of nutrient status listed in Table 6, serum parathyroid hormone (PTH) was monitored.

iv. *Thirty-nine week VR study.* The 39-week VR study consisted of the following four groups of 10 pigs each (5 castrated males and 5 females): baseline, control, 0.25 percent olestra, and 0.25 percent olestra with 150 IU vitamin A/kg diet (60 IU/g olestra) and 1.71 mg d- α -tocopherol acetate/g olestra. There was no UV exposure in this study and the diet was modified by increasing the vitamin D level to two times the NRC requirement to produce more readily measurable levels of vitamin D₂ in the serum. In addition, vitamin K level in the basal diet was lowered to one-fifth the level that was fed in the other three studies.

In addition to the measurements of nutrient status listed in Table 6, serum parathyroid hormone (PTH) was monitored.

b. *Study design of the 4-week DC study.* Young pigs, 7 to 9 weeks of age at the start of the study were fed a casein-based diet formulated to contain at least one times the NRC requirements of micronutrients. Five groups of 10 pigs each were fed 0 percent or 2.2 percent olestra for 4 weeks. A sixth group of 10

pigs provided baseline data for vitamin A, D, and E tissue concentrations. The olestra was fed either admixed in the diet, as chips prior to each meal, as chips prior to the noon meal only, or as chips fed between the noon and evening meal.

The petitioner evaluated the change in status of vitamins A, D, and E at the end of the 4-week study through serum measurements of the concentrations of vitamin A (retinol), vitamin E (α -tocopherol), and vitamin D (25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃) and liver measurements of vitamin A (total retinol and retinyl esters) and vitamin E (α -tocopherol).

c. *Results and conclusions from pig studies.* The results of the 4-week DC study will be discussed in section V.B.4.a. of this document.

i. *Vitamin A.* Data on the dose-response effect of olestra on liver vitamin A stores were collected in the 12-week DR study and the 26-week DR/VR study. The petitioner observed that olestra caused a nonlinear dose-response reduction in hepatic vitamin A stores, in which lower amounts of olestra had a greater proportional effect on stores, in both the 12-week DR and 26-week DR/VR studies. In the 26-week DR/VR study, the decreases in liver vitamin A (relative to controls) were 45 percent (0.25 percent olestra), 57 percent (0.5 percent olestra), 65 percent (1.1 percent olestra), and 88 percent (3.3 percent and 5.5 percent olestra). The reductions observed in the 12-week DR study were very similar, with the highest olestra intake (7.7 percent) causing a greater than 90 percent decrease. Serum vitamin A levels also decreased in a dose-response manner

with increasing olestra intake in both studies.²⁸

In both the 12-week VR and the 26-week DR/VR studies, the addition of varying levels of vitamin A to the diet resulted in a linear increase in liver vitamin A stores. For the 12-week VR study, the petitioner calculated that the effect of olestra on liver vitamin A stores could be offset by adding 58.1 IU of vitamin A/g olestra in the diet. FDA calculates the appropriate compensation level separately for each level of olestra in the diet, because the required compensation level in IU/g changed as a function of dietary olestra level, and determined that the compensation level ranged from 130.8 IU vitamin A/g olestra at 0.1 percent olestra to 45.8 IU vitamin A/g olestra at 7.7 percent olestra (Ref. 49).

For the 26-week DR/VR study, the petitioner calculated that 170 IU vitamin A/g of olestra compensates for olestra's effects on vitamin A liver status, which is equivalent to 93 μ g retinyl palmitate/g olestra, or 0.34 RDA of vitamin A per 1-oz serving of snacks containing 10 g olestra. FDA agrees that this calculation is appropriate and that when olestra is present at 0.25 percent of the pig diet, approximately 170 IU of retinol/g olestra maintains the liver vitamin A levels at control values²⁹ (Ref. 49). One hundred and seventy IU of retinol/g olestra is equivalent to 51 retinol equivalents/g olestra.

The petitioner concluded and FDA agrees that the results of the 39-week VR

²⁸ Unlike adult pigs, weanling pigs do not have large stores of vitamin A so liver stores are not able to compensate for olestra's interference with absorption of vitamin A; thus the effect on vitamin A status is also manifest in the serum levels.

²⁹ The estimates from the 12-week study are somewhat smaller than estimates obtained from the 26-week pig study; in the 12-week study, the required supplementation level for 0.25 percent olestra was 128 IU/g olestra.

study confirm olestra's effect on vitamin A liver stores, although FDA notes that the amount of vitamin A added to the diet in the 39-week study (60 IU vitamin A/g olestra) was not sufficient to compensate for olestra's effect on vitamin A.

ii. Vitamin E. In the 26-week DR/VR study, the decreases in liver vitamin E (relative to controls) were 24 percent for 0.25 percent olestra, 31 percent for 0.5 percent olestra, 53 percent for 1.1 percent olestra, 71 percent for 3.3 percent olestra, and 75 percent for 5.5 percent olestra. In the 12-week DR study, the reductions were slightly larger (e.g., 60 percent for 1.1 percent olestra, 69 percent for 2.2 percent olestra, 75 percent for 3.3 percent olestra, 78 percent for 4.4 percent olestra, 80 percent for 5.5 percent olestra, and 81 percent for 7.7 percent

olestra). Vitamin E concentration in adipose tissue showed a slightly smaller decrease in both studies; for example, with 5.5 percent olestra, adipose vitamin E concentration had fallen by about 73 percent in both the 12-week DR and 26-week DR/VR studies.

The results of the 12-week DR and 26-week DR/VR studies showed that effects of olestra on vitamin E status were similar in the serum and liver, although the percent decrease in vitamin E was slightly larger for liver than for serum. The petitioner concluded, and FDA concurs, that this relationship confirms that serum vitamin E concentration is a reliable measure of vitamin E status. The concentration of vitamin E in adipose tissue also changed in a similar fashion to the changes in serum and liver concentrations although the

magnitude and rate of change were not as great.

The petitioner concludes that 2.09 IU of vitamin E/g olestra offset olestra's effects in the 12-week VR study; in the 26-week DR/VR study (where olestra was fed at a lower level), 2.79 IU of vitamin E/g olestra (which translates to 2.06 mg d- α -tocopheryl acetate/g olestra) offset olestra's effects. FDA concurs with the petitioner's general conclusions and with the calculated level of 2.79 IU vitamin E/g olestra from liver measurements in the 26-week VR/DR study. FDA's calculated compensation levels for the other studies, as shown in Table 9, differ slightly because of small differences in the choices of variables to fit the curves in the statistical analyses (Refs. 50 and 51).

TABLE 9.—FDA-CALCULATED COMPENSATION LEVELS OF VITAMIN E TO RESTORE LIVER AND SERUM LEVELS BASED ON 12-WEEK VR AND 26-WEEK DR/VR STUDIES

Study	Olestra level (%)	Vitamin E compensation (IU/g olestra)	
		Liver compensation level	Serum compensation level
26-week DR/VR	0.25	2.79	2.98
12-week VR	1.1	2.66	2.76
12-week VR	4.4	2.27	2.34

iii. Vitamin D.—a. Petitioner conclusions. The petitioner concluded that the 12-week DR study established a dose-response effect for olestra on dietary vitamin D at olestra levels up to 4.4 percent of the diet, as measured by serum concentration of 25-OHD₂; the serum concentration of 25-OHD₂ was about 10 percent less than control in the 1.1 percent olestra group and about 35 percent less than control in the 2.2 percent, 3.3 percent, and 4.4 percent groups. At higher olestra levels, changes in the dietary contribution to total circulating 25-OHD were confounded by changes in the contribution from vitamin D₃ synthesized in the skin.

The petitioner also concluded that in the 12-week VR study, serum concentration of 25-OHD₂ increased in a dose-response manner as the amount of vitamin D₂ added to the basal diet was increased, at all levels of olestra. However, interpretation of the serum 25-OHD₂ data at the mid- and high-olestra levels (4.4 and 7.7 percent) was confounded because the proportion of 25-OHD₃ in the serum decreased with increasing levels of olestra at these treatment levels. The petitioner has suggested, that this decrease in serum 25-OHD₃ may have resulted from the effect of the high levels of olestra on the reabsorption of biliary vitamin D₃. Reduced reabsorption of biliary vitamin D₃ would tend to increase the serum concentration of 25-OHD₂ because of diminished vitamin D₃ competition for the liver 25- α hydroxylase.

Using the serum 25-OHD₂ concentrations from the groups fed 1.1 percent olestra in the 12-week VR study, the petitioner calculated that the amount of vitamin D required to restore serum 25-OHD₂ to the control level was 13.0 IU vitamin D/g olestra, which is equivalent to 0.33 RDA/1 oz serving of chips containing 10 g olestra. The petitioner considers that the confounding effect of vitamin D₃ was absent or minimal when olestra was fed at 1.1 percent of the diet.

The petitioner concluded that in the 26-week DR/VR study, 5.5 percent olestra (no extra vitamins) reduced plasma 25-OHD₂ by 20 percent at week 26. At week 16, serum 25-OHD₂ levels in the 3.3 percent and 5.5 percent olestra groups were significantly lower than controls by 23 percent and 35 percent, respectively.

The petitioner concluded that in the 39-week VR study, olestra decreased serum levels of 25-OHD₂ by the same magnitude as in the 26-week DR/VR study, while serum 25-OHD₃, total serum 25-OHD, and serum 1,25-(OH)₂D were not affected. Serum 25-OHD₂ levels were 13 to 15 percent lower than

week 12 and week 26. At week 39, the values were 6 to 11 percent lower than controls, but this difference was not statistically significant.

b. FDA conclusions. FDA concludes that the results of the pig studies are of limited utility for quantifying olestra's effects on vitamin D, for several reasons. First, FDA notes that vitamin D levels were never measured in the diet as fed in any of the pig studies. This lack of measurement leaves open the possibility that addition or mixing errors might have occurred, affecting the vitamin D levels in the feed. Second, the confounding effect of UV exposure in several of the studies makes interpretation of the results difficult.

The 26-week DR/VR study was designed to prevent UV light exposure to any group except the 5.5 percent olestra/low vitamin group where 2 minutes of exposure were to be provided per day. However, an accidental UV light exposure (not more than 13 hours) to this group on day 23 of the study likely caused the very high 25-OHD₃ levels and very low 25-OHD₂ levels observed at week 4. In addition to the accidental exposure of the 5.5 percent olestra/low vitamin group to UV light, it appears that at least 10 other animals may have been exposed to UV light in at least the 12th week of the study, as evidenced by their elevated serum 25-OHD₃ levels. Because a definitive cause for these elevated serum 25-OHD₃ values could not be determined, FDA considers the vitamin D data from the 26-week DR/VR study to be confounded (Ref. 52).

Although pigs in the 39-week study were not exposed to UV light, pigs consumed only one level of olestra, therefore no dose-response information was obtained.

FDA agrees with the petitioner that in the 12-week VR study, serum concentration of 25-OHD₂ increased in a dose-response manner as the amount of vitamin D₂ added to the basal diet was increased, at all levels of olestra. FDA further agrees with the petitioner that the decrease in serum 25-OHD₃ observed in the mid- and high-level groups may have resulted from olestra's effects on the reabsorption of biliary vitamin D₃. However, FDA also believes that the serum 25-OHD₂ levels may have been confounded by the daily 2-minute exposure to UV light, which caused an increase in serum levels of 25-OHD₃ in both 12-week studies. Therefore, FDA concludes that the results from the mid- and high-dose groups in the 12-week VR study cannot be used to determine a quantitative compensation value for vitamin D₂ because of the apparent

interaction between serum 25-OHD₃ and 25-OHD₂ levels.

FDA believes that the most useful data from the pig studies comes from a comparison of the control and 1.1 percent olestra groups in the 12-week VR study. Accordingly, FDA believes that the petitioner's calculation based on the 12-week VR study that 13 IU vitamin D/g olestra will compensate for olestra's effects in pigs exposed to daily UV light may be an approximation of appropriate supplementation level for vitamin D. However, the agency believes that it cannot rely on the 12-week VR data by themselves to establish a compensation value for vitamin D₂, because of the possible confounding effects of UV exposure and the lack of measurements of vitamin D levels in the diets as fed (Refs. 53 and 54).

iv. Vitamin K. There were no statistically significant effects of olestra on prothrombin time in any of the pig studies. The petitioner concluded, therefore, that olestra does not affect vitamin K status. Although FDA agrees that prothrombin time was not affected by olestra consumption, the agency does not believe that these results are adequate to determine the potential effects of olestra on vitamin K status, because, as discussed below, prothrombin time is not a sufficiently sensitive analytical method and the diets of the test animals appear to have been overfortified with vitamin K.

Prothrombin time is an insensitive indicator of vitamin K status. The petitioner agrees that there are more sensitive indicators of vitamin K status such as direct measurements of clotting factors in blood, urinary excretion of γ -carboxyglutamic acid, and plasma levels of des-carboxylated or under-carboxylated vitamin K-dependent proteins (the PIVKA-II assay). The petitioner states however, that these methods were not used because they had not been used previously or validated in the pig and no body of historical data exists. Nevertheless, FDA believes that use of an insensitive indicator limits the conclusions that can be drawn from these pig studies regarding vitamin K status.

FDA believes that the usefulness of the data from the 12-week and 26-week DR/VR studies is further limited because test animal diets were oversupplemented with vitamin K. Because vitamin K is a highly lipophilic fat-soluble vitamin, FDA considers it reasonable to assume that it will partition into the olestra in the GI tract, in the same manner as the other fat-soluble vitamins. Thus, oversupplementation is significant

because it could mask any effect of olestra on vitamin K status.

FDA believes the pig diets were oversupplemented with vitamin K in the 12-week and 26-week DR/VR studies for two reasons. First, the NRC requirement for vitamin K in swine is in terms of amounts of menadione, not phyloquinone (the form of vitamin K fed to the pigs). The NRC requirement for menadione, 500 µg/kg, is in a corn-soybean meal base and this likely exceeds the requirements needed for a casein-based semisynthetic diet that should not contain any substance that might inhibit vitamin K metabolism. Second, FDA disagrees with the petitioner's assumption that phyloquinone is necessarily of equal potency on a weight basis as menadione. Unlike phyloquinone, menadione is biologically inactive and must be alkylated in the liver to menaquinone to become biologically active. Phyloquinone, following intracardiac administration, was 10 times more active than menadione on a weight basis at restoring the prothrombin response in rats that were partially depleted of vitamin K (Ref. 55). Therefore, FDA cannot rule out the possibility that phyloquinone is a more potent source of vitamin K on a weight basis than menadione in swine following oral administration, which would lead to further oversupplementation (Ref. 56).

4. Overall Conclusions Regarding Olestra's Effects on Fat-Soluble Vitamins

a. Consumption scenarios. The petitioner has asserted that in the 8-week human studies and in all of the pig studies (except the 4-week DC study), olestra's effects on fat-soluble nutrients are exaggerated because the additive was always consumed with meals. In addition, in the pig studies, olestra was admixed with all the feed, rather than being present in only select dietary ingredients (such as chips). The petitioner hypothesizes that if olestra is eaten in a snack between meals (instead of being eaten with a meal), there will be fewer nutrients available with which it can interact, and that olestra's effects on nutrients would be expected to be greatest when olestra and the nutrients are intimately intermixed in the GI tract at the same time.

The petitioner has provided results of consumption surveys showing that in the United States, at the estimated 90th percentile consumption level, savory snacks are eaten only four times per week, and one-third of those occasions are between meals. With this consumption pattern, olestra savory

snacks will be eaten 32 times in an 8-week period (as compared to 168 meals during that time), and 20 of those times will be with meals. (In other words, during the 8-week period, 148 meals (or 88 percent) will be consumed without a savory snack.) These data mean that, although a majority of snacks are eaten with meals, because of the infrequency of snack consumption, a majority of nutrient intake will occur in the absence of olestra savory snacks. In contrast, in both 8-week studies, olestra was eaten 165 times in 8 weeks with every meal, which means that essentially all of the nutrient intake occurred with olestra consumption.

The petitioner presented the following examples of the consequences of consumption patterns on olestra's effects on nutrients. First, the petitioner calculated the expected effect of olestra on β-carotene in consumers eating snacks with the eating patterns reported in the MRCA survey data.³⁰ In the first scenario, the petitioner assumed that absorption of β-carotene eaten with olestra would be decreased by 60 percent and absorption of β-carotene eaten at all other times would not be affected. In a second scenario, presented at the Olestra Working Group and FAC meetings,³¹ the petitioner assumed that absorption of β-carotene eaten with olestra would be decreased by 60 percent, absorption of β-carotene eaten at eating occasions either before or after the olestra eating occasion would be decreased by 30 percent, and absorption of β-carotene eaten at all remaining times would not be affected. Using these assumptions the petitioner calculated that an average snack consumer would have a decrease in serum β-carotene levels of 5.6 percent in the first scenario and about 6.8 percent in the second scenario. For the heaviest consumers (top 10 percent), the first scenario would result in a decrease in serum levels of about 10 percent, while the second scenario would result in decreases of 13 to 14 percent.

The petitioner further asserts that the 4-week DC study in pigs and 16-week vitamin E study provide evidence that olestra's effects on fat-soluble nutrients measured in the pig studies and in the 8-week human studies exaggerate the effects expected with a normal savory snack consumption pattern. This effect is confirmed by a comparison of the 8-week DR study (where olestra and the vitamins were always consumed concurrently) with results of the 16-week vitamin E study (in which free-living subjects consumed olestra

throughout the day but not necessarily concurrently with the consumption of all vitamin E or carotenoids). In the 8-week DR study, the effects on vitamin E status and serum β-carotene concentration measured in the 20 g/d olestra group are about three-fold greater than those measured in the free-living subjects in the 16-week vitamin E study consuming 18 g/d olestra.

In the 4-week DC study in pigs, the reduction of vitamin A liver stores in pigs fed 2.2 percent olestra was about 44 percent compared to controls when olestra was fed admixed in the diet and about 14 percent when olestra was fed in potato chips with all meals. Similarly, the reduction of liver and serum vitamin E concentrations in pigs fed 2.2 percent olestra admixed in the diet was about twice as large (60 percent for liver and 52 percent for serum compared to controls) when olestra was fed admixed as when olestra was fed in potato chips with all meals (30 percent and 20 percent for liver and serum, respectively). Therefore, the petitioner has concluded that the effects of olestra that were measured in the 12-week DR, 12-week VR, 26-week DR/VR, and 39-week VR pig studies were exaggerated by about 3-fold for vitamin A and about 2-fold for vitamin E over what would have been observed if the olestra were fed in chips with meals.

FDA agrees that when savory snacks containing olestra are eaten without other foods, olestra's effects on fat-soluble vitamins will be less than the effects measured in the 8-week human studies or in the 12-, 26-, and 39-week pig studies. However, FDA concludes that, given the wide variety of possible dietary patterns, the most protective approach is to ensure that compensation levels that accommodate most, if not all of those dietary patterns. Slight overcompensation with vitamins A, E, D, and K that might occur if an individual were to eat all olestra-containing snacks separate from other foods would not raise any health concerns, as discussed below. In contrast, the potential for developing vitamin deficiencies in some of the population that preferentially eat olestra-containing snacks with meals is of sufficient concern to merit this approach. Further, calculating compensation levels using the with-meal study results provides an additional measure of safety, because based on the MRCA data, it is probable that not all olestra consumed in savory snacks will be eaten with meals. Therefore, FDA is not relying on the results of the contextual studies or calculations based on eating patterns in

³⁰ Transcript, vol. 1, p. 84 and vol. 3, p. 234.

³¹ Transcript, vol. 3, p. 234.

evaluating the safety of olestra with regard to nutrient effects.

b. Vitamin A. FDA and the petitioner agree that olestra's effects on vitamin A present significant health concerns and, therefore, compensation for olestra's interference with this vitamin's absorption should be made. The pig studies show that olestra consumption has a dose-response effect on vitamin A that is nonlinear, having the greatest effect (on a per-gram-of-olestra basis) at low olestra consumption levels. The level of vitamin A compensation was calculated using data from the pig studies in which the effect of olestra and olestra with added retinyl palmitate on vitamin status were determined. Thus, the pig studies provide the most direct measure of vitamin A status. Calculations were based on the effect at the lower olestra doses to ensure that compensation is sufficient for all consumers.

Both the petitioner and FDA have calculated that 170 IU of vitamin A/g olestra (51 retinol equivalents/g) compensates for olestra's effects on vitamin A (from both preformed vitamin A and the provitamin A carotenoids). This amount is equivalent to 0.34 times the RDA in a 1-oz serving of savory snacks containing 10 g of olestra.

The results of the vitamin A/fat study in humans showed that only the highest dose of olestra (32 g/d) had a measurable effect on preformed vitamin A absorption. This direct measurement of olestra's effect on absorption of preformed vitamin A in humans shows less of an effect than the observed effect on vitamin A stores in the pig studies, a difference likely due to the decreased absorption of carotenoids in the pig studies, which are therefore less available as provitamin A sources. Vitamin A added to olestra in the 12-week DR, 26-week DR/VR and 39-week VR pig studies compensated for both the loss of preformed vitamin A and carotenoids as provitamin A sources, as it would when olestra is compensated in savory snacks. Therefore, FDA concludes that relying on the pig data to calculate the compensation level will account for olestra's effects on absorption of both preformed vitamin A and carotenoids as contributors to the vitamin A body stores.

During the Olestra Working Group meeting, the members of the Olestra Working Group unanimously agreed that FDA had appropriately evaluated the amount of vitamin A with which olestra should be compensated.³²

At the FAC meeting, Dr. Rodier, an embryologist and member of the FAC,

expressed concern about the potential toxicity, especially teratogenicity, of the vitamin A that would be added to olestra.³³ She pointed out that since 1986, the Teratology Society has recommended that vitamin supplements not contain preformed vitamin A, but that they contain carotenoids instead. FDA is aware of a recent study investigating the teratogenicity of vitamin A intake (Ref. 57), in which an association was found between the prevalence of defects associated with cranial-neural-crest tissue in babies and consumption by their mothers of preformed vitamin A supplements during pregnancy. The researchers found an apparent threshold for the effect of about 10,000 IU of supplemental preformed vitamin A (i.e., in addition to vitamin A consumed in the diet). Consumers eating large amounts of olestra might obtain a small amount of bioavailable vitamin A from olestra because the compensation level was calculated from low olestra doses where the effect/g olestra is the highest. However, because the teratogenic effects seen by Rothman et. al., occur with vitamin A intakes more than 10,000 IU above that which is consumed in the daily diet, and because most of the vitamin A in olestra will remain in the olestra as it passes through the body, FDA concludes that there is no reasonable scenario of olestra consumption from savory snacks that would lead to vitamin A leaching out of the olestra at levels anywhere near 10,000 IU. Therefore, the agency is requiring vitamin A compensation at 170 IU/g olestra (51 retinol equivalents/g).

c. Vitamin E. FDA and the petitioner agree that olestra's effects on vitamin E present significant health concerns and, therefore, compensation for this vitamin should be made. Serum data from the human studies provide the basis for calculating the appropriate compensation level for vitamin E, and the calculations are supported by the results of the pig studies. The petitioner has calculated that 1.9 mg α -tocopherol equivalents (2.8 IU vitamin E) should be added per g of olestra to compensate for olestra's effect on vitamin E levels. This amount is equal to 0.94 times the RDA in a 1-oz serving of snack containing 10 g of olestra. The compensation level calculated from the pig studies for the lowest olestra consumption level (which shows the largest effect when calculated per g of olestra) is 2.79 IU vitamin E/g olestra, which is essentially the same as

the compensation level calculated from the 8-week human studies.

During the Olestra Working Group meeting, the members of the Olestra Working Group unanimously agreed that FDA had appropriately evaluated the amount of vitamin E with which olestra should be compensated. Therefore, FDA is requiring vitamin E compensation at 2.8 IU/g olestra (1.9 mg α -tocopherol equivalents/g olestra), which will adequately compensate for olestra's effects in all realistic consumption scenarios.

d. Vitamin D. The petitioner concluded that the effects of olestra on vitamin D₂ concentration do not warrant compensation with vitamin D. As support, the petitioner cites the absence of changes in serum 1,25-OH₂D concentration in the pig studies as evidence that olestra has no significant effect on overall vitamin D status despite the decrease in dietary vitamin D₂ status. Typically, the contribution of dietary vitamin D to total vitamin D status in the general population is from 10 to 20 percent (the rest from sunlight-induced synthesis in the body). Therefore, the petitioner reasons that a 23 percent decrease in dietary vitamin D status would result in only a 2.3 to 4.6 percent reduction in overall vitamin D status in a normal healthy human under the exaggerated conditions of olestra consumption used in the studies. In worst-case situations, where dietary vitamin D can contribute up to 50 percent of total vitamin D, the petitioner calculates that the reduction in overall vitamin D status would be 11.5 percent when olestra was consumed with every meal.

FDA disagrees with the petitioner's position that the effect of olestra on vitamin D is not sufficient to warrant compensation. Although most individuals can produce vitamin D through exposure to sunlight, there are some people who may not synthesize sufficient vitamin D to compensate for potential decreases due to olestra effects, either because they are not exposed to sufficient sunlight or because they utilize sunlight poorly to synthesize vitamin D. Therefore, FDA concludes that compensation for vitamin D should also be required for olestra-containing foods.

From the 8-week human studies, the petitioner calculated that 0.07 μ g vitamin D₂/g olestra (0.07 times the RDA per 10 g of olestra) would be sufficient to compensate for the olestra-induced decrease in 25-OH D₂. FDA notes that in the 8-week VR study, 0.2 μ g vitamin D₂/g olestra slightly overcompensated for olestra's effects on vitamin D status, as measured by total 25-OH D levels.

³³Dr. Patricia Rodier, is a senior scientist in the Department of Obstetrics and Gynecology, University of Rochester. Transcript, vol. 4, p. 99.

³²Transcript, vol. 3, pp. 220-225.

However, these values are based on only two compensation levels, and may be confounded by the fact that serum vitamin D levels continued to decrease over time in the study.

The petitioner has also calculated, from the 1.1 percent olestra group of the 12-week DR pig study, that 13.0 IU vitamin D/g olestra (0.33 times the RDA per 10 g of olestra) would compensate for olestra's effects in that group. Although the design of that study also contains some weaknesses, FDA believes that the results of both the pig study and the 8-week human studies, considered together, support the need for a compensation level and provide an approximation of an appropriate level.

Given the importance of vitamin D, FDA concludes that it is preferable to compensate consistent with olestra's demonstrated effects on vitamin D, rather than risk a deficiency (Ref. 58). FDA concludes that addition at levels of 12 IU vitamin D/g olestra (0.3 µg/g olestra) or 0.3 times the RDA per 10 g of olestra, is adequate to compensate for any vitamin D that is lost due to diminished absorption caused by olestra. This level of vitamin D includes the amount that was observed to compensate for olestra's effects in the 12-week DR pig study and is slightly higher than the 0.2 µg/g that was observed to be sufficient in the 8-week VR human study. During the Olestra Working Group meeting, the members of the Olestra Working Group unanimously agreed that FDA had appropriately evaluated the amount of vitamin D with which olestra should be compensated.

This level of vitamin D compensation does not raise any toxicity concerns, even if olestra as actually consumed has no effect on the absorption of vitamin D, because it is generally accepted in the medical community that one would have to ingest five times the RDA (the RDA is 400 µg of vitamin D) before toxicity effects begin to occur (Ref. 59). Thus, slight overcompensation with vitamin D would not cause health concerns. Assuming that the daily diet contains an RDA of vitamin D, olestra would have to contribute four times the RDA (or 1,600 IU), which is equivalent to the amount added to about 13 oz of potato chips, to reach levels where toxicity effects begin. However, most of the vitamin D in olestra would not be bioavailable. Therefore, FDA is requiring compensation with 12 IU vitamin D/g olestra (0.3 µg/g olestra).

e. Vitamin K.—i. Petitioner conclusions. The petitioner concluded that the effects of olestra on serum phylloquinone levels will not pose a potential public health concern, and

therefore, compensation of olestra savory snacks with vitamin K is not necessary. The petitioner based this conclusion on: (1) The absence of olestra effects on the sensitive measures of vitamin K function under exaggerated conditions of the studies conducted in humans; (2) the presence in the U.S. diet of significantly more vitamin K than the single RDA fed in the studies in which no effects on sensitive measures were observed; (3) the fact that the dietary level of vitamin K associated with detectable effects on sensitive functional parameters is well below the RDA; and (4) the absence of either a dietary pattern consistent with, or clinical evidence for, the existence of subgroups within the U.S. population at risk of vitamin K deficiency.

The petitioner concluded that functional measures of vitamin K status provide a reliable basis for public health decisions regarding this vitamin, because these measures provide a direct assessment of the ability of the vitamin K supplied to the tissues to maintain normal vitamin K function. Because, unlike vitamins A, D, and E, there are no significant phyloquinone stores in the body and serum concentrations of the vitamin fluctuate significantly throughout the day, these functional measures provide an integrated picture of the supply of vitamin K over a time period as short as 2 to 3 days. Fasting serum measures of phyloquinone, on the other hand, may not reflect the true status of vitamin K because of the very short half-life of the vitamin in the plasma (less than 2 hours). At any given time during the day, the serum concentration of phyloquinone may suggest low or inadequate vitamin K supply, while the tissues may be receiving more than adequate amounts to support maximal rates of carboxylation.

The petitioner further concluded that urinary Gla excretion and plasma *des-γ*-carboxylated prothrombin (PIVKA-II) are the markers of vitamin K function that best reflect the integrated vitamin K status of the individual over time. If the phyloquinone supply from the diet falls below a level adequate to support maximal synthesis of vitamin K-dependent proteins in the body, PIVKA-II and urinary Gla will change to reflect the inadequate supply. The half-lives of prothrombin (Factor II) and of the vitamin K-dependent proteins which contribute the majority of the urinary Gla excretion (60 hours or more) are significantly longer than the half-life of phyloquinone in plasma (about 2 hours). Therefore, the petitioner argues, these functional measures provide a sensitive index of potential chronic

effects on the adequacy of vitamin K in the diet. Urinary Gla is particularly important because it reflects carboxylation of vitamin K-dependent proteins in all tissues, including bone and kidney. Although the petitioner believes that compensation for vitamin K is unnecessary, the petitioner has evaluated olestra's effect on vitamin K by comparing serum vitamin K levels with vitamin K dietary intake at varying olestra levels, and has determined that 3.3 µg vitamin K/g olestra will restore serum vitamin K levels to those of the control group. This level is less than one-half of the 80 µg RDA, when contained in a 1-oz serving of savory snacks containing 10 g olestra. Because the 8-week DR study was not designed to assess the olestra dose response for vitamin K, the compensation level calculated by the petitioner is only an estimate of an appropriate compensation level.

ii. FDA conclusions. FDA concludes that the data from the 8-week human studies show that serum vitamin K levels were decreased by consumption of olestra, and that the lack of effect on functional assays could be attributable to the use of a subject population that is not at risk for vitamin K deficiency. Similarly, as noted, the lack of an olestra effect on prothrombin time in the pig studies may be explained by the insensitivity of the analytical method and oversupplementation of the test diet with vitamin K. While olestra may not pose a health risk due to moderate reductions in serum vitamin K levels for healthy adults consuming diets that, on average, provide them with the minimum RDA for fat-soluble vitamins and other nutrients, these reductions of vitamin K could be of concern for segments of the population at risk for vitamin K deficiency or where the control of blood clotting is more critical.

There were no studies designed to assess the dose-response nature of olestra's effect on vitamin K. The pig studies are not useful in this case because of the uncertainty regarding the activity of menadione and phyloquinone in the swine diet and the likelihood that the NRC requirements for swine are much higher than actual need. In contrast, the 8-week DR study in humans is useful for estimating an appropriate compensation level because the diet contained approximately 1 RDA of vitamin K and the dietary levels of vitamin K on the day before blood draws varied for each blood draw.

FDA believes that the consequences of vitamin K depletion are sufficiently serious and their onset so sudden as to warrant addition of vitamin K to olestra-containing food. Also, it is well

recognized in the medical community that large doses of vitamin K can be tolerated with no toxic effects.³⁴ Thus, even if compensation with vitamin K is not necessary for all olestra consumers, such compensation poses no safety concern. FDA further believes it is appropriate to require compensation at a level somewhat higher than that calculated from the 8-week DR study, to provide a greater assurance of safety. Given that the RDA is 80 µg/d and vitamin K exhibits no known toxicity, FDA recommended at the Olestra Working Group and the FAC meetings that a level of 8 µg vitamin K/g olestra, or one times the RDA per 10 g of olestra, would provide an adequate compensation level of vitamin K and would not cause any concern over toxicity.

During the Olestra Working Group meeting, the members of the Olestra Working Group unanimously agreed that FDA had appropriately evaluated the amount of vitamin K with which olestra should be compensated. Although there was no disagreement among FAC members that slight overcompensation with vitamin K would not be of concern to the general public, a Working Group member³⁵ and two presenters³⁶ expressed concern about the effect that olestra consumption (whether or not compensated with vitamin K) would have on persons for whom blood clotting should be controlled, such as persons taking coumarin drugs.

Dr. John Suttie, a researcher in the vitamin K field,³⁷ responded to these concerns. Dr. Suttie stated that monitoring of Coumadin therapy is a well-recognized problem, and that Coumadin doses must be titrated because of a number of adverse influences in such therapy. He and the petitioner³⁸ stated that diet is usually not one of the primary factors of

concern in anticoagulation therapy, even though dietary vitamin K intake can vary day-to-day by three- to four-fold. Dr. Suttie asserted that changes due to consumption of vitamin K-compensated olestra would likely be within the normal range of dietary variation.

FDA concurs with Dr. Suttie's statements and concludes that olestra should be compensated with 8 µg vitamin K/g olestra. The majority of the FAC members also agreed that olestra should be compensated with vitamin K, and that the level selected by FDA is appropriate. FDA notes that if, in the future, the petitioner develops data that demonstrate that a lower level of compensation would be adequate, a petition could be submitted requesting an appropriate change in the required compensation level.

f. Carotenoids.—i. Data and information regarding carotenoids. The human studies demonstrate that consumption of olestra affects serum carotenoid levels. The petitioner concludes, and FDA concurs, that supplementing olestra with vitamin A will compensate for olestra's effects on the provitamin A function of carotenoids. There was no disagreement with this conclusion during the discussions at the Olestra Working Group and FAC meetings. The petitioner also concluded that it is not necessary to compensate olestra with any carotenoids, as there are no established beneficial health effects (aside from their provitamin A role) and further, that olestra's effect on carotenoid availability in the body is likely to be much smaller than that shown in the 8-week studies.

At the Olestra Working Group and FAC meetings, there was a thorough discussion of the possible beneficial health effects of carotenoids in preventing illnesses such as macular degeneration, prostate and lung cancer, and heart disease and whether olestra's effects on carotenoids would increase the risk of disease. In addition, the White Paper which was provided to the Committee, addressed the potential detrimental health impact of olestra's effect on carotenoids (Ref. 3). Information was also presented on whether carotenoids themselves have beneficial health effects, or whether it is other substances in the fruits and vegetables that provide the health benefits, and that carotenoids are serving solely as markers for fruit and vegetable consumption.

In his presentation to the Olestra Working Group,³⁹ Dr. Meir Stampfer, a professor of nutrition, stated that the results of an epidemiological study showed that higher levels of carotenoid intake, particularly lutein and zeaxanthin (which concentrate in the macula), have a marked protective effect against macular degeneration (Ref. 60). In addition, he stated that epidemiologic data show that individuals with high levels of lycopene intake were at a lower risk for developing prostate cancer a reduction that was statistically significant (Ref. 61). Dr. Stampfer also stated that there are many epidemiologic studies showing that individuals with high levels of plasma or serum carotenoids have a lower risk of lung cancer. Written information provided to the Committee also discussed the role of carotenoids in preventing cataracts, cardiovascular disease, and stroke.⁴⁰

Dr. Alvan Feinstein critiqued the epidemiological data for carotenoids in his presentation to the FAC.⁴¹ Dr. Feinstein stated that the epidemiologic evidence is not conclusive that carotenoids reduce the incidence of cancer or any other disease. Dr. Feinstein stated that epidemiologic case-controlled or other observational studies are problematic because the baseline state of those studied is not identified. In the studies of macular degeneration and of various cancers, for example, the health or disease state of participants before exposure is not known and differences may not be noted or adjusted for. Also, the compared agents are ascertained in retrospect, after they were taken; that ascertainment may be inaccurate or biased by a knowledge of outcome events. In addition, epidemiological studies lack reliability in terms of participants' accounts of what they ate or did not eat in the past. Finally, in such epidemiologic studies it is difficult to determine and adjust for the agent of interest (e.g., carotenoids, fruits, vegetables, or lycopenes).

Dr. Feinstein stated that, given these limitations with epidemiological studies, researchers, in general, are very reluctant to draw causal conclusions from epidemiologic data and prefer to rely, whenever possible, on randomized trials. One reason that randomized, experimental trials are preferable for

³⁴ FDA is not aware of any toxic effects of phyloquinone. In addition large quantities are routinely given for certain specific situations. For example, infants usually receive a single dose of 0.5 to 1.0 mg vitamin K injected intramuscularly shortly after birth to protect against bleeding.

³⁵ Donna Richardson, J.D., R.N., Howard University, Midlantic Women's Health Initiative. Ms. Richardson is a member of the FAC (Transcript, vol. 3, p. 255).

³⁶ Dr. Michael Jacobson, CSPI (Transcript, vol. 3, p. 179 and vol. 4, p. 15), and Dr. Ian Greaves, Associate Professor, and Deputy Director, Minnesota Center for Environmental and Health Policy, University of Minnesota School of Public Health. Dr. Greaves presented at the request of CSPI (Transcript, vol. 2, p. 267).

³⁷ Dr. John Suttie is a biochemist and nutritionist at the University of Wisconsin. Dr. Suttie consulted with the petitioner and presented at its request. Transcript, vol. 3, p. 256.

³⁸ Dr. John Peters, Procter and Gamble, Transcript vol. 1, p. 147.

³⁹ Dr. Meir Stampfer is a professor of nutrition at Harvard University School of Public Health. Transcript, vol. 1, p. 154. CSPI also provided FDA with a letter from Dr. Stampfer and Dr. Walter Willett prior to the FAC meeting. Dr. Stampfer presented at the request of CSPI.

⁴⁰ See for example Refs. 3 and 62.

⁴¹ Transcript, vol. 1, p. 172.

establishing cause and effect relationships is that the baseline state is clearly specified by the admission criteria, and the randomization produces an equal distribution for the differences in susceptibility to disease.

Dr. Feinstein discussed the results of the randomized trials concerning the health effects of carotenoid. He stated that to date, there have been five randomized trials of the effects of carotenoid consumption on disease, and that the data thus far have shown no convincing beneficial effect. A 1994 study in Finland assessed the effects of dietary supplements containing β -carotene versus placebo with lung and other cancers and identified a possible harmful effect of the carotenoid supplements.⁴² Other studies assessing the possible association between carotenoid supplement intake and nonmelanoma skin cancer (Ref. 64), and colorectal cancer (Ref. 65) also established no difference between the carotenoid and placebo groups in the selected outcome or in effects in the eye or coronary disease. Finally, a study examined the association between a combination of supplements (no placebos) and the death certificate diagnoses of cancer and found no statistically significant differences (Ref. 66).

The assessment of the significance of olestra's depletion of serum carotenoid should include consideration of the magnitude of the effect compared to variations in carotenoid utilization. Dr. James Olson, a professor of biochemistry,⁴³ noted in his presentation to the Olestra Working Group, that in the broader context of the diet, the effects of olestra on carotenoid utilization when used in savory snacks will be relatively minor, because a number of other factors influence carotenoid utilization, including carotenoid stability, bioavailability, and absorption. In the presence unsaturated fatty acids such as vegetable oils, for example, carotenoid are very rapidly destroyed. Similarly, carotenoid bioavailability can vary from almost zero to about 50 percent, depending on the vegetable concerned, cooking practice, and the presence and type of oils in the GI tract. (For example, in butter fat or coconut oil, carotenoid are

only about 50 percent as well absorbed as in more unsaturated oils.) Inhibitors to carotenoid absorption also exist, including fiber, particularly acidic pectins, and high concentrations of vitamin E. Dr. Olson subsequently provided FDA with a published study that shows that the increase in plasma β -carotene concentration 30 hours following consumption of a controlled meal containing 25 mg β -carotene and 12 g citrus pectin was only half as large as the increase observed in the absence of citrus pectin (Ref. 67). Furthermore, Dr. Olson noted that competitions occur between various carotenoid for absorption; in particular, lutein, canthaxanthin, and β -carotene mutually inhibit each other's absorption.

Although olestra does affect carotenoid absorption, the petitioner asserted that only the more lipophilic carotenoid would likely be affected by olestra. The petitioner presented data regarding the octanol:water partition coefficients (PC's), a measurement of how fat-soluble a substance is,⁴⁴ for the various carotenoids, and noted that substances with a \log_{10} PC above about 7.5 can be affected by olestra if they are consumed simultaneously with the olestra.⁴⁵ Three of the four carotenoids monitored (α -carotene, β -carotene, and lycopene) are the most lipophilic carotenoids with octanol:water PC's of approximately 17.6 each and would thus be expected to be the most affected by olestra. Indeed, the 8-week studies and 16-week vitamin E study show that the effects of olestra on the serum levels of these carotenoids are very similar. Lutein and zeaxanthin, which have more hydroxyl groups, are about 1,000 times less lipophilic (PC's of 14.82 and 14.95, respectively) than β -carotene (Ref. 68).

In addition, it is possible that serum carotenoid levels are not good indicators of carotenoid availability in the body. Dr. Olson pointed out that the plasma carotenoids amount to approximately one percent of the total tissue content of carotenoids. Plasma carotenoid concentrations can vary fairly rapidly within 1 to 4 weeks whereas tissue concentrations change much more slowly. Because protective aspects of carotenoids would be expressed at the intracellular level, plasma carotenoid concentrations, particularly in short-term studies, may not be very accurate indicators of useful carotenoid levels.⁴⁶

Similarly, Dr. Leonard Cohen,⁴⁷ in a presentation to the Olestra Working Group, also pointed out that serum measurements are single-point at a certain time of the day, but that carotenoid levels have Circadian rhythms. Therefore, one cannot tell at one point of the day whether levels will be the same at another point of the day.

Finally, Dr. Olson noted that five different conferences or reviewing groups have examined the relationship between carotenoids and disease: A U.K. Committee on the medical aspects of food policy (1987); the Life Science Research Offices of the Federated American Societies of Experimental Medicine in Biology; a European Union of Scientific Committees for Food (1992); an International Life Sciences Workshop on Antioxidants and Health (1993); and an FDA Conference on Antioxidant Nutrients (1993). He stated that all of these groups concluded that there is insufficient evidence to recommend specifically consumption of carotenoids, except to encourage the consumption of vegetables and fruit.

After considering all the presentations and information submitted by CSPI in their White Paper (Ref. 3), a substantial majority of the Olestra Working Group felt that there is a reasonable certainty of no harm from olestra's effects on serum carotenoid levels.

However, some members of the Olestra Working Group voiced concern about olestra's effects on carotenoid serum levels. Because of this concern, FDA subsequently consulted with scientists at the National Institutes of Health (NIH) and requested their views on whether olestra's effects on lipophilic carotenoids raise any significant public health issues with respect to the possible association between carotenoids and cancer risk⁴⁸ and macular degeneration⁴⁹ (Refs. 69 and 70). The agency provided these scientists with copies of letters concerning carotenoids that the agency had received (including the letter from Dr.'s Willett and Stampfer (Ref. 62)), submissions by the petitioner, excerpts discussing carotenoids from the White Paper, and relevant sections of the Transcript from the Olestra Working Group and FAC meetings.

Regarding cancer risk, Dr. Peter Greenwald stated that the effects of olestra on carotenoid utilization under

⁴² Dr. Greaves mentioned that blood draws at the beginning of the Finland study showed that men in the lower quartile for serum β -carotene in the blood had significantly higher incidence rates of lung cancer than the men with the high levels of β -carotene in blood (Ref. 63).

⁴³ Dr. James Olson, Professor, Biochemistry and Biophysics Department of Iowa State University, researcher in the field of carotenoid and vitamin A. Dr. Olson has consulted with the petitioner and presented at its request. Transcript, vol. 3, p. 190.

⁴⁴ Octanol:water partition coefficients (PC's) are generally expressed on a log scale so that a substance with a PC of 12 is 10 times as fat soluble as a substance with a PC of 11.

⁴⁵ Transcript, vol. 2, p. 125.

⁴⁶ Transcript, vol. 3, p. 192.

⁴⁷ Dr. Leonard Cohen, Section Head, Nutrition and Endocrinology, American Health Foundation. Transcript, vol. 3, p. 149.

⁴⁸ Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control, National Cancer Institute, NIH.

⁴⁹ Dr. Carl Kupfer, Director of the National Eye Institute, NIH.

the conditions of use would be expected to be relatively minor, that the provitamin role of carotenoids is the only function that has been adequately documented, and that plasma carotenoid concentration (which were used in the reported epidemiological studies) probably is not a reliable indicator of tissue levels and may in fact be misleading. Therefore, he concluded that no significant health issue was raised by the reported effects of olestra on lipophilic carotenoids. Furthermore, he recommended against supplementing olestra with β -carotene or other carotenoids at this time (Ref. 71).

Regarding macular degeneration, Dr. Carl Kupfer stated that although theoretical considerations have raised the possibility that carotenoids might play some protective role in macular degeneration, there are currently no convincing clinical data to substantiate the hypothesis. Furthermore, he asserted that no clear eye health benefit has been demonstrated for carotenoids (Ref. 72).

ii. *FDA's evaluation of olestra's effects on carotenoids.*

On balance, having considered all the comments, data, and information that the agency has received on this subject, FDA has determined that the information currently available show that olestra's effects on the absorption of the lipophilic carotenoids is reasonably certain to be insignificant from a public health standpoint. First, FDA has determined that the available data do not establish any identifiable nutritional or prophylactic benefits for the carotenoids, either individually or collectively. Specifically, controlled randomized studies have been performed to test the potential cancer-protective effects of carotenoid consumption and have shown no association between carotenoid consumption and cancer.⁵⁰ Also, there have been no controlled studies to examine the association between carotenoid consumption and eye disease.

The agency believes that its conclusion regarding the absence of harm from olestra's effect on some carotenoids, which conclusion is based on the scientific evidence currently available, is not inconsistent with the currently available epidemiological studies. This is because the epidemiologic studies show an association between diets rich in fruits and vegetables and decreased cancer risk and do not evaluate the association

between carotenoids *per se* and lower disease risk. Thus, there is no direct evidence from these epidemiologic studies that carotenoids are the substances responsible for the protective effect. In fact, as noted by several experts, serum carotenoid levels may simply be markers for consumption of fruits and vegetables.

The agency's determination that olestra's effects on the absorption of carotenoids is reasonably certain to be insignificant is bolstered by the fact that the actual magnitude of olestra's effects on carotenoid absorption is likely to be within the range of the normal variation due to diet and bioavailability because the percentage of consumed carotenoids that are actually available to the body is highly variable and affected by a number of factors. In fact, the agency believes that it is likely that olestra's effects on carotenoid absorption will likely be substantially less than those observed in the 8-week studies and will be more similar to the effects observed in the 16-week vitamin E study.⁵¹ Finally, the association between serum carotenoid levels and the availability of carotenoids at the cellular level is unclear. Hence, the relationship between olestra's effects on serum carotenoids and the body's utilization of carotenoids is also unclear.

Therefore, FDA has determined, based upon the scientific evidence that exists at this time, that there is currently no justification or need to require compensation of olestra-containing foods with specific carotenoids.⁵²

C. Effects of Olestra on Water-soluble Nutrients that are Hard-to-Absorb or Limited in the Diet

The two 8-week clinical studies in the human and the two 12-week, the 26-week DR/VR, and the 39-week VR studies in the pig were used to assess olestra's potential effects on water-soluble nutrients. Iron, folate, vitamin B₁₂, and zinc status were measured in both the pig and human studies. Vitamin B₁₂ absorption was also measured in the human studies. Calcium status was measured only in the pig studies, because there are no

⁵¹While FDA finds that the petitioner's hypothesis that actual reductions in carotenoid levels will be affected by consumption patterns and will therefore be even less than those observed in the 16-week vitamin E study is plausible, the actual magnitude of the effect is not supported with data at this time.

⁵²This conclusion is consistent with the recommendations of the various conferences that have been held to examine the relationship between carotenoids and disease and is also consistent with FDA's decisions regarding health claims for antioxidant vitamins and cancer (58 FR 2622, January 6, 1993.)

non-invasive methods sufficiently sensitive to assess calcium status in humans. The human and pig studies are described in section V.B. of this document, and the methods used to measure the status of calcium, zinc, iron, folate, and vitamin B₁₂ are summarized in Table 4 (human studies) and Table 6 (pig studies).

1. Results and Conclusions from Human Studies

a. *Vitamin B₁₂.* In the 8-week human DR and VR studies, there was no change in serum measures of vitamin B₁₂. However, 8 weeks is insufficient to observe effects in serum, and the presence of excess vitamin B₁₂ in the diets likely reduced the sensitivity of the studies to evaluate vitamin B₁₂ status. The petitioner also found that absorption of vitamin B₁₂ did not change as a result of olestra consumption in either 8-week human study, as measured by the Schilling test. FDA notes that dietary levels of vitamin B₁₂ were approximately 2.2 and 1.7 times the RDA in the DR and VR studies, respectively. However, this overfortification does not affect interpretation of the results of the Schilling test because the level of vitamin B₁₂ in the diet is not a factor in the Schilling test.⁵³ FDA concludes that the results of the Schilling test shows that olestra has no effect on vitamin B₁₂ absorption in humans.

b. *Iron.* Measures of iron status were performed in the 8-week VR study. The petitioner concluded that olestra had no effect on iron status, and that sporadic, statistically significant trends with olestra dose in one or more of the measures at one or more time points resulted from differences in status at baseline or from a general decrease in iron stores resulting from phlebotomy (drawing blood for analysis). FDA agrees with the petitioner's conclusion that there were no changes in all measures of iron stores, with the exception of serum ferritin levels for both treatment and control groups. FDA further concludes that the decreased serum ferritin levels were consistent with loss due to phlebotomy (Ref. 73).

c. *Folate.* Folate status was monitored in the 8-week DR study in which folate was consumed at levels between 80 and 120 percent of its RDA. There was no olestra dose response on the indices for folate (serum and red blood cell folate concentration). FDA considers red blood cell folate levels to be excellent

⁵³The Schilling test is an acute test that measures the absorption of a dose of radiolabeled vitamin B₁₂

⁵⁰In fact, well-controlled studies indicate that there may be higher incidence of lung cancer in smokers consuming high levels of β -carotene.

indicators of folate status.⁵⁴ Thus, the agency agrees with the petitioner's conclusion that olestra consumption does not affect folate status.

d. *Zinc*. Zinc status was evaluated in the 8-week DR study. There was no olestra dose response on the indices for zinc that can be measured noninvasively in humans (serum and urinary concentration). FDA agrees with the petitioner's conclusion that there is no evidence that olestra affects zinc status. However, the agency notes that serum and urinary concentrations are not sensitive indicators of zinc status in humans. Although these data are not particularly sensitive indicators of zinc status, FDA finds that the data support a finding of no effect. However, FDA does not consider the data sufficiently sensitive to support, in and of themselves, a conclusion of no effect.

2. Results and Conclusions from Pig Studies

Data from the studies of olestra consumption in pigs generally corroborate the findings from the human studies regarding the effect of olestra on iron and zinc status. Although, the results of the pig studies regarding vitamin B₁₂, calcium, and folate, do not indicate any effect of olestra, these studies are of limited utility in assessing olestra's effects because of several weaknesses in study design, as discussed below.

a. *Vitamin B₁₂*. There were no statistically significant effects of olestra on liver vitamin B₁₂ in the 12-week VR, the 26-week VR/DR, and the 39-week VR pig studies. In the 12-week DR study, a statistically significant downward trend in liver vitamin B₁₂ levels, produced by a low value in the 7.7 percent olestra group, was observed. There were no statistically significant decreases in the 1.1 percent, 2.2 percent, 3.3 percent, 4.4 percent, or 5.5 percent olestra groups. The low value in the 7.7 percent olestra group was not accompanied by an elevation in mean corpuscular volume, and thus, the petitioner concluded that this decrease did not represent a change in vitamin B₁₂ status. (FDA notes that the downward trend was not found in other pig studies.)

FDA concludes that the pig studies are limited in their usefulness in assessing olestra's effects on vitamin B₁₂. FDA's principal reservation is that the level of vitamin B₁₂ was measured only in the diet premix and not in the complete diets; such analysis of the premix is not as reliable as analysis of the complete diet because an accidental

mixing error may have occurred or the vitamin may have been degraded or spared from degradation by an interaction with another ingredient during the mixing process or during storage. Accordingly, FDA finds that, although there was no consistent effect of olestra on vitamin B₁₂, these pig studies are inadequate by themselves to evaluate olestra's effect on vitamin B₁₂.

b. *Iron*. A battery of tests (liver iron concentration, serum total iron binding capacity, and serum total iron concentration) conducted in the 12-week VR, 26-week DR/VR, and 39-week VR studies showed no adverse effects on iron status when olestra was fed at any level (up to 7.7 percent of the diet). There were statistically significant decreases in liver iron values in the 12-week DR study in both the 5.5 percent and 7.7 percent olestra groups. However, in these groups, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell count were unaffected by olestra consumption. The petitioner postulated that the trend in liver iron concentration was probably secondary to the poor vitamin A status of the animals, and thus, concluded that iron status was not affected by olestra.

FDA notes that there was a large variability in liver iron values in all pig studies. FDA postulates that the variability in liver iron levels may have been due to several factors, such as blood loss from gastric ulcers, dewclaw lesions or abscesses, or differences in the amount of blood present in the liver after sacrifice. FDA further notes that the test diets were oversupplemented with iron in that the diets contained between 1.7 to 2.4 times the NRC requirements. FDA finds that these results make it possible to rule out gross effects on iron status but the foregoing factors make it difficult to exclude subtle effects in these studies (Ref. 56). Accordingly, FDA finds that the pig studies are inadequate by themselves to evaluate olestra's effect on iron.

c. *Folate*. The petitioner stated that there were a few statistically significant differences in plasma folate concentration at week 4 in the 26-week DR/VR study, but the values in the olestra groups were greater than the control. There were no statistically significant changes in plasma folate in the two 12-week studies, nor in the 39-week VR study. Therefore, the petitioner concluded that folate status in pigs was not affected by olestra consumption.

FDA finds that a conclusion on folate status cannot be drawn from the pig studies for several reasons. First, no measurements of folacin, either in the premix or in the diet as fed, were made

in any of the studies. Second, folic acid was added to the diet, rather than foyllypolyglutamates, the predominant form of folate in the American diet. Folic acid (foyllymonoglutamate) is absorbed directly, while foyllypolyglutamates must be cleaved by foyllypolyglutamate hydrolase in the intestine prior to being absorbed. Therefore, folacin is not a hard-to-absorb nutrient when it is supplied as folic acid, as in these studies. Finally, plasma folate is not as sensitive a measure of folate status as red blood cell folate (the method used in the human studies). Therefore, FDA concludes that the pig studies are of limited utility in assessing olestra's effects on folate (Ref. 56).

d. *Zinc*. There were no significant effects of olestra on liver, bone, or serum zinc levels in the 12-week DR study or the 26-week DR/VR study. The only significant differences from control values in these three measures of zinc status in the 12-week VR and 39-week VR studies were small (and probably spurious) increases in liver zinc in the 0.25 percent low vitamin group in the 39-week VR study and in serum zinc in four olestra groups at week eight in the 12-week VR study. Accordingly, the petitioner concluded that liver, bone, and serum zinc concentrations were not affected by olestra in any of the pig studies.

In general, FDA concurs with this conclusion, with some qualifications, as discussed below.

Although they did not show any significant differences, the bone zinc measurements are less than an ideal means of assessment because the methodology used to analyze the bone has several flaws that limit the power and reliability of the results. (These flaws are discussed in the calcium section below.) Because of these methodological flaws, FDA concludes that the bone zinc measurements of the pig studies do not provide a completely reliable assessment of zinc status.

FDA notes that liver and serum measurements of zinc, in controlled swine studies, are acceptable measurements of zinc status that have sensitivities comparable to properly performed bone measurements. A potential confounding factor in the assessment of zinc status in the pig studies is the amount of zinc in the test animal diets. FDA estimates that zinc consumption in the 12-week VR, 26-week DR/VR, and 39-week VR studies exceeded the NRC requirements by at least 68 percent. However, a review of the literature shows that serum and liver zinc measurements will reflect dietary zinc over a wide range of dietary

⁵⁴ Transcript, vol. 3, p. 117.

concentrations in controlled swine studies. Therefore, FDA believes that this oversupplementation would not mask any effects of olestra on zinc status. FDA concludes, therefore, based on the results of the liver and serum measurements in these studies, that there is no evidence that consumption of olestra affects zinc status.

e. *Calcium.* Bone ash and bone calcium levels were not affected by olestra consumption in the 12-week VR, 26-week DR/VR, or 39-week VR pig studies. The only change was seen in the 12-week DR study where bone ash but not bone calcium was less (60.6 ± 2.0 vs. 61.1 ± 1.0 percent) in the 4.4 percent olestra dose group than in the control group (Refs. 74 and 75), a difference that was statistically significant. The other dose groups showed no statistically significant change in bone ash or bone calcium. The petitioner concludes that these results demonstrate that olestra consumption does not have an effect on calcium status.

FDA concludes that the results from the pig studies are not useful for determining whether olestra has any subtle effects on calcium status; the results show only that there were no gross changes in calcium status. FDA's determination that these studies are seriously limited in their utility to determine calcium status changes is based on two factors:

oversupplementation of calcium in the diet and flawed methodology in measuring bone ash and bone calcium.

FDA believes that the bone ash measurements are not reliable because the test animals' diet was oversupplemented with calcium. Specifically, test animals received approximately 1.0 to 1.3 times the NRC calcium requirements during the 12-week studies (with the greater amounts during the last 7 weeks) (Refs. 76 and 53), and 1.2 to 1.7 times the NRC requirement during the 26-week DR/VR and 39-week VR studies (Ref. 52). Based on published studies (Refs. 77 and 78), FDA believes that bone ash will reach maximum levels when dietary calcium is approximately 1.2 times the NRC requirement and adequate levels of phosphorus are provided (Ref. 56). Therefore, the supplementation above 1.2 times the NRC requirement would mask any subtle effect on calcium absorption.

In the 26-week DR/VR and 30-week studies, olestra would have to have inhibited the absorption of approximately 30 percent of the calcium before any adverse effects on bone ash would have been observed (Ref. 56). Thus, the bone ash data from these

studies are not a stringent test of calcium status. Although the oversupplementation in the 12-week studies would not mask olestra effects on calcium as much as it would in the 26-week DR/VR and 39-week VR studies, methodological factors in obtaining the data on bone ash, as described below, in combination with the slight oversupplementation during the last 7 weeks, make the calcium data only useful in determining whether there were gross effects of olestra on calcium status.

Factors that CFSAN considers contributing to the limitations of the methodology that was used to evaluate bone ash include the following: (1) Only half of the bone selected for analysis (the L5 lumbar vertebra) was used, rather than using the whole bone; (2) after drying and grinding the half bone, an aliquot of the ground bone (approximately 1.5 g) was taken for fat extraction, rather than extracting the entire sample; (3) an aliquot (approximately 0.5 g) of the fat-free bone powder was ashed, rather than ashing the entire sample; and (4) ashing was performed at 500 °C for 8 hours, rather than more typical conditions of > 550 °C for > 12 hours (Ref. 79).

Because of these methodological flaws, FDA concludes that the bone ash and bone calcium measurements performed in the pig studies do not provide a reliable assessment of calcium status.

Although FDA finds that the data from the pig studies are of limited use in determining whether olestra affects the absorption of calcium because the test diet was overfortified with calcium and appropriate measures of bone were not made, FDA notes that the animals grew normally and all outward observations indicated that they had normal skeletal growth.

3. Overall Conclusions Regarding Olestra's Effects on Water-Soluble Nutrients

The agency received no significant comments expressing concern about olestra's effects on water-soluble nutrients. Similarly, Dr. Connie Weaver, FDA's consultant on water-soluble nutrients, also found no basis for concern (Ref. 75). FDA's specific conclusions on these nutrients follow.

a. *Vitamin B₁₂.* FDA has determined that there is no need for compensation of olestra-containing foods with vitamin B₁₂. In reaching this conclusion, the agency relied primarily on the 8-week human DR and VR studies in human to evaluate the effect of olestra on vitamin B₁₂. Both studies showed no effect of olestra on vitamin B₁₂ using the

Schilling test, which is a sensitive test that is not affected by dietary vitamin B₁₂ levels. The vitamin B₁₂ results of the pig studies are consistent with the results of the human studies. In the pig studies, no effect of olestra was seen in the 12-week DR, the 26-week DR/VR, or 39-week VR studies. There was a statistically significant decrease in liver B₁₂ levels in the highest olestra dose group (7.7 percent) in the earliest pig study (the 12-week VR study). Because this result was not corroborated by results of any of the other studies, FDA concludes that, collectively, the data establish that olestra does not affect vitamin B₁₂ absorption.

b. *Folate and iron.* The results from the 8-week human studies establish that folate and iron status were not affected by olestra consumption. These studies were well designed, the methods used were sufficiently sensitive to evaluate olestra's effects, and the duration of the studies was long enough to see any such effect. Although there were limitations in the quality of the results of the pig studies with regard to folate and iron, in general, the results of the pig studies support the conclusion drawn from the human studies that olestra consumption does not adversely affect iron or folate status.

c. *Zinc.* Zinc status was evaluated by three acceptable methods: serum and urinary zinc in the 8-week human studies, and serum and liver zinc in the pig studies. None of these analyses, in any of the studies, demonstrated an effect of olestra consumption on zinc status. The analysis for zinc in bone has methodological limitations. Therefore, although these results are consistent with the other zinc measurements, FDA is not relying on the bone results.

FDA concludes that the totality of the results, in both the human and pig, using all three methods, provides strong evidence that olestra consumption does not affect zinc absorption. In addition, FDA is not aware of any hypothesis that would support an effect of olestra on zinc status.⁵⁵ Therefore, FDA concludes that consumption of olestra does not affect zinc status.

d. *Calcium.* With respect to calcium, FDA concludes that there is no basis for concluding that calcium absorption would be adversely affected by olestra consumption. First, there is no plausible hypothesis for how olestra could affect calcium absorption other than by

⁵⁵ At the Olestra Working Group meeting, Dr. Schneemna, FDA's overarching nutritional consultant, stated that the only mechanism she could envision of olestra to affect any water-soluble nutrient would be a general mechanism causing lower bioavailability for a variety of nutrient. Transcript, vol. 2, p. 97 and vol. 3, p. 130.

vitamin D depletion. Unlike the fat-soluble vitamins, calcium is water soluble and would not be expected to partition into olestra. Other mechanisms by which olestra might affect calcium absorption are: (1) by forming a physical barrier that would prevent calcium from reaching the mucosal cell surface, where it is absorbed; or (2) by decreasing GI transit time so drastically that there is little chance for calcium to make mucosal contact. However, these mechanisms would also be expected to affect the absorption of folate, vitamin B12, and iron, yet, importantly, as discussed above, these nutrients are unaffected by olestra consumption. Also, published studies (Refs. 80 and 81) indicate that olestra does not significantly alter gastric emptying or overall GI transit time.

Further, it is likely that the effect of variations in calcium intake in the normal diet (especially as a result of dietary choices concerning calcium-rich foods such as dairy products) would be much greater than any effect from olestra consumption on calcium absorption (Ref. 75). Also, the compensatory homeostatic mechanisms the body has for calcium, and the fact that studies have shown that high-fat diets do not affect absorption of vitamin B₁₂, folate, iron, or zinc, are additional reasons for reduced concern about the potential effect olestra on the absorption of calcium. Finally, studies of mineral oil (a substance much like olestra in that, like fats, it is non-polar and is not absorbed) in the published literature support the conclusion that any effect by olestra on calcium is likely to be vitamin D-mediated rather than a direct effect on its absorption (Refs. 82 and 83). Compensating for olestra's effects on vitamin D will thus preclude any effects of olestra consumption on calcium produced by vitamin D depletion.

Thus, given the lack of effect on other water-soluble nutrients and the lack of any probable mechanism for olestra to affect calcium, FDA concludes that there is no basis for concern regarding olestra's effects on calcium status.

Effect of Olestra on the Gastrointestinal (GI) Tract

A. Introduction

Because olestra is not digested or absorbed and passes unchanged through the GI tract, it has the potential to affect GI physiology and function. Therefore, the petitioner conducted several studies to assess olestra's potential to affect the GI tract.

For example, the petitioner assessed the potential for olestra to elicit GI

symptoms such as cramping, bloating, loose stools, and diarrhea-like symptoms by collecting adverse effect reports in studies designed primarily to assess potential effects of olestra on absorption of nutrients from the diet. The petitioner also collected data on GI symptoms in a human study (the oil loss study) designed to set a specification for olestra stiffness (i.e., viscosity). (The oil loss study sought to establish the viscosity that would prevent olestra from separating from other fecal contents in the colon and leaking past the anal sphincter (passive oil loss)). Other studies addressed the potential for olestra to cause GI symptoms in the young and in patients with inflammatory bowel disease (IBD). The study in patients with IBD also assessed the potential for olestra to adversely affect disease activity. Finally, the petitioner conducted several studies to assess the potential for olestra to affect the normal metabolic activity of intestinal micro flora and the potential for olestra to affect the absorption, synthesis, and excretion of bile acids.

B. Effect of Olestra on GI Symptoms

1. Study of GI Symptoms in 8-week Studies in Normal Subjects

Data on GI symptoms were collected in the two 8-week human clinical studies conducted to determine olestra's potential to affect nutritional status. The design and methodology of these studies are described above in detail in Section IV.B.1.a. The petitioner believes that data from the two 8-week studies are particularly useful in understanding the potential for olestra to produce GI symptoms because the olestra doses used were large (up to 32 g/d) and were consumed every day, the studies were lengthy (8 weeks), and details of the GI symptoms were recorded by the subjects for each day they reported symptoms. Specifically, subjects were questioned daily about changes in their health, including GI symptoms. If a GI symptom was experienced, a subject completed a detailed questionnaire which asked about the type, severity, and duration of symptoms experienced. To facilitate collection of GI symptom data, the questionnaire provided a list of common GI symptoms along with general definitions of each. This served to remind subjects of other possible symptoms in addition to the one that first prompted completion of the GI symptom report.

The petitioner noted two considerations relevant to the evaluation of the GI symptom reports. First, the subjects were prompted every day to report symptoms and were

provided with a list of commonly experienced GI symptoms; this would be expected to amplify the reporting of GI symptoms, relative to data collected under unprompted conditions. In addition, the collected symptom data will closely reflect actual incidence, rather than capturing only those symptoms that subjects judged significant enough to report. Second, the petitioner stated that the two 8-week studies were not intended to examine GI symptoms under real-life consumption conditions where snacks are not consumed every day with every meal and where people may moderate intake if they experience GI symptoms; therefore, the GI symptom data from these studies may have exaggerated what will occur in young, healthy adults consuming olestra snacks under real life conditions.

a. *Petitioner's evaluation of GI symptoms.* Because the two 8-week studies were run under nearly identical protocols, the petitioner combined the GI symptom data from the two studies for analysis. GI symptoms were reported by subjects in all groups, including placebo. The petitioner stated that the number of people reporting GI symptoms in the two 8-week studies increased in a dose responsive manner with olestra dose. The number of individuals who ate eight g/d olestra⁵⁶ for 8 weeks and reported at least one GI symptom (62 percent) was greater than the number who ate a corresponding amount of a triglyceride for 8 weeks and reported at least one GI symptom (45 percent). The petitioner noted that the GI symptoms reported by the control and 8 g/d groups of subjects were essentially not different in severity, length of episodes, or total number of symptom days (number of days on which symptoms occurred times the number of symptoms). The petitioner also noted that GI symptoms reported by subjects who consumed larger amounts of olestra (20 g/d or 32 g/d) were of the same kind and severity as those reported by subjects in the placebo and eight g/d olestra groups; however, the total number of symptom days was greater in the two groups consuming the higher levels of olestra.

The petitioner concluded that none of the GI symptoms reported by subjects eating either triglyceride or olestra at any level (8, 20, or 32 g/d) were clinically significant. According to the petitioner, the GI symptoms spontaneously abated and recurred during the course of the study in all

⁵⁶ Eight g/d olestra intake approximates the lifetime average 90th-percentile intake for snack eaters.

groups and stopped within 5 days after the study ended. The petitioner also stated that the GI symptoms experienced by an individual eating olestra-containing foods are self-limiting in the sense that the symptoms either stopped in the face of continued consumption of such foods or ceased when the individual stopped eating the olestra-containing food or reduced the amount consumed. The number of subjects reporting symptoms at any given time and the severity of the symptoms remained essentially constant over time among the different treatment groups, indicating that symptoms did not worsen with prolonged consumption of olestra. In addition, clinical laboratory data collected at the time subjects were reporting symptoms did not show clinically significant effects such as hemoconcentration, electrolyte imbalance, or increased urinary creatinine or specific gravity.

The petitioner stated that the symptoms were, on average, mild to moderate in all groups. As an indication of the mildness of the symptoms, the petitioner stated that few individuals reporting GI symptoms in the two 8-week studies dropped out of the studies because of the symptoms. (Four of a total of 115 subjects in the 20 and 32 g olestra per day groups dropped out; out of these 4, only 1 was attributed to GI symptoms experienced (heartburn)).

Although most of the symptoms were reported as mild on average, the petitioner stated that at least one symptom described as severe was reported by some subjects: 5 percent (placebo), 10 percent (8 g/d olestra), 26 percent (20 g/d olestra), and 22 percent (32 g/d olestra). All severe symptoms reported by the placebo and eight g/d olestra groups were limited to 1 day. For the 20 g/d olestra group, the maximum duration of severe symptoms was 2 days, and for the 32 g/d group, it was 4 days. According to the petitioner, GI symptoms reported by people eating 20 or 32 g/d olestra are similar to those reported by people eating high amounts of common food ingredients that elicit GI symptoms. The petitioner asserted that high fiber diets produce GI symptoms such as stomach cramps, loose stools, diarrhea, bloating, and flatulence. Therefore, the petitioner concluded that persons eating olestra-containing foods, even at levels beyond the expected consumption from snacks, are unlikely to experience GI symptoms that are different from those they might normally experience consuming other foods or from dietary changes.

b. *FDA's evaluation of the GI symptoms.* Unlike the petitioner, in its original analysis, FDA evaluated the

adverse effects reports from the two studies separately, because there did not appear to be any reason or need to combine the two data sets. In analyzing the two studies, FDA, however, did combine reports of loose stools and diarrhea (Ref. 84), for the following reason. The petitioner defined loose stools as bowel movements that were unformed but not watery, and diarrhea-like stools as watery stools that were difficult to control and had little or no solid material.⁵⁷ However, the difference was between loose stools and diarrhea-like stools may not have always been clear to the subjects. Further, substantial fluid and electrolyte losses could potentially result from either form of stools. Thus, FDA believes that it is preferable to combine these two reported effects for analysis.

In its presentation of the GI symptom data to the Olestra Working Group and the FAC, FDA did combine the data from the two studies; combining the data is acceptable for the following reasons: (1) Both studies used the same olestra dosages (placebo, 8 g/d, 20 g/d, and 32 g/d); (2) similar criteria were used in both studies for selecting and excluding study subjects; (3) the studies were of the same duration; and (4) the same methods were used to monitor for adverse GI experiences. By pooling the data, the statistical power of the study increased.⁵⁸

At the Olestra Working Group and FAC meetings, there was some discussion regarding the advisability of pooling data from the two studies. For example, CSPI stated in their White Paper that the two studies were analyzed separately because one of the studies had a very high rate of GI problems in the control group that masked the difference between the placebo and the 8 g/d groups and also because the second study had a low level of GI problems in the control group.⁵⁹ Others stated that not only could the studies be combined, but that the conclusions were the same whether or not the data were pooled, i.e., there was increased reporting of GI effects with increasing olestra doses.⁶⁰

⁵⁷ Reporting of diarrhea was based on subjects' perception of diarrhea. There was no measurement of water-content made. However, subjects' electrolyte levels were monitored. FDA recognizes that the effect observed may not be diarrhea in the clinical sense but is using that term in this preamble because it is the term used in the study report.

⁵⁸ Transcript, vol. 2, p. 185.

⁵⁹ Statement of Dr. Michael Jacobson, CSPI, Transcript, vol. 1, p. 171.

⁶⁰ Statements of Dr. David Allison, Dr. Joann Lupton, and Dr. Karl Klontz. Dr. Allison is an Associate Research Scientist at New York Obesity Research Center, Saint Luke/Roosevelt Hospital. He

FDA's analysis of the data from the two 8-week studies showed there was a dose-response effect for olestra with respect to two endpoints, reported diarrhea/loose stools and fecal urgency. For example, in the 8-week DR study, the percentage of subjects who experienced loose stools or diarrhea (at any time during the study) was 19 percent (control group), 45 percent (8 g/d olestra group), 74 percent (20 g/d olestra group), and 67 percent (32 g/d olestra group). In general, whether the data from the two studies were analyzed separately or together, the incidence of GI symptoms in the eight g/d olestra group was not statistically different from that of the control group; the differences in the incidences of GI symptoms between the control group on the one hand and the 20 or 32 g/d olestra groups were statistically significant.

Although FDA agrees that, in general, the GI symptoms started and stopped in all groups, FDA notes that, in some olestra-fed subjects, the GI symptoms persisted for a long period of time. For example, over the course of the 56 days, two study subjects in the 20 g/d olestra group reported loose stools for 38 and 40 days, respectively, and another subject in the same group reported experiencing fecal urgency and loose stools for 55 days. In the 32 g/d olestra group, three subjects reported loose stools for more than 50 days. FDA agrees that these GI symptoms cease when olestra is no longer consumed. However, FDA believes it is important that consumers know that the GI symptoms they are experiencing may be due to consumption of olestra. This need for information is discussed in section VII of this document.

As noted, the petitioner contends that the nature and severity of the GI symptoms observed among the olestra-consuming participants were comparable to symptoms experienced by persons consuming diets moderate or high in fiber. FDA does not agree. While high-fiber diets have been associated with increased gas manifested as belching, flatulence, and mild abdominal distention, diarrhea and staining of underwear (discussed in following section) have not commonly been reported (Refs. 85 and 86).

Finally, FDA concurs with the petitioner that there was no evidence in either study that subjects experiencing olestra-related symptoms described as

was a temporary member of the FAC. Dr. Lupton is an Associate Professor of Human Nutrition at Texas A&M. She was FDA's consultant on GI issues. Dr. Karl Klontz is with FDA. Transcript, vol. 3, pp. 49-54.

“diarrhea” also experienced significant fluid and electrolyte loss.

2. GI Symptoms in the Oil Loss Study

The petitioner conducted an oil loss study.⁶¹ This study had three objectives to determine: (1) The minimum olestra stiffness that would control passive oil loss, as measured by underwear staining, to the level experienced by a triglyceride placebo group; (2) the relationship between olestra stiffness⁶² and the occurrence of oil in the toilet (OIT); and (3) whether the stiffness of olestra affected the incidence of common GI symptoms experienced by the subjects.

The oil loss study was a double-blind, placebo controlled, parallel design study with seven groups of 18 to 44 year old male and female subjects (173 to 182 per group). Six groups consumed 34 g/d of olestra of varying stiffness (18, 45, 50, 66, 78, or 103 kPa/s) in potato chips for 5 days. A placebo group consumed an equivalent amount of potato chips prepared with triglycerides. All groups consumed the potato chips as part of a normal diet.

At the end of the 5 days, the subjects completed a questionnaire answering specific questions about underwear staining due to passive oil loss and incidence of oil droplets in the toilet (OIT) following defecation. In addition, reports of adverse GI experiences (e.g., diarrhea, abdominal pain, indigestion) were collected during the consumption period as well as the 3 days following the treatment phase.

a. *Effect of olestra stiffness on passive oil loss.* From the results of this study, the petitioner concluded that the incidence of passive oil loss in subjects who consumed olestra with a stiffness

⁶¹ Passive oil loss can occur when people consume large amounts of nonabsorbable oil that is liquid at body temperature, such as mineral oil or liquid olestra; liquid oil separates from other fecal material in the colon and leaks past the anal sphincter. The petitioner observed that early formulations of olestra caused passive oil loss, but that oil loss could be decreased by increasing the stiffness of olestra at body temperature. Stiffer olestra has less of a tendency to separate from the fecal matrix.

⁶² The stiffness of olestra was characterized by measuring a rheological parameter called the thixotropic area, which is determined by measuring the shear stress on olestra as the shear rate is first increased and then decreased. The area between the ascending and descending shear stress versus rate curves is the thixotropic area. Olestra that is liquid at body temperature has thixotropic areas approaching zero. Highly saturated olestra that is largely solid at body temperature has thixotropic areas well above 100 kilopascals/sec (kPa/s). In practical terms, olestra with a stiffness of 18 kPa/s had a consistency similar to a typical catsup at room temperature; olestra with a stiffness of 50 kPa/s has a consistency similar to mayonnaise; olestra with a stiffness of 103 kPa/s is similar to cold margarine.

less than or equal to 45 kPa/s (i.e., those in the two lowest treatment groups) was significantly increased relative to the incidence reported by the subjects consuming triglycerides (the placebo group). The incidence of passive oil loss in subjects consuming olestra of greater than 50 kPa/s was not significantly different from the incidence reported by subjects in the placebo group. FDA's analysis of these data agreed with the petitioner's analysis.

At the Olestra Working Group and FAC meeting, CSPI stated that their analysis showed that there are statistically significant increases of passive oil loss above control with olestra at the higher stiffness levels.⁶³ However, no details on how the data were analyzed were given. FDA had the data from the passive oil loss study analyzed independently by Dr. Joanne Lupton, FDA's consultant on GI issues. Dr. Lupton's analysis was consistent with FDA's analysis, i.e., there would be an increase in passive oil loss in subjects consuming olestra having a stiffness of under 50 kPa/s but not in subjects consuming olestra with stiffness of 50 kPa/s or higher.⁶⁴

Therefore, FDA concurs with the petitioner's conclusion that there would not be an increased incidence of passive oil loss in subjects consuming olestra of a stiffness greater than or equal to 50 kPa/s (Ref. 87). FDA also notes that passive oil loss is not a hazard to health or otherwise an adverse effect per se and that the purpose of conducting the study was to determine the stiffness specification of olestra above which passive oil loss would not occur.

b. *Effect of olestra stiffness on OIT.* The petitioner stated that the incidence of reported OIT was significantly increased in all olestra groups relative to the incidence in the placebo group. The incidence of OIT in the 18 kPa/s olestra group was also significantly greater than the incidence in any other olestra group. However, there was no consistent trend in the incidence of OIT reported by the subjects who consumed olestra of stiffness greater or equal to 45 kPa/s.

FDA agrees that the incidence of OIT was significantly greater in all olestra treatment groups (13.5 percent to 32 percent) compared to the placebo group (4.7 percent). FDA also agrees that there was no predictive relationship between olestra stiffness and OIT when the stiffness was greater or equal to 45 kPa/s (Ref. 87).

c. *Effect of olestra stiffness on GI symptoms.* With respect to GI

symptoms, the petitioner stated that 9 percent of the subjects in the placebo group and from 10 percent to 16 percent of the subjects in the olestra groups reported GI symptoms including (in decreasing order of occurrence) gas/stomach gurgle, diarrhea, abnormal (loose, soft) stools, abdominal pain, and indigestion/heartburn. The petitioner concluded that there was no consistent trend with olestra stiffness in the number of GI symptoms reported. The petitioner also concluded that, consistent with the results of other studies, the GI symptoms do not present a safety concern because: (1) When they occur, the symptoms are generally mild or moderate in severity; (2) they subside when olestra consumption is stopped; and (3) they do not differ substantially from the GI symptoms normally experienced when diets high in fiber are consumed.

FDA agrees with the petitioner that there was no trend in reported GI effects based on olestra stiffness. However, the percentage of subjects who reported at least one of the eight gastrointestinal effects assessed was significantly greater in four of the six olestra stiffness treatment groups (18, 66, 78, 103 kPa/s) compared to the placebo group (Ref. 87).

In addition, the percentage of subjects in the olestra groups reporting GI symptoms in response to directed questions was 0 percent to 19 percent greater than the percentage of subjects reporting symptoms in the placebo group. The GI effects that were reported significantly more often in some of the olestra groups compared to the placebo group were urgent bowel movements, difficulty wiping, and soft stools (Ref. 87).

An increase in the number of daily bowel movements over that occurring in the placebo group was reported by subjects in all of the olestra stiffness treatment groups except one (45 kPa/s). Twenty-seven percent of subjects in the placebo group reported an increased number of bowel movements per day compared to a range of 35 to 48 percent for olestra recipients (Ref. 87).

FDA agrees that, when reports of loose stools and diarrhea are analyzed separately, with only one exception, no statistically significant increase in either loose stools or diarrhea-like stools was reported among olestra recipients versus placebo recipients. However, as is the case with analysis of the GI symptoms in the two 8-week studies, FDA believes that it is appropriate to combine reports of loose stools and diarrhea for analysis. This is because the difference between loose stools and diarrhea-like stools may not have always been clear to the study

⁶³ Transcript, vol. 4, p. 163.

⁶⁴ Statement of Dr. Joanne Lupton, Transcript, vol. 2, p. 222.

subjects and may be simply variable manifestations of the same effect. When reports of loose stools and diarrhea like stools are combined, the analysis shows that during the 5 day study, 42.3 percent (447/1056) of olestra recipients experienced loose stools or diarrhea-like stools compared to 33.1 percent (57/172) of placebo group subjects; this difference is statistically significant ($P=0.03$). (Ref. 87).

Finally, FDA notes that, in general, the results of analysis of the GI symptoms data in the oil loss study are consistent with those obtained in the 8-week studies. In addition, FDA agrees that, like the GI symptoms reported in the 8-week studies, GI symptoms in the oil loss study subside when olestra consumption is stopped. As discussed above, however, FDA does not agree with the petitioner that the GI symptoms experienced with olestra consumption are similar to those experienced with high fiber consumption.

3. Study of Selected Fecal Parameters in Subjects Consuming Olestra

a. *Study design.* The petitioner conducted a study designed to examine fecal composition of subjects reporting diarrhea when consuming olestra. Normal healthy males and females (18 to 60 years of age) were selected for the study from a population of subjects who had reported GI symptoms while consuming olestra in previous product acceptance studies. The study consisted of two phases. A screening phase was conducted to identify subjects who reported GI symptoms from olestra consumption. The second phase was a study phase during which the identified subjects ate different amounts of olestra and GI symptoms were recorded and fecal measurements were made.

The screening phase was a 4-week, cross-over design with two treatment groups, 0 and 20 g/d olestra. Fifty-two adults who had reported GI symptoms in previous olestra studies were recruited for the study. The olestra was substituted for 20 g of triglyceride in the three daily meals with roughly one-third of the dose provided in each meal. The study participants were acclimated to the study procedures during a 3-day baseline period in which they ate placebo meals. They were then divided into two groups and ate either placebo meals or meals providing 20 g/d olestra for 5 days. After a 7-day washout period, the subjects again ate placebo meals (containing triglycerides) for 3 days, and then crossed-over to olestra or placebo meals for 5 days. After the second treatment period, the subjects were monitored for a 4-day washout

period. All meals during baseline, treatment, and washout periods were eaten under supervision at the clinical site.

The frequency, duration, and severity of nine predefined GI symptoms were documented daily by the subjects, starting at the beginning of the baseline period and continuing through the final 4-day washout period. Diarrhea was defined as "excessive frequency of very loose/watery stools that are extremely difficult or impossible to control." Loose stools were defined as "a bowel movement that is easier to pass than normal, but is not watery and unformed."

At the completion of the screening phase, those subjects who reported an increase in the frequency, severity, or duration of GI symptoms during the olestra period, relative to the placebo period, were selected to take part in the study phase. Eighteen subjects met the selection criteria.

The study phase was a crossover, placebo-controlled, single-blind (subject) design with three treatment groups, 0, 10, and 20 g/d olestra. Each subject received each treatment for 7 days. The treatment periods were separated by 7-day washout periods. Subjects ate all treatment meals under supervision at the clinical site, and ate their habitual diets at home during the washout periods.

GI symptoms were ascertained during the treatment periods and the first 4 days of the washout periods by GI assessment records completed daily by the subjects. For each GI symptom episode, the subject recorded the date, time of day, and intensity. The intensity scale for GI symptoms was graded as follows: 0 (none); 1 (slight); 2 (mild); 3 (moderate); and 4 (severe). Total fecal collections were made for the last 3 days of each treatment period and the daily collections were pooled. To complete the study and have data included in the analyses, a subject had to provide at least one fecal sample for each 3-day collection period.

Stools were collected into plastic containers and immediately frozen. Wet weight, volume, and density measurements were made on each stool. Fecal samples from each subject during the 3-day collection period were then pooled. Three-day pooled fecal samples for each subject were analyzed for water concentration, dry weight, olestra analysis, Na, K, Cl, total and individual bile acids, free fatty acids, triglycerides, and total lipids.

b. *Petitioner conclusions.* Of the 15 subjects completing the study, 6 subjects reported diarrhea while eating 20 g/d olestra. The petitioner concludes

that this study further confirms that the diarrhea reported by subjects consuming olestra does not present potential for harm. This conclusion is based on the observation that there was no significant increase in stool weight, water content, or number of bowel movements per day for subjects reporting diarrhea while consuming olestra at 20 g/d.

c. *FDA conclusions.* The number of subjects who reported diarrhea increased with increasing dose of olestra; three subjects (20 percent) reported diarrhea while eating 0 g/d olestra, six (40 percent) subjects while eating 10 g/d olestra, and 11 (69 percent) while eating 20 g/d olestra. The difference in incidence of reported diarrhea between the 20 g/d and 0 g/d consumption levels was statistically significant. In addition, the mean number of diarrheal bowel movements per subject reporting any diarrhea and the severity of the diarrhea both increased with increasing olestra consumption. Although there was an increase in the number of subjects reporting loose stools with increasing olestra dose, this increase was not statistically significant. FDA concludes that these results are qualitatively similar to the results of the 8-week studies.

Measurements of the concentration of stool water and electrolytes (Na, K, and Cl) suggest these parameters did not differ in persons reporting diarrhea during the 20 g/d olestra period from those of their nondiarrheal stools during the placebo period. However, it was not possible to analyze stool electrolyte values by individual stools or by individual days because the stools were pooled from the 3-day collection period, as is normally done when measuring fecal parameters. FDA notes that there appears to be an increase weight of stools in those subjects reporting diarrhea when eating 20 g/d olestra that is not completely accounted for by the presence of olestra in the stools. FDA concludes that the results of this study indicate that there is no difference in stool composition (e.g., water and electrolyte content) between those subjects consuming olestra who reported diarrhea and those who did not (Ref. 88).

4. Study in Patients with Inflammatory Bowel Disease

The petitioner conducted a multi-center study in both ulcerative colitis (UC) patients and Crohn's disease (CD) patients. The objective of the study was to assess whether the presence of olestra in the GI tract exacerbates conditions in which the GI epithelium is compromised. Inflammatory bowel

disease (IBD) represents an extreme example of such a condition. In the study the petitioner conducted, 45 IBD patients with at least a 2-year history of diagnosed disease, who were in remission (21 UC and 24 CD), were given 20 g/d of olestra in cookies and potato chips for 4 weeks. Forty-four control subjects were given cookies and potato chips prepared with conventional vegetable triglycerides. At the end of the 4-week consumption period, the disease status of each patient was assessed and classified as in remission, worsened, or relapsed. Four weeks after the end of the consumption period, the patients were contacted by telephone and asked about the status of their disease. If judged appropriate, they were seen by the investigator. In addition, bowel permeability was assessed at the beginning and end of the consumption period by measuring urinary excretion of polyethylene glycol (PEG).

The petitioner stated that IBD patients are good surrogates in which to determine whether olestra will have an adverse impact on a wide range of GI diseases involving acute and chronic inflammation, ulcerations, and possibly a compromised intestinal barrier. The petitioner also asserted that this patient population was chosen because UC and CD are thought to be exacerbated by a range of stimuli, some of which may be dietary in nature. According to the petitioner, IBD patients in remission are also good models for people who are asymptomatic but who may have underlying predisposing conditions or subclinical GI diseases which, when exacerbated, may become active.

FDA agrees that a study in persons with IBD is useful to assess whether olestra may have adverse health effects on potentially sensitive subpopulations with bowel disease. FDA believes that persons with IBD are an appropriate target population for such a study because the disease is prevalent, because the acute disease status of such patients can be significantly influenced by factors that change bowel habits, and because such patients can have increased bowel permeability which, if further increased, could have long-range health significance.

The petitioner concluded that, in the placebo group, out of 44 subjects, 40 remained in remission, disease activity worsened for 4, and none relapsed. For the olestra group, out of 45, 41 remained in remission, disease activity worsened for three and one relapsed. The petitioner concluded that the relapse was not test-related. Further, hematologic parameters indicative of disease activity were not different

between the groups. The one relapse was not unexpected and is consistent with the spontaneous relapse rate among IBD patients (about 30 percent per year (Ref. 89), or about 1 percent for the population size studied). There was no increase in bowel permeability in either the UC or CD patients. Because there was no difference between olestra and placebo groups in the number of patients whose disease activity worsened during the study, the petitioner concluded that consumption of 20 g/d olestra for 4 weeks did not affect disease activity of the IBD patients.

FDA notes that for any study with a small number of subjects and relatively low background relapse rate (e.g., 2.5 percent per month projected in the control group), an effect of treatment (olestra) compared with control (triglyceride) would be seen only if the effect was large (Ref. 90). Thus, the study can be used to address the possibility that consumption of 20 g of olestra per day will consistently—about 30 percent of the time—exacerbate IBD. The study gives some reassurance that consumption of olestra at 20 g/d for up to 31 days would not cause a large detrimental effect in special populations such as UC and CD patients. This study was too small and too brief, however, to rule out a moderate detrimental effect (e.g., relapse rates that are two or three times those of control) (Ref. 91).

5. GI Symptoms in Young Children

GI symptoms in the young were reported in three studies. Two of these, a study in 5 to 8-year-old children that lasted 7 days and another in 3 to 5-year-old children that lasted 5 days, were designed to address the potential effects of olestra on GI symptoms. The third study, while conducted to determine whether children (2 to 5 years of age) adjusted their energy intake in response to variations in the proportion of energy from dietary fats, also provided information on GI symptoms. In this third study, children consumed olestra for five 2-day periods over 5 weeks.

After reviewing the reports on GI symptoms from these studies, the petitioner concluded that there were no differences in incidence of any GI symptoms among treatment groups, and no significant health effects from consumption of olestra by children.

Potential GI effects in the young were discussed at the meetings of the Olestra Working Group and FAC. CSPI commented that the studies on children were too short to provide enough meaningful data on gastrointestinal

problems.⁶⁵ In addition, Dr. Herbert Needleman stated that he had reviewed the petitioner's two 8-week studies and CSPI's White Paper on olestra and that he had concluded that olestra had not been demonstrated to be safe for consumption by children.⁶⁶

On the other hand, Dr. William Klish⁶⁷ stated that he had reviewed all the relevant data on olestra and concluded that olestra should in no way be considered harmful to children. Dr. Klish added that, while children are born with an immature gastrointestinal tract, their digestive and absorptive physiology, as well as gastrointestinal motility, are similar to that of an adult at about 1 year of age and therefore, the adult data on olestra can be extrapolated to children. Dr. Klish also noted that the feeding of a nonabsorbable oil to children has been occurring without adverse effects for at least the last 50 years in the form of mineral oil to treat constipation, a symptom seen frequently in children. (Mineral oil was normally given in doses of about 15 g to about 45 g/d for months or years in the child who is chronically constipated.)

Dr. Charles Hargrove, a pediatric gastroenterologist with whom FDA consulted regarding pediatric GI issues, stated that, in view of the physiologic maturity of the GI tract by 9 to 12 months of age, there should be no serious harmful effect in the toddler/preschool child if the consumer parent has appropriate labeling information to associate potential GI symptoms with olestra. He added that the differential diagnosis for numerous GI upsets in the young, i.e., loose stools, stomach cramps, would have to be expanded to include olestra despite the apparently low incidence of the latter, and that physicians should be made aware of olestra's potential to induce loose stools, for example, as they should be aware that apple or grape juice can produce loose stools in some toddlers.⁶⁸

Dr. Ronald Kleinman, a pediatric gastroenterologist and a member of the Olestra Working Group concluded that olestra does not pose any danger to health in the young. He added that the effect of excessive consumption of

⁶⁵ Statement of Dr. Myra Karstadt, CSPI, Transcript, vol. 3, p. 9.

⁶⁶ Statement of Dr. Herbert Needleman, Professor of Psychiatry and Pediatrics, University of Pittsburgh School of Medicine. Transcript, vol. 3, p. 14.

⁶⁷ Statement of Dr. William Klish, Professor of Pediatrics at Baylor College of Medicine, Head of the Section of Gastroenterology and Nutrition at the Texas Children's Hospital in Houston, TX. Transcript, vol. 2, p. 260.

⁶⁸ Statement of Captain Charles Hargrove, M.D., Transcript, vol. 2, p. 225.

potato chips with olestra by children is analogous to "toddlers' diarrhea," one of the causes of which is excess fruit-juice consumption. Dr. Kleinman observed that just as the number of stools per day decreases when consumption of the fruit juice decreases, stools will begin to firm up once consumption of olestra-containing foods decreases. Dr. Kleinman noted that as is the case for many constituents of foods and foods currently available, some individuals who are intolerant to olestra or foods containing olestra include children, and that children, like adults, can relate symptoms to foods and will be able to stop eating such foods when they have reached a level of intolerance for it.⁶⁹

FDA notes that, in general, the GI symptoms seen in the studies in children conducted by the petitioner are consistent with those seen in the 8-week studies in adults discussed above. Although the short duration of the studies in children makes it difficult to compare the GI effects to those seen in the 8-week studies in a meaningful way, FDA has concluded that the data regarding GI effects obtained in adults can be extrapolated to the young and that this approach is fully consistent with the expert views provided at the Olestra Working Group and FAC meetings. FDA also notes that despite CSPI's criticism that the studies in children were not of adequate length, CSPI did not contradict the basis for the agency's conclusion that extrapolation from studies in adults is appropriate.

C. Effect of Olestra on Intestinal Microflora Metabolism

Olestra passes intact through the colon where it has the potential to affect adversely the normal metabolic activity of the intestinal microflora. The indigenous microflora of the colon carry out a variety of reductive, degradative, and hydrolytic processes that are important to the host. Therefore, it is important to know whether consumption of olestra affects microflora populations, alters fermentation processes or normal microflora metabolism of host-produced substrates, or acts as a substrate for microflora.

1. Effect of Olestra on Breath Gas and Microflora-Associated Characteristics

The petitioner used an analysis of breath hydrogen as a noninvasive

technique for studying microbial fermentation in the human colon under "normal" and "high" dietary fiber intakes (within the range recommended as "healthy" fiber intake in the United States), with and without olestra. An analysis of breath methane was also used in this study to provide additional information on microbial fermentation activity in methanogenic individuals.

In addition, because normal metabolic function of colonic microflora can be assessed by measurement of several endpoints of metabolic activity (microflora-associated characteristics⁷⁰), the petitioner measured microflora-associated characteristics to provide additional information on the effect of the presence of olestra in the colon on normal bacterial metabolism.

The breath gas study was a parallel, double-blind, placebo-controlled study 5 weeks in length. The subjects were 97 normal healthy males and females from 18 to 58 years of age. Subjects were randomly assigned to four treatment groups. Following an 8-day baseline period during which subjects consumed a placebo breakfast low in dietary fiber, they were fed breakfast meals daily containing moderate (7 g) or high (24 g) levels of fiber, with 24 g of either olestra or triglyceride for 28 days. Breath gas and fecal samples were collected at the end of the baseline period and at the end of the test period. The breath gas samples were analyzed for hydrogen and methane. The fecal samples were examined for viable microbial counts and direct microscopic cell counts for fecal bacteria. (Fecal bacteria have been demonstrated to be directly representative of the indigenous human intestinal microflora and their metabolic activities.) In addition, the fecal samples were analyzed for microflora-associated characteristics.

The petitioner concluded that, although there was a trend toward lower breath hydrogen production in the olestra groups (20 percent reduction in the olestra high fiber group compared to placebo high fiber group) there were no statistically significant differences in cumulative breath hydrogen production between olestra and placebo groups. Further, the petitioner stated that olestra did not affect the total number of direct or viable counts of the fecal microflora. The petitioner also stated that olestra had no statistically significant effect on cumulative breath methane production following consumption of either the

moderate or high fiber meal and that breath methane production values for individuals in the olestra groups were similar to individual values in the respective placebo groups.

According to the petitioner, olestra had no effect on fecal microbial counts, and did not interfere with the normal degradation of beta-aspartylglycine, mucin, or trypsin. The concentration and distribution of short chain fatty acids (SCFA) was not consistently or significantly affected by olestra, indicating the absence of an adverse effect on microbial metabolism. Finally, the petitioner stated that urobilinogen and coprostanol concentrations were not adversely affected by olestra consumption. The petitioner concluded that the results of this study demonstrate that olestra will not interfere with normal intestinal fermentation of dietary fiber.

FDA notes that the best direct information on microbial imbalances of concern would have been adequate direct microscopic cell counts and viable cell counts. Although these tests were performed, the data cannot be used due to improper handling of the samples (Ref. 92). The study did show that the microflora-associated characteristics that are generated by the majority of the bacterial genera found in the colon (e.g., the proteases, peptidases) and production of SCFA were not affected or only slightly affected by the presence of olestra in the GI tract. However, FDA's analysis of the data further shows lowering of hydrogen breath gas in some subjects, appearance of undergraded mucin in some subjects, a reduction of microbial formation of coprostanol from cholesterol, and reduced bilirubin conversion in those subjects consuming olestra (Ref. 92). FDA notes that these variations in microflora-associated characteristics are not different from those observed from dietary changes, for example, from low to high fiber diets, and that there are large variations in normal healthy subjects with respect to microflora-related parameters (Ref. 93). In addition, although there was some dampening of hydrogen production when olestra was added to a high-fiber diet, this dampening was not significant.⁷¹

2. Potential for Intestinal Microflora to Metabolize Olestra

The petitioner stated that the pivotal studies that demonstrate that olestra is not metabolized by microflora in the GI tract are a clinical study in humans and the rat absorption and metabolism

⁶⁹ Statement of Dr. Ronald Kleinman, Chief of the Pediatric GI and Nutrition Unit, Massachusetts General Hospital and Associate Professor of Pediatrics, Harvard Medical Center. Dr. Kleinman was a temporary member of the FAC. Transcript, vol. 4, p. 177 and 192.

⁷⁰ Microflora-associated characteristics include degradation of beta-aspartylglycine and mucin, conversion of cholesterol and bilirubin to their respective metabolites, inactivation of trypsin, and production of short-chain fatty acids (SCFA).

⁷¹ Statement of Dr. Joanne Lupton, Transcript, vol. 4, p. 87.

studies. The clinical study showed no production of radiolabeled metabolic breakdown products, and no changes in either olestra fatty acid composition or ester distribution following incubation of radiolabeled olestra with fecal microflora from humans who consumed 7 g/d olestra for up to 31 days.

As noted, in the rat absorption studies, virtually all radiolabel was recovered in feces and GI contents, with insignificant amounts recovered as metabolic byproducts in CO₂, urine, and tissues after animals were fed olestra for 28 days and then dosed with radiolabeled olestra.

The petitioner also submitted a published study (Ref. 94) that demonstrates that olestra is not metabolized by the microflora of the GI tract. In this study, radiolabeled (¹⁴C-fatty acids) olestra was incubated for 72 hours in either minimal or organically enriched anaerobic media inoculated with feces from seven healthy subjects who had consumed 9 g/d of olestra for 3 to 4 weeks. The petitioner stated that no significant quantities of ¹⁴CO₂, ¹⁴CH₄, or ¹⁴C-volatile fatty acids were detected during the incubation, indicating that olestra was not metabolized by colonic microflora. At the Olestra Working Group and FAC meetings, the petitioner also pointed out that human gut microflora have never adapted to breakdown fat or cellulose. In addition, the petitioner reasoned that because the breakdown of fat requires beta oxidation, which requires oxygen, it is unlikely that in the anaerobic environment of the human intestine, microorganisms will adapt to metabolize olestra.⁷²

FDA notes that there is a hypothetical possibility that an organism capable of metabolizing olestra at a low level could arise among the intestinal microflora (Ref. 95). The *in vitro* study on minimal medium did suggest that olestra might be metabolized by microflora at a low level when olestra is the only carbon source (Ref. 95). Such conditions are unlikely to exist in the intestinal tract. Because of the possibility that olestra might be metabolized, FDA asked Dr. Joann Lupton, a consultant for FDA who specializes in the effect of diet on the GI tract, to review the breath gas and *in vitro* studies. Dr. Lupton did not observe any metabolism of olestra by microflora.⁷³ Dr. Lupton concluded that because no long chain fatty acids were

released from the olestra, and because the olestra was actually recovered without any change in chain length or degree of saturation, olestra is not metabolized by the microflora (Refs. 96 and 97). Further, given the findings in the human and animal material balance studies (discussed in section III.A of this document), which showed that olestra was excreted quantitatively and was unchanged in the feces, FDA believes that the available evidence shows that there is no metabolism of olestra by the intestinal microflora.

D. Effect of Olestra on Bile Acid Metabolism

The petitioner submitted several published and unpublished studies in animals and humans to demonstrate that consumption of olestra will have no meaningful effect on the absorption, synthesis or excretion of bile acids. The studies included: (1) A 2-year rat study where olestra was fed at 5 percent of the diet and total fecal bile acid excretion was measured after 1, 2, and 24 months; (2) a study in rats on the effect of olestra on the absorption of chenodeoxycholic acid, one of the more lipophilic bile acids; (3) studies on the effect of olestra on bile acid excretion in humans ingesting 8 to 40 g/d olestra for 30 days or 90 g/d olestra for 37 to 55 days; (4) a study in rats on olestra's effect on biliary acid profiles; and (5) a study examining the effect of olestra on bile acid pool size and bile composition in African Green Monkeys.

The petitioner stated that olestra had no effect on the rate of recovery or the amount of chenodeoxycholic acid, that neither bile acid synthesis nor excretion are affected by olestra, that the absorption of bile acids is not affected by olestra, and that olestra had no effect on biliary or fecal bile acid profiles.

FDA reviewed the studies and, although some of the studies have limitations in experimental design or execution, has concluded that the studies as a whole show that olestra would not be expected to produce major changes in bile acid metabolism and absorption (Ref. 98).

E. Overall Conclusions on Effects on the GI Tract

The issues of potential concern with respect to the effect of olestra on the GI tract are: (1) The potential for loose stools or diarrhea to result in electrolyte and fluid loss; (2) whether the GI effects have the potential to interfere with normal daily life of consumers, (3) whether the GI effects seen are of special concern to subpopulations where proper fluid control is important (e.g., individuals with underlying

cardiovascular or GI diseases, the young and the elderly); and (4) whether changes observed in microflora-associated characteristics associated with olestra consumption are meaningful to health.

These issues were discussed at the meetings of the Olestra Working Group and the FAC. After presentation and discussion of the data relating to the potential GI effects that olestra may cause, most members of the Olestra Working Group and FAC, including all of the gastroenterologists, felt that there was reasonable certainty of no harm with respect to the potential for olestra to cause GI effects.⁷⁴ These members felt that, while olestra may cause certain GI effects, including loose stools, these effects are not adverse effects because they do not threaten health. For example, effects described as "diarrhea" were not diarrhea in the medical sense because they were not associated with water loss or electrolyte imbalance.

On the question of whether the "diarrhea" experienced by subjects was diarrhea in the medical sense, the petitioner presented additional data on fecal water content to the Olestra Working Group.⁷⁵ (The study from which these data were derived is described in more detail in section VI.3. of this document). According to the petitioner, the results of the study showed that, even in olestra-consumers experiencing what they described as diarrhea, these subjects had no change in the stool water content, and also, no change in electrolytes or the pH of the stool; the only difference was that the stools of these subjects had more lipid, which was completely accounted for by the olestra consumed. Dr. Lawrence Johnson, a gastroenterologist member of the Olestra Working Group, agreed with the petitioner's analysis and stated that when one looks at stool by weight, the gross weight will increase because olestra is not absorbed and increases the weight of the stool. (Increased stool weight is one criterion for diarrhea.) Dr. Johnson added that one would next determine whether fat or fluid is responsible for stool weight increase. He noted that the amount of fluid in the stool was about 200 cc, which is the amount that would be in stool in normal physiologic amounts.⁷⁶ Dr. Joanne Lupton, the FDA consultant on GI issues, added that, in looking at the clinical data, the larger the proportion of the stool that is olestra, the softer the

⁷² Transcript, vol. 1, p. 152. Accordingly, the petitioner concluded that there was no evidence of degradation of the olestra (i.e., no change in ester distribution or fatty acid composition) by intestinal microflora.

⁷³ Statement of Dr. Joanne Lupton, Transcript, vol. 2, pp. 216-226.

⁷⁴ Transcript, vol. 3, p. 78 and vol. 4, p. 196.

⁷⁵ Transcript, vol. 1, p. 112.

⁷⁶ Statement of Dr. Larry Johnson, Professor of Medicine and Director of the Digestive Diseases Division, Uniformed Health Service University, Transcript, vol. 4, p. 83.

stool is going to be but that there is no evidence of dehydration, or electrolyte imbalance in those subjects reporting "diarrhea".⁷⁷

In addition, at the Olestra Working Group and FAC meetings, the question of whether olestra in the feces represented steatorrhea was raised. Drs. A. R. Colon and J. S. DiPalma⁷⁸ stated that initial human studies on olestra revealed steatorrhea, in addition to diarrhea, as an apparent dose-related side effect and that there were no data that assessed 72-hour fecal fat excretion or dose-steatorrhea correlations. In response to a question of whether the effects seen with olestra are steatorrhea and not diarrhea, the petitioner stated that the effects seen with olestra are unrelated to steatorrhea, which, according to the petitioner, is the presence of unabsorbed free fatty acids in the lower bowel which results in an osmotic and an inflammatory and irritative response in the bowel.⁷⁹ The petitioner stated that the only identified change between feces from subjects consuming olestra and those consuming triglyceride was that the lipid content of the stool in the olestra group was increased, an expected result because olestra is not absorbed and is excreted in the feces. The petitioner added that their analysis showed that there was no additional lipid in the stool of subjects consuming olestra.⁸⁰ Dr. Joanne Lupton agreed that the available data do not reflect any steatorrhea.⁸¹

FDA notes that steatorrhea (the passage of large amounts of fat in stool) usually occurs in conjunction with pancreatic disease and malabsorption syndrome. FDA has reviewed the data on the lipid content in feces of subjects consuming olestra and concludes that there was no evidence of steatorrhea in any subject in the study (Ref. 99). Most members also felt that consumers can deal with the GI effects of olestra in the same manner as similar effects caused by other foodstuffs in the food supply, i.e., by limiting intake of the material causing the effect. For this reason, most members felt that foods containing olestra should be labeled in a manner to alert consumers to the potential GI effects of olestra but also in a manner that will not preclude the consumers from seeking health care for more

serious concerns. (Labeling for olestra is discussed in more detail in section VII. of this document.)

Based upon the available data and information, FDA concludes that consumption of olestra causes GI symptoms such as bloating, loose stools, abdominal cramps, and diarrhea-like symptoms. There is no clear association between the onset of these effects and time of ingestion. In some cases, the effects occurred the few first days of consuming olestra products; in others, such products were consumed for several weeks before effects were seen. In addition, there were some people in whom the effects never were reported. With some consumers, the olestra-induced effects were seen at low olestra doses and with others, it took a higher dose to elicit the effects. In addition, the agency notes that few individuals reporting GI symptoms in the olestra clinical studies dropped out of the studies because of the symptoms and that study subjects were able to carry out their daily functions while they were on the studies.

While olestra caused GI effects such as those mentioned above, there is no evidence that these effects represent adverse health consequences. The effect of olestra on stool consistency is similar to that produced by liquid petrolatum, which softens fecal contents and interferes with the development of firm, well-formed stools. The "diarrhea" experienced by the study subjects was not diarrhea in the medical sense because it was not associated with loss of water or electrolytes. Indeed, those subjects who experienced loose stools or diarrhea continuously for several weeks during olestra consumption did not show any evidence of fluid loss such as hemoconcentration or electrolyte imbalance. This is consistent with published studies (Refs. 80 and 81) that show that olestra does not significantly alter gastric emptying or overall GI transit time.

With respect to whether olestra's potential to cause diarrhea-like symptoms or loose stools raises concern for special subpopulations where proper fluid and electrolyte control is important, FDA notes that, as discussed above, the soft stool and "diarrhea" appear to be caused by disruption of the fecal matrix and are not associated with clinical signs of fluid loss, which is the case in classical diarrhea. Therefore, FDA has determined that there is no basis to conclude that these subpopulations would be at special risk due to consumption of olestra.

FDA recognizes that nutritionists generally do not recommend reduced-calorie products for consumption by

children. Nevertheless, there is the potential that olestra-containing products may be eaten by children. Although the studies FDA reviewed with respect to the effect of olestra on GI symptoms in the young were not sufficiently long, FDA notes that the GI physiology of children older than approximately 9 months is comparable to that of adults⁸² (Ref. 100). Therefore, FDA concludes that there is no basis to conclude that the effect of olestra on the GI tract would be any different in children than in adults, and thus, the results of studies conducted in adults to address the effects of olestra consumption on the GI tract can be extrapolated to the young (Ref. 101).

With respect to differences seen in microflora-associated characteristics as a result of olestra consumption, FDA notes that such variations are no different than those observed with other dietary changes (for example, from low to high fiber diets), and that there are large variations in normal healthy subjects with respect to microflora-related parameters. Also, FDA believes that the available evidence shows that there will be no significant metabolism of olestra by the intestinal microflora. Therefore, FDA concludes that, collectively, the data do not establish an adverse effect of olestra consumption on microbial metabolism or function.

Notwithstanding the fact that FDA finds no safety concerns with respect to the effect of olestra on the GI tract, FDA believes that it is important for consumers to be aware of the GI symptoms associated with ingestion of olestra-containing foods so that they are able to associate olestra with the GI symptoms that it may cause. This information would also preclude unnecessary concerns and inappropriate medical treatment. Appropriate labeling for olestra-containing foods is discussed in section VII. of this document.

VII. Labeling of Foods Containing Olestra

As discussed above, because olestra is not absorbed and passes through the GI tract intact, it affects the absorption of certain fat-soluble vitamins and nutrients, which partition into it. Olestra also has the potential to cause certain GI effects such as abdominal cramping and loose stools. The agency has considered whether these effects warrant special labeling of foods containing olestra. As discussed in detail below, FDA has determined that

⁷⁷ Statement of Dr. Joanne Lupton, Transcript, vol. 3, p. 89.

⁷⁸ Letter from Drs. A. R. Colon and J. S. DiPalma, Georgetown University Medical Center, read at the FAC meeting; Transcript, vol. 3, p. 19.

⁷⁹ Statement of the petitioner, Transcript, vol. 1, p. 141.

⁸⁰ Transcript, vol. p. 97.

⁸¹ Statement of Joanne Lupton, Transcript, vol. 3, p. 24.

⁸² Statements of Drs. Charles Hargrove and Dr. William Klish, Transcript, vol. 2, pp. 226 and 260, respectively.

foods containing olestra shall be labeled with the following statement:

This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added.

A. Labeling Authority

Under the act, the agency has the mandate to ensure that labeling provides truthful and nonmisleading information to consumers. Thus, the law provides the agency with authority to require specific label statements when needed for reasons other than to ensure the safe use of food.⁸³ Specifically, section 409(c)(3)(B) of the act (21 U.S.C. 348 (c)(3)(B)) prohibits FDA from approving a food additive if the proposed use would result in the misbranding of food within the meaning of the act (21 U.S.C. 348(c)(3)(B)). Under section 403(a)(1) of the act (21 U.S.C. 343(a)(1)), a food is misbranded if its labeling is false or misleading in any particular.

Section 201(n) of the act (21 U.S.C. 321(n)) amplifies what is meant by "misleading" in section 403(a)(1) of the act. Section 201(n) of the act states that in determining whether labeling is misleading, the agency shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations made or suggested in the labeling or material with respect to consequences which may result from use of the article to which the labeling relates under the conditions of use prescribed in the labeling or under such conditions of use as are customary or usual (see 21 CFR 1.21). Thus the omission of certain material facts from the label or labeling of a food causes the product to be misbranded within the meaning of 21 U.S.C. 343(a)(1) and 321(n). In general, the agency believes the concept of "material fact" is one that must be applied on a case-by-case basis. The agency has required special labeling in cases where information is necessary to ensure that consumers are aware of special health risks associated with consumption of a particular product. For example, although protein products intended for use in weight reduction are

⁸³ Under section 409(c)(1)(A) of the act (21 U.S.C. 348(c)(1)(A)), the agency has the authority to prescribe the conditions of safe use of a food additive, including the authority to require label statements needed to ensure safety. Thus, in a food additive regulation, the agency may rely on this provision for requiring statements to appear on labels of products containing food additives. In the case of olestra, however, FDA is not requiring the labeling of olestra-containing foods in order to ensure the safe use of olestra.

not inherently unsafe, FDA requires a warning statement for such products that states, in part, that very low calorie protein diets may cause serious illness or death. Another example of required information is the use of the term "milk derivative" following the ingredient declaration of sodium caseinate when used in a product labeled "non dairy" (21 CFR 101.4(d)).

FDA believes that such a labeling statement is appropriately established as part of the rulemaking for a food additive approval under section 409 of the act. As noted, under section 409(c)(3)(B) of the act a food additive regulation cannot issue if the available data show that "the proposed use of the additive would *** result in *** misbranding of food within the meaning of the Act." Thus, the status of foods containing a particular additive, in terms of misbranding under the act, is always an issue to be considered and determined by the agency for each food additive petition. (In most cases, the proposed use of the additive presents no issue regarding misbranding of foods that contain the additive.) Accordingly, the notice of filing of a food additive petition published under 21 U.S.C. 348(b)(5) necessarily includes notice that proper labeling under the act of foods containing such additive is a question before the agency. In the case of olestra, the notice of filing published in the Federal Register of June 23, 1987 (52 FR 23606), was a public announcement that the olestra food additive petition had been filed, and that all issues regarding the approval of the proposed use, including the proper labeling of foods containing olestra, would be considered by FDA.⁸⁴

As discussed below, FDA has determined that all foods containing olestra should bear a label disclosing olestra's GI effects and its effects on nutrients, and disclosing that certain vitamins have been added back. The agency believes that these labeling statements can be imposed as final requirements as part of the food additive petition process of section 409 of the act, and that it is important that once approved, products containing olestra be properly labelled so as not to be misbranded. Thus, FDA is imposing an immediately effective labeling requirement. However, the agency

⁸⁴ FDA's regulation regarding the failure to reveal material facts, (21 CFR 1.21), states that "affirmative disclosure of material facts *** may be required, among other appropriate regulatory procedures, by *** regulations in this chapter promulgated pursuant to section 701(a) of the act; or direct court enforcement action (emphasis added)." Thus, establishing a requirement for a label statement for olestra-containing foods as part of a section 409 proceeding is consistent with 21 CFR 1.21.

acknowledges the importance of the opportunity for interested members of the public to express their views on the labeling for olestra. In addition, the petitioner, Procter & Gamble, intends conduct focus group testing of the required olestra label (Ref. 103). Accordingly, the labeling requirement for foods containing olestra, while immediately effective, is an interim requirement only. The agency requests comments on this label from interested persons, on such issues as the need for such labeling, the adequacy of its content, the agency's word choice, and the configuration of the label. Three copies of such comments shall be submitted to the Dockets Management Branch (address above) April 1, 1996. FDA will then evaluate and respond to any comments received, as well as any studies or other information from focus group testing conducted by the petitioner. As noted below, under section 409(f)(1) of the act, interested persons have the opportunity to file objections to the final rule; such objections shall be filed within 30 days of the final rule, and shall conform to certain requirements in terms of format and content, which are articulated below. Commenters on the labeling for olestra who intend their comments to be treated and function as objections under section 409(f)(1) of the act shall conform to the time restrictions, format, and content requirements for objections. Any labeling comments received more than 30 days from the date of this final rule and any comments not otherwise conforming to the requirements for objections shall be considered by FDA as simply a comment and not an objection under 409(f)(1) of the act and addressed by the agency accordingly.

In these circumstances, FDA has concluded that it is appropriate for the agency to establish labeling requirements for olestra-containing foods that are effective concurrent with the promulgation of a final rule regulating the additive.

B. Labeling with Respect to GI Effects

As discussed in section VI. of this document, consumption of olestra may cause GI symptoms such as abdominal cramping and loose stools. However, there is no evidence that these effects represent adverse health consequences. As noted, the effect of olestra on stool consistency is similar to that produced by mineral oil, which softens fecal contents and interferes with the development of firm, well-formed stools. Further, the "diarrhea" experienced by the study subjects was not diarrhea in the usual medical sense because it was not associated with loss

of water or electrolytes. Nonetheless, while the agency has concluded that based upon the evaluation of the available evidence there are no safety concerns with respect to the effect of olestra on the GI tract, the agency believes that consumers should be provided with information to enable them to associate olestra with the GI symptoms that it may cause. The agency believes that providing this information to consumers would preclude unnecessary concerns about the origin of GI effects, were they to be observed, and may also prevent unnecessary or inappropriate medical treatment of those symptoms. Accordingly, FDA has determined that the relationship between GI symptoms and consumption of foods containing olestra is a fact that is material in light of the consequences of consuming olestra in savory snacks. In such circumstances, this relationship must be disclosed to consumers consistent with sections 201(n) and 403(a)(1) of the act.

C. Labeling with Respect to Effects on Nutrients

As discussed in section V. of this document, olestra interferes with the absorption of the fat-soluble vitamins A, E, D, and K and therefore, these vitamins will be required to be added to olestra-containing foods to compensate for that amount of the vitamins that is not absorbed due to olestra's effects. As required under section 403(i)(2) of the act, these vitamins will be declared in the ingredient listing.

The added vitamins, however, may not be considered in determining nutrient content of the food for the nutritional label or for any nutrient claims, express or implied. This is because the added vitamins will simply compensate for the amounts lost due to decreased absorption of the vitamins from other foods but will not contribute significant amounts of these vitamins to the diet. In other words, the purpose of adding the four fat-soluble vitamins is to ensure that no significant change in vitamin availability (neither decrease nor increase) occurs.

Olestra also decreases absorption of some lipophilic carotenoids, which can lead to lower serum levels of those nutrients. As noted, the agency has concluded that supplementing olestra with vitamin A will compensate for olestra's effects on the provitamin A function of carotenoids. Except for the provitamin A function (which is taken care of by addition of vitamin A), other specific health benefits for carotenoids have not been established.

As noted, labeling may be considered misleading not only if it fails to reveal

facts that are material in light of consequences which may result from use of a food, but also if it fails to reveal facts that are material in light of representations made. As discussed above, FDA concludes that no consequences will result from inhibition of lipophilic nutrients by olestra because vitamins A, D, E and K will be added back to compensate. However, the mandatory listing of these vitamins on the ingredient statement could confuse consumers by implying that the food would provide significant amounts of these vitamins. Therefore, FDA is requiring a statement indicating that olestra inhibits the absorption of vitamins and other nutrients to set the context for why they are added. FDA is including the term other nutrients because any nutrient that is as lipophilic as these vitamins would also be affected, although there is currently no basis for adding them back. Thus, in light of the disclosure in the ingredient statement that vitamins A, D, E, and K have been added, FDA has determined that the label statement explaining such compensation must be made.

FDA is not requiring a specific statement on carotenoids in this labeling statement because doing so could falsely imply that their decreased absorption is known to be of significance. As stated previously, the current evidence does not show that inhibition of carotenoid absorption would result in any significant health consequences. This decision is consistent with FDA's policy for nutrient content claims, as required by 21 CFR 101.54. In that regulation, claims that a food is a "good source" of, "high" in, or contains "more" of a nutrient can be made only if the difference is significant with respect to a recommended daily intake (RDI) or daily reference value (DRV) for a nutrient, as established by regulation, so that consumers are not confused by implications that are of no nutritional significance. Such claims may not be made for substances for which a RDI or DRV has not been established. FDA believes that its policy concerning when a company may state that a food provides more of a nutrient should guide FDA in when it requires a company to disclose that a food would decrease availability of a nutrient. Therefore, FDA concludes that the label of foods containing olestra should not state that olestra inhibits the availability of carotenoids because to do so may imply that the inhibition of carotenoid absorption is of nutritional significance.

D. FAC Discussions Regarding Labeling

1. GI Effects

Both the Olestra Working Group and the FAC discussed the importance of labeling that would disclose the association between olestra and the additive's potential GI effects. The FAC members agreed with the agency that it is important that consumers be able to associate the GI effects that olestra may cause with the additive. Committee members, however, recommended some amendments to a tentative label statement discussed at the FAC meeting ("Foods containing olestra may cause intestinal discomfort or a laxative effect").

First, members of the Committee suggested⁸⁵ that the label read "Olestra may cause***" instead of "Foods containing olestra may cause***" to make clear that the GI effects experienced are caused by the additive, olestra. The agency agrees that the suggested change results in a clearer and more succinct label, and thus is following this suggestion.

Second, some Committee members felt that significant increases in the frequency of GI effects were seen only at the higher olestra doses (20 and 32 g olestra/day) in the 8-week studies (see discussion in section VI.B.1 of this document) and therefore, that the label statement should be amended to state that it is excess consumption of olestra that may cause the GI symptoms.⁸⁶ Others felt that a test of trends might show a dose-response effect, i.e., that the more olestra one consumes the more one experiences symptoms; in addition, significant differences might be observed at eight g/d olestra if the power of the study was increased sufficiently.⁸⁷

The agency agrees that there is a clear dose response effect with respect to olestra's ability to elicit GI effects. The agency also agrees that the lack of statistical difference between the placebo group and the eight g/d group in the two 8-week studies might be due only to the lack of power of the studies. In addition, the agency notes that consumption of 20 g/day olestra (equivalent to two 1-oz bags of potato chips, for example), for which there was a clearly significant difference from the placebo group with respect to GI effects, may not be considered excessive consumption by many consumers. As noted above, a scenario-driven estimate of 20 g/p/d, based on consumption of 2 oz of chips per day is a reasonable

⁸⁵ Transcript, vol. 3, p. 91.

⁸⁶ Transcript, vol. 3, p. 93.

⁸⁷ Transcript, vol. 3, p. 52.

estimate of a "short-term" high consumer. Therefore, the agency does not agree that the label statement should be amended to indicate that only excessive consumption could lead to GI symptoms.

Third, some Committee members expressed concern that the presence of a label statement could lead some consumers to disregard GI symptoms caused by factors other than olestra consumption and that erroneous attribution to olestra might unnecessarily cause them to delay consulting their healthcare provider.⁸⁸ Therefore, several Committee members recommended that a second sentence be added to the proposed label to advise consumers that they should consult their healthcare provider should symptoms persist after consumption of olestra-containing foods ceases.

Data submitted in the petition show that GI symptoms caused by olestra do not persist more than 2 days after consumption of olestra ceases. Thus, the agency agrees that persistent GI symptoms are unlikely to be related to consumption of olestra. Nevertheless, the agency believes that it should not require a label to bear information about medical advice unrelated to the food in the package.

Finally, some Committee members questioned whether it is appropriate to refer to the stool softening effect of olestra as a "laxative effect." As discussed above, the effect of olestra on stool consistency is similar to that produced by mineral oil, an over the counter laxative that works by lubricating the intestinal tract, softening the fecal contents, and facilitating the passage of feces. However, unlike mineral oil, olestra would be consumed for a purpose other than its potential laxative effect. In this case, FDA believes that requiring use of the term laxative may imply the therapeutic use of a laxative.

Therefore, instead of the term "laxative effect," the agency believes it is more appropriate to use "may cause loose stools" on the label to indicate clearly to consumers, olestra's potential to affect stool consistency.

2. Fat-Soluble Vitamins and Carotenoids

Some Committee members felt that consumers, upon seeing vitamins A, E, D, and K in the ingredient listing of olestra-containing foods, could be confused into thinking that the product is fortified with these vitamins. Therefore, they suggested that the ingredient list ought to contain a parenthetical note explaining that the

vitamins were added to restore what would be lost due to olestra's interference with vitamin absorption.⁸⁹ Other Committee members recommended that the agency handle this issue consistent with similar prior cases.⁹⁰

With respect to olestra's potential to decrease the bioavailability of carotenoids, most members of the Committee agreed with the agency that, given the current state of knowledge, the observed degree of reduction in carotenoid bioavailability does not raise concern. Given this conclusion, most Committee members further agreed that the effect of olestra on the bioavailability of carotenoids is not a fact material in light of consequences that may result from consumption of foods containing olestra and therefore, does not warrant disclosure on the labels of such foods.⁹¹ Others felt that it was necessary to inform consumers that consumption of olestra may lower serum carotenoid levels.⁹²

The agency notes that there are no prior cases on which to base how labeling with respect to the vitamins that are added to olestra-containing foods might be handled. The agency has not previously approved an additive which interferes with the absorption of vitamins to a degree that necessitates requiring that foods containing the additive be compensated with such vitamins to mitigate the effect of olestra.

As stated above, the agency believes that consumers who see the added vitamins listed on the ingredient listing could be misled and believe that the food is fortified with the vitamins unless they are given information explaining why the vitamins are added to the olestra-containing food. Therefore, the agency believes that the fact that the olestra inhibits vitamin absorption and that vitamins have been added back are material facts that should be disclosed to consumers.

E. Agency Conclusions Regarding Labeling of Foods Containing Olestra

Based on the entire record before the agency, FDA has concluded that foods containing olestra should bear the following label statement:

This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added.

In the absence of such labeling, the agency would consider olestra-containing foods to be misbranded (21

U.S.C. 343(a) and 321(n)). FDA believes that this information will be used by consumers both in their decisions on purchases and to help them adjust their consumption to minimize side effects. To ensure that the required labeling statement will be readily recognized and easy to read, FDA is requiring a standardized format that specifies among other things, type style and type size. FDA's recent experience with graphic requirements for the new Nutrition Facts label, as well as focus group discussions of the new Nutrition Facts label requirements, show that messages put in a boxed area help consumers distinguish the message from other information as well as draw attention to it (see 60 FR 67176 at 67181, December 28, 1995). Therefore, FDA is requiring that the message on the label of olestra-containing foods be surrounded by a box. Additionally, FDA is also specifying the minimum type size to ensure proper prominence. FDA welcomes any comments on the adequacy of this label requirement, including the format, as it reassesses this interim rule.

The agency would not object to any additional truthful nonmisleading information that a manufacturer may wish to include in the label statement, including, for example, a telephone number that consumers can call to obtain additional information regarding GI effects caused by olestra or olestra's effect on the absorption of fat-soluble nutrients.

VIII. Response to Comments

FDA received approximately 2,300 comments on the olestra petition. Comments were received from health care professionals, scientists, nutritionists, members of academia, consumer organizations, and professional associations as well as individual consumers. These comments, together with the Olestra Working Group and the FAC deliberations on the issues raised by the comments, have been taken into account in FDA's final decision on the olestra petition.

Most of the comments opposing olestra's approval (about 2,000 comments) were from individual consumers who identified themselves as members of CSPI and simply stated that fat substitutes must be absolutely safe and urged the agency to reject the "petition to approve the unsafe fat substitute olestra." These comments did not provide any factual information or any rationale to support the opinion expressed. Because these comments raise no factual issue, they will not be discussed further.

⁸⁹ Transcript, vol. 3, p. 218, 259, 261.

⁹⁰ Transcript, vol. 3, p. 263.

⁹¹ Transcript, vol. 3, p. 271.

⁹² Transcript, vol. 3, p. 258.

⁸⁸ Transcript, vol. 3, p. 90.

Most of the remaining comments opposing olestra's approval (the majority of which were form letters with some of the writers declaring affiliation with CSPI) expressed similar views on one or more of the following issues that were discussed extensively at the meetings of the Olestra Working Group and the FAC: (1) The potential for olestra to cause GI effects (including the nature of the GI effects); (2) the potential for olestra to deplete fat soluble vitamins, carotenoids, and other phytochemicals, and whether such depletion increases the risk for certain cancers and other diseases such as coronary heart disease, stroke, macular degeneration, and other eye diseases; (3) whether adding vitamins to olestra-containing foods to compensate for depletion is efficacious or raises vitamin toxicity issues; (4) whether olestra, with or without supplemented vitamin K, interferes with coumadin therapy; (5) whether labeling with respect to GI issues and nutrient issues should be required for foods containing olestra (including the nature of the information that should be included in the label statement); (6) adequacy of the length of the studies to assess long term effects of olestra consumption and whether adequate studies have been conducted in special populations; (7) whether liver lesions seen in two rat studies and lung tumors in one mouse study are meaningful to human health; (8) whether vitamin A-supplemented olestra raises teratogenic concerns; and (9) whether the petitioner's estimates of olestra intake from savory snacks are credible.

Because the agency's analysis of these comments has already been incorporated at the appropriate places throughout this document, that analysis will not be repeated here. Comments raising issues that have not been previously discussed in this document and the agency's responses are given below.

The agency also received many comments supporting the approval of olestra. These comments were from individual consumers as well as scientists, clinicians, and nutritionists. Several of the comments cited problems with obesity in the population and the need for a fat replacer such as olestra and that the health benefits from lower fat intake far outweigh the perceived adverse side effects. These comments stated that under the intended conditions of use, olestra is safe and that it provides those who wish to use products made with olestra with an option for low fat, low saturated fat salty snacks. One comment signed by nine scientists and clinicians countered

point-by-point arguments made in the CSPI White Paper; the comment added that their in-depth review of the olestra research program shows that olestra is safe for use as a fat replacer. Other comments stated that the Olestra Working Group and FAC meetings were conducted in an open and fair manner, that the meetings permitted a thorough exchange of scientific information, that all issues were adequately addressed, and that the commenters concurred with the majority of the FAC members who concluded that olestra was safe for its intended use.

A. Comments on Procedures

CSPI made several comments about the agency's process for review of the olestra petition. None of these procedural comments raise issues regarding the olestra safety data. Nevertheless, because the agency greatly values public participation and has provided a substantial opportunity for such participation regarding FDA's review of the olestra petition, FDA is addressing these procedural comments in this preamble. Importantly, however, none of these comments, even if correct, undermines the agency's safety determination here.

1. One comment from CSPI stated that the period allotted for comments following the Olestra Working Group and FAC meetings of November 14 through 17, 1995, was unjustifiably brief. The comment added that the comment period was too brief a time for review of transcripts and other data to prepare a thoughtful and complete postmeeting comment. The comment suggested that an additional 50 days be provided for comment.

The point raised by this comment is moot because FDA granted CSPI additional time (Ref. 105) to prepare its comments. The agency notes that CSPI did submit extensive comments prepared after the Olestra Working Group and FAC meetings on December 1, 1995, the date for submission of comments announced in the Federal Register of November 16, 1995 (60 FR 57586), the deadline to which CSPI objected. The agency granted CSPI additional time because the agency accepted CSPI's representation that it needed additional time to obtain and review a new study presented by the petitioner at the Olestra Working Group and FAC meeting, and to prepare comments on the study. The data were delivered to CSPI on December 8, 1995, with the letter extending the time for submission of comments (Ref. 105). FDA notes that CSPI submitted additional comments on December 21, 1995, but that these additional

comments did not mention the new study.

2. One comment from CSPI asserted that FAC members could not reach well-reasoned positions because they did not receive copies of CSPI's White Paper until noon on Friday, November 17, 1995.

The agency believes that both Working Group and FAC members had sufficient access to CSPI's White Paper and the organization's views and thus, FDA does not agree with this comment. FDA distributed copies of a revised draft that the agency had received from CSPI the week preceding the November meetings to each Olestra Working Group member, guest, or consultant prior to convening of the Olestra Working Group meeting. Nine FAC members served on the Olestra Working Group and received copies of the CSPI White Paper. Also, several other FAC members attended part or all of the Olestra Working Group meeting and therefore, heard CSPI's presentations and responses to questions during the Working Group meeting. Thus, the assertion that *no* Committee member had access to or time to consider CSPI's views prior to noon on Friday, November 17, 1995, is incorrect.⁹³

Finally, it is important to consider the roles of the FAC and the Olestra Working Group. The Olestra Working Group was composed of FAC members with expertise directly relevant to the safety issues for olestra and of additional temporary members with needed expertise not available from standing FAC members. FDA fully expected that this specialized subgroup would conduct the focused consideration of the olestra petition; under the FAC charter, however, subgroup views can only be passed on to FDA through the full FAC. Thus, the purpose of the FAC meeting was to apprise FAC members of the Working Group discussion, and for the FAC to consider whether to pass the Working Group views on to FDA, to pass the views on with additional commentary, or to return the matter to the Working Group for further discussion.

3. One comment from CSPI challenged the way in which

⁹³In addition, CSPI itself selectively sent a draft of the White Paper document to 11 of the standing 18 FAC members who participated in the Friday, November 17, 1995, meeting. (This direct distribution was squarely contrary to the applicable regulations, 21 CFR 14.35(d).) Of the other seven, two were also members of the Working Group and received copies of the revised draft on the first day of that meeting. Three of the seven attended the Working Group meeting (and therefore heard CSPI's oral presentations). Only 2 of the 18 FAC members potentially were unaware of CSPI's written or oral views until the public hearing on the morning of Friday, November 17, 1995.

consultants and special, temporary members were appointed to the Olestra Working Group and FAC. CSPI contended that FDA failed to consider experts on vitamin K and carotenoids that CSPI had suggested for the Olestra Working Group, and that FDA did not appoint any other experts in those subject areas to either the Working Group or the FAC. CSPI alleged that therefore, the FAC was ill-prepared to discuss these matters.

The agency carefully considered CSPI's suggested experts on carotenoids and vitamin K. However, several of these experts had already provided written views on the issues to CSPI (apparently in response to a solicitation by CSPI). Statements by some of these experts were included as part of CSPI's mailing to selected FAC members, and statements by some or all of these experts were included in materials distributed during the Olestra Working Group and FAC meetings. Because the individuals appear to have had previously established views regarding olestra, FDA concluded that they could not appropriately be included in the Olestra Working Group. Furthermore, there is no reason to believe that the nutrition (10 members or consultants) and toxicology (3 members) experts participating at the Committee meeting were not able to comprehend or interpret the information and views on carotenoids and vitamin K presented orally or in writing by experts on behalf of either CSPI or the petitioner.

4. Another comment from CSPI argued that Dr. Fergus Clydesdale was an inappropriate choice as chair of the Olestra Working Group, asserting that Dr. Clydesdale had a pro-industry stance.

First, it is significant to note that CSPI does not allege that Dr. Clydesdale conducted the Olestra Working Group meeting unfairly or did not allow for an open and orderly exchange of views. Second, FDA notes that all advisory committee members undergo an evaluation for conflicts of interest with respect to specific issues to be presented to a committee. Dr. Clydesdale was subjected to that review, and his participation was ultimately determined to be consistent with the applicable conflict of interest laws and regulations.

5. A comment from CSPI asserted that FDA's interpretation of conflict of interest is too restrictive in that it only applies to interests in the petitioner or its competitors. CSPI would disqualify any member who holds strong views, pro or con, regarding the food industry or food additives.

FDA believes that the agency's policies, procedures, and practices

comport with the applicable conflicts of interest laws and regulations and thus, disagrees with CSPI's comment on this point.

6. CSPI also claimed that the amount of time Olestra critics were allotted at the Olestra Working Group and Committee meetings was insufficient in contrast to the "ample amounts" of time given to the petitioner and to FDA staff.

FDA disagrees with this comment for several reasons. First, the agency believes that the appropriate question is whether there was ample opportunity for public participation, not whether a particular participant had enough time. Second, CSPI was provided with substantial opportunities to present its views to both the Olestra Working Group and Committee, much more than customarily provided to any single group or individual during advisory committee public hearings and much more than that provided to any other group or individual during the public hearing portions of the meetings.

FDA notes that at a typical advisory committee meeting concerning a product approval application or petition, FDA presents its analysis of the data, and the applicant/petitioner is permitted to "defend" its application or petition. Although there is always a public hearing portion to the meeting, the bulk of the meeting is devoted to Committee discussion, including questioning by committee members of FDA, the applicant/petitioner, or other presenters.

FDA policy is to provide a minimum of 1 hour of public hearing time at each advisory committee hearing. Because of the substantial interest in olestra, and because FDA desired comments focussed on specific issues, considerably more public hearing time than the minimum was allotted. (A total of nearly 6 hours of public hearing time occurred during the Olestra Working Group and FAC meetings.) A significant portion of that time was allotted to CSPI or other participants who presented views consistent with those of CSPI. In addition to time specifically allotted to it, CSPI was permitted to respond to questions posed by the Working Group and the FAC. Finally, CSPI participated in an unscheduled public hearing session along with the petitioner near the close of the FAC meeting.

7. One comment urged that the FAC should be reconstituted because of a perceived strong pro-industry orientation of its members and Dr. Clydesdale (chair of the Working Group), and the "lack of consumer health activists." The comment added that advisory committees should include "a preponderance of public-

health advocates" in order to provide the best advice to the agency.

FDA disagrees with this comment. FDA appoints Committee members based on their scientific, medical, or other technical expertise, members are screened before each meeting with respect to conflict of interest in the particular matters to be brought before them, and members are expected to provide an unbiased evaluation of the information presented to them. Furthermore, consumer representatives were members of both the Working Group and the FAC, members who were nominated by a consumer consortium for consideration by FDA. Finally, the FACA requires that advisory committees be fairly balanced. The agency believes that both the Working Group and the FAC meet this standard. Thus, FDA does not agree with this comment.

8. One comment from CSPI stated that the Committee could not formulate well-reasoned positions because CFSAN staff failed to provide Committee members with a study published in the *American Journal of Clinical Nutrition* 2 months earlier demonstrating that 3 g of olestra caused remarkable declines in serum carotenoid levels, and a second study published in the *New England Journal of Medicine* in early November that found a strong correlation between low lycopene levels in blood and optic neuropathy. In addition, the comment stated that CFSAN staff failed to mention that olestra caused premature liver foci in rats and a statistically significant increase in lung tumors in male mice and further failed to provide any evidence that carotenoids may reduce the risk of cancer, cardiovascular diseases, and age-related macular degeneration.

The agency disagrees with this comment in its entirety. First, with regard to the first published study, the agency notes that the effect of olestra on serum carotenoids was discussed at length at the Olestra Working Group and FAC meeting. Not only were the results of the study cited by the comment presented by CSPI, a study conducted by the petitioner showing olestra effects on serum carotenoids that were much greater than those shown in the cited study were presented by FDA.

With regard to the second published study, FDA notes that CSPI and other presenters submitted and presented detailed information regarding the potential relationship between carotenoids and disease, and after consideration of this information, most Olestra Working Group and FAC members determined that there is a reasonable certainty of no harm with

respect to olestra's effects on serum carotenoids.

Finally, with regard to liver foci and lung tumors, FDA presented data on olestra's effect on liver foci in rats and in on lung tumors in male mice. In addition, this topic was thoroughly discussed at the Olestra Working Group and FAC meetings.

B. Substantive Comments

9. One comment questioned whether an acceptable daily intake (ADI) based on a "no observed-effect level" has been established for olestra. One comment asserted that even applying even a minimal safety factor of 10 to the 8 g/d consumption level tested by the petitioner, and at which carotenoids were depleted by up to 60 percent within 2 weeks after the start of olestra consumption, would preclude the approval of olestra for use in snack foods, because the estimated daily intake (EDI) would greatly exceed the 0.8 g/d ADI.

The agency acknowledges that it has not established a numerical value for an ADI for olestra. First, as noted earlier, safety factors are applied to toxic effects observed in animal studies; the purpose of the safety factor is to allow for any discrepancy when extrapolating from animals to humans. Because olestra is intended for use as a macroingredient, it is not possible to feed it to test animals at sufficiently high amounts to elicit toxic effects and thereby establish an ADI using the traditional 100-fold safety factor. The agency notes, however, that no toxic effects were observed when test animals were fed olestra at up to 10 percent of the diet. Furthermore, as discussed at length in this preamble, the clinical data establishing the safety of olestra for its intended use are nutrition studies conducted in humans to which the traditional 100-fold safety factor is not applied.

With respect to olestra's effect to decrease serum carotenoid levels, the agency has concluded, as discussed in detail above, that based upon the available data, this effect does not represent an adverse health effect and therefore, cannot appropriately be used for establishing an ADI for olestra.

10. A comment stated that the NCI and other public health leaders have been encouraging Americans to eat at least five servings a day of fruits and vegetables. The comment added that this advice is grounded, in part, on the presence of carotenoids in fruits and vegetables and the belief of senior scientists at the NCI and elsewhere on chemoprotective activities of carotenoids and similar nutrients. The

comment asserted that if FDA were to approve olestra, it would be undercutting NCI's scientific judgement and stand in favor of protecting public health. Another comment stated, specifically with respect to the carotenoids and their potential importance, that the issue receive an impartial review by the National Research Council or a specially convened advisory group of researchers in the carotenoid field.

FDA agrees with the comments that the issue with respect to the potential importance of carotenoids deserves special attention. This is why FDA convened a working group for olestra and the full FAC to examine the issue along with others. The Olestra Working Group and the full FAC were supplemented with appropriate experts in the field of nutrition; in addition, noted experts in the carotenoid field as well as epidemiology experts who could speak to the epidemiological data on carotenoids and incidence of diseases such as cancer and macular degeneration made presentations to the Olestra Working Group and FAC. Finally, because of significant discussion of this issue and because the agency received additional comments since the Olestra Working Group and FAC meetings on the potential chemoprotective function of carotenoids, FDA consulted with Dr. Greenwald at NCI and Dr. Kupfer at the NEI regarding whether olestra's effects on carotenoids raise any significant health issues (Refs. 69 and 70). FDA provided letters concerning carotenoids that the agency had received and excerpts discussing carotenoids from: (1) Submissions from the petitioner, (2) the White Paper, (3) FDA's briefing document for the Olestra Working Group, and (4) the transcript of the Olestra Working Group and FAC meetings to Dr.'s Greenwald and Kupfer.

After reviewing the data, Dr. Greenwald concluded that there is no significant public health issue raised by the effects of olestra on lipophilic carotenoids and that supplementing olestra with beta carotene or other carotenoids was not warranted (Ref. 71). Dr. Kupfer from NEI concluded that although theoretical considerations have raised the possibility that carotenoids might play some protective role in macular degeneration, there are currently no convincing clinical data to support the hypothesis, and there are no demonstrated eye health benefits for carotenoids (Ref. 72). Given the NIH conclusions, FDA does not agree that FDA would be undercutting NCI's scientific judgement if it were to approve olestra. Further, FDA notes that

by approving olestra, FDA is not contradicting or undercutting the NCI advice to eat fruits and vegetables.

11. One comment stated that 30-300 mg/day of beta-carotene was used to prevent or lessen the photosensitivity characteristic of the disease erythropoietic protoporphyria (EPP). The comment added that if a significant amount of the beta-carotene taken by the EPP patients, who also eat foods containing olestra, is not absorbed, the patients will suffer from photosensitivity and will have to curtail markedly the activities the beta-carotene ingestion would permit. The comment added that it was not enough to theorize that supplementation of olestra with carotenoids will cure the problem and suggested the design of two studies on the effect of olestra on the absorption of beta-carotene, which should be conducted and evaluated before approval of olestra is considered.

The comment raises the issue of food-drug interactions; in this instance, beta-carotene is being used as a drug, i.e., to treat patients with EPP. Food-drug interactions are generally handled through labeling for the drug product or through advice of the physician prescribing the drug. The agency fully intends to apprise physicians regarding the effect of olestra on the absorption of beta-carotene and other lipophilic carotenoids so that physicians will in turn be able to advise EPP patients appropriately. Further, because the agency believes that this potential drug-food interaction problem can be adequately addressed through education of physicians and their patients, the agency does not agree that the suggested studies on the effect of olestra on the absorption of supplemented beta-carotene are necessary.

12. One comment cited an association between retinitis pigmentosa and steatorrhea and asserted that olestra causes steatorrhea and that chronic consumption of olestra may result in retinitis pigmentosa. The comment also stated that the studies show that vitamin supplementation results in reversal of the condition.

The agency does not agree that olestra causes steatorrhea; the basis for that conclusion is discussed above. However, the agency acknowledges that loss of fat soluble vitamins due to the presence of olestra in the GI tract has the potential for harm. For this reason, the agency is requiring, as a condition of safe use, that olestra be supplemented with vitamins A, D, E and K in such a way that the bioavailability of these vitamins from the diet remains unchanged. Thus, any potential consequence of decreased absorption of

fat-soluble vitamins will be offset by the vitamin compensation required by the final rule.

13. Some comments stated that approval of the petition will result in unnecessary medical care associated with olestra's GI effects. Another comment questioned whether FDA has evaluated the potential impact of olestra on the health care delivery system, specifically, on the cost of office visits and diagnostic procedures by primary care physicians and gastroenterologists who evaluate GI disturbances that may occur from the use of the additive. The comment added that it seemed ill advised for FDA to approve the introduction of a product which may increase expenditures for healthcare.

The agency does not agree that approval of the petition will result in unnecessary medical care associated with olestra's GI effects and therefore, does not agree that use of the additive will lead to increased costs associated with medical care for these effects. This is because the agency has determined that foods containing olestra shall be labeled so that consumers will be able to associate olestra with the GI symptoms that it may cause. The agency believes that this will significantly reduce or eliminate any unnecessary or inappropriate medical treatment. Therefore, the agency does not believe that it is necessary to evaluate the potential impact of olestra on the cost to the health care delivery system.

14. One comment stated that while a general reduction in fat intake, especially saturated fat, is desirable, it seems unlikely that substituting olestra for part of the fat in a few products will have, or can be shown to have substantial benefit and added that benefits should be substantial to warrant the use of materials like olestra. Other comments stated that when GI disturbances are considered in conjunction with depletion of fat-soluble vitamins that are critical to the maintenance of health and depletion of other fat-soluble materials whose importance is not yet fully understood, the potential benefits that could result from the use of olestra are outweighed by the risk to the public health.

The agency notes that, unlike approval of drugs, the law applicable to the approval of food additives does not permit consideration of, or require a showing of, benefits. As stated above, before a food additive can be approved, it has to be established that there is a reasonable certainty that the additive will not be harmful under the prescribed conditions of use. Further, as discussed in detail above, the agency does not agree that the GI symptoms

that may occur due to consumption of foods containing olestra represent risk to the public health. Similarly, as discussed above, because the agency is requiring¶that olestra be supplemented with the affected vitamins, the agency does not agree that olestra's potential to decrease the absorption of fat-soluble vitamins and other nutrients with purported uses represent risk to the public health.

Finally, the agency notes that the petitioner is not required to show that olestra has health or other benefits for consumers of the additive. Likewise, FDA is not permitted to consider such benefits in its evaluation of the safety of olestra for its intended use.

15. Several comments stated that once approved for use in savory snacks, olestra will be used in everything and urged the agency to prevent its use in other products such as fat-free cakes and fast-food fries.

The agency notes that the final rule that is being promulgated restricts the use of olestra for only in prepackaged ready-to-eat savory (i.e., salty or piquant but not sweet) snacks. Use of olestra in any other foods, including fat-free cakes and fast-food fries, is not permitted. Any additional use will require an evaluation of that use through a food additive petition in accordance with 21 CFR 171.1.

16. Two comments expressed concern that olestra may cause allergic reactions in many people and, therefore, should not be approved.

These comments did not provide any data to substantiate the assertion that olestra would be an allergen. FDA does not agree with these comments. FDA notes that, in general, food allergens are known to be protein or glycoprotein in nature. Olestra, composed of six, seven, or eight fatty acids esterified to sucrose, is neither a protein nor a glycoprotein and does not contain these substances even as minor constituents. Therefore, the agency believes that olestra is unlikely to cause any allergic reactions and finds that these comments are without merit.

17. One comment stated that unless olestra can be converted into an acceptable energy source for livestock/poultry and pet rations or properly removed from the environment, a major disposal problem would result. The comment added that since olestra has no energy value, neither the spent frying olestra nor the waste savory snacks will be recycled. The comment asserted that this issue needs to be addressed prior to approval of olestra.

The agency agrees that the question of whether disposal of olestra or olestra-containing products raises

environmental concerns needs to be addressed before olestra can be approved. In fact, the National Environmental Policy Act (NEPA) mandates that FDA review the environmental consequences of its actions. In accordance with NEPA, FDA required the submission of, and reviewed, an environmental assessment (EA) for olestra prepared by the petitioner. Among other things, the EA addresses whether disposal of olestra or olestra-containing products has the potential to cause adverse environmental effects. As discussed below, the agency has consulted with the U.S. Environmental Protection Agency (EPA), has reviewed the petitioner's EA, and has concluded that approval of olestra will not have any ¶significant adverse environmental impacts from its manufacture, use, or disposal.

IX. Environmental Impact Considerations

The petitioner submitted an environmental assessment (EA) with its food additive petition for the use of olestra as a replacement for fats and oils in food. In May 1987, shortly after the food additive petition was filed, FDA was contacted by EPA regarding olestra. EPA was interested in whether the use of olestra would have an adverse effect on water quality and wastewater treatment processes. FDA agreed to consult with EPA regarding olestra and give EPA an opportunity to comment on the petitioner's environmental submission after FDA had completed its evaluation. In July 1990, the petitioner submitted a request to limit the intended use of olestra to substitution for conventional fat in the preparation of savory snacks. At that time, the petitioner submitted a revised EA for the limited use of olestra in savory snacks.

The expected route of environmental introduction for olestra is through wastewater treatment systems and, subsequently, to aquatic and terrestrial environments. The petitioner performed studies on primary and secondary wastewater treatment processes which demonstrated that olestra does not have an adverse effect on the effective functioning of wastewater treatment plants. The petitioner provided studies on the fate and effects of olestra in aquatic and terrestrial systems which establish that, at the expected concentrations, olestra would not have an adverse effect upon organisms exposed in the water column, in sediments, or in soil following land application of sewage sludge. After analysis of the information provided,

FDA tentatively concluded that approval of this petition would not cause significant environmental effects.

Before reaching a final conclusion on the environmental effects of olestra, however, FDA requested that EPA review the information provided by the petitioner on the potential effect of olestra on wastewater treatment systems; exposed aquatic organisms, such as fish and sediment dwelling animals; soil physical and chemical properties subsequent to sewage sludge applications; and possible effects resulting from an accidental spill or treatment plant malfunction. EPA concluded that these issues had been satisfactorily addressed by the petitioner in the EA for the olestra food additive petition, and did not raise any environmental objection to the use of olestra in savory snacks. In light of the consultations with EPA, and based upon its own review, FDA has concluded that adverse environmental effects are not expected to result from the manufacture of olestra or from production or consumption of savory snacks containing olestra.

Accordingly, the agency has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

X. FDA's Overall Conclusions

The question before FDA regarding olestra is whether the additive is safe for its intended use as a fat substitute in savory snacks. (21 U.S.C. 409(c)(3)(a).) To determine that olestra is safe, the agency must conclude, based upon a fair evaluation of the evidence of record, that there is a reasonable certainty that olestra is not harmful under the intended conditions of use. (21 CFR 170.3(i).) This determination of reasonable certainty of no harm necessarily involves the application of scientific judgement. Under the act, the

agency has a duty to deny approval to an additive that has not been shown to be safe within the meaning of the act; the agency has a parallel duty to permit the marketing of those additives where the available scientific record establishes safety.

It is not uncommon for an agency safety decision regarding a regulated product, including a food additive, to be very difficult. The decision regarding the food additive olestra is one such decision. The difficulty presented by the olestra food additive petition results from a relatively unique intersection of a number of factors, including the following.

First, the volume of available safety evidence for olestra is enormous, all of which FDA was obligated to review, evaluate, and synthesize. Second, as a macro-ingredient, olestra is intended to replace a sizeable portion of the diet, and thus, will likely be consumed in relatively large amounts; this alone sets olestra apart from almost all food additives previously reviewed by FDA. Third, olestra presents a number of questions regarding nutritional effects, most of which have not been presented previously to FDA. Fourth, much of the pivotal scientific safety evidence for olestra comes from studies in humans; human studies, even well conducted ones like those for olestra, are necessarily limited in terms of the number of subjects that can reasonably be tested in a clinical trial conducted prior to marketing, the length of the trial, and the endpoints measured. Finally, under the act, once approved, olestra may be consumed by the entire U.S. population of 250 million people. This potentially widespread consumption for olestra does not, of course, set it apart from other foods and food additives. It does, however, distinguish this decision from those that FDA makes regarding drug and medical device products.

It is important to emphasize that the coalescing of the foregoing factors does not preclude an agency decision at this time; it does, however, make the determination challenging. Similarly, it is worth noting that because of the challenge presented by olestra, the

agency used an expanded approach to its evaluation of the petition, and established and utilized the internal Regulatory Decision Team, sought out and utilized the expertise of five subject-specific experts, and held a lengthy public meeting of the agency's Food Advisory Committee and a subgroup of that Committee (the Olestra Working Group) to foster an open and public discussion of the safety issues presented by olestra.

Consistent with the act and its applicable standards, FDA has conducted an evaluation and synthesis of the evidence of record concerning olestra, including the proceedings of the FAC and comments submitted to the agency. In this process, FDA has applied its best scientific judgement, aided by the scientific judgement of the experts and public participants who contributed to the evaluation process. As the foregoing discussion makes clear, and as the proceedings of the FAC illustrate, olestra presents a number of important scientific questions. For some questions, there is arguably evidence, including support from recognized experts, on both sides of the question, ultimately requiring FDA to evaluate and weigh the data currently available and apply its scientific judgement. The agency has, as a result of this process, determined that there is a reasonable certainty that no harm will result from the use of olestra in savory snacks.

Based upon a fair evaluation of the evidence of record, FDA concludes that olestra is not toxic, carcinogenic, genotoxic, or teratogenic. Olestra is essentially not absorbed or metabolized. Heating olestra, as would occur in the commercial preparation of snacks made using olestra, does not increase the absorption of the additive. FDA further concludes that the studies conducted show that olestra has an effect on the absorption of vitamins A, E, D, and K. FDA also concludes that it is possible to supplement foods containing olestra with all four vitamins in such a way as to compensate for the amounts that are not absorbed from the diet due to the action of olestra. FDA concludes that the amounts that should be provided are those listed below:

TABLE 10.—COMPENSATION LEVELS FOR VITAMINS A, D, E, AND K

Vitamin	Compensation level
Vitamin A	51 retinol equivalents/g olestra as retinyl palmitate or retinyl acetate)(170 IU/g olestra or 0.34 X RDA/10 g olestra
Vitamin E	1.9 mg α-tocopherol equivalents/g olestra (0.94 X RDA/10 g olestra)
Vitamin D	12 IU vitamin D/g olestra (0.3 X RDA per 10 g olestra)
Vitamin K	8 μg vitamin K ₁ /g olestra (1.0 X RDA per 10 g olestra)

As discussed previously, in order to avoid confusion about the purpose of the added vitamins in olestra-containing foods, FDA is requiring a label statement to indicate that olestra affects the absorption of some nutrients and that in order to compensate for olestra's effects on vitamins A, D, E, and K, these vitamins have been added.

As discussed above, at present, carotenoids have no identifiable health benefit role (except for the provitamin A role of beta carotene.) Further, randomized studies have failed to show an association between selective carotenoid repletion and cancer. Although epidemiological studies show an association between diets rich in fruits and vegetables (including those that contain carotenoids) and decreased cancer risk, there is no direct evidence that carotenoids themselves are responsible for or contribute in a significant way to that protective benefit. In addition, the level of effects on carotenoids from olestra may well be within the normal variation due to diet and bioavailability. In light of the current state of the scientific evidence, FDA believes that there is a reasonable certainty of no harm from olestra's effects on carotenoid absorption. Accordingly, the agency concludes that there is currently no justification or need to require compensation of olestra-containing foods with specific carotenoids.

Regarding water soluble nutrients, given the totality of the study results, FDA concludes that there is a reasonable certainty that olestra will not cause any harmful effects on vitamin B₁₂, calcium, iron, zinc, or folate or other water soluble nutrients. Collectively, the clinical data on the water-soluble vitamins that are hard to absorb (folate and vitamin B₁₂) show that olestra does not affect the absorption of these nutrients. Similarly, the data on two of the nutrients that are limited in the diet (iron and zinc) show that olestra does not interfere with their absorption.

Although the data on the third nutrient that is limited in the diet, calcium, are not sufficiently rigorous to detect possible subtle changes, the lack of any plausible argument for expecting an effect, the lack of any olestra effect on folate, iron, or zinc, the fact that supplementation with vitamin D will preclude any vitamin D-mediated calcium depletion, and the insignificance of any subtle effect compared to variations in the human diet, lead FDA to conclude that there is a reasonable certainty that olestra will not have any harmful effect on calcium absorption.

With respect to the potential effect of olestra on the GI tract, FDA concludes that the effects seen do not represent significant adverse health consequences and therefore, do not preclude approval of the petition. However, while FDA believes that there are no direct safety concerns with respect to olestra's potential effect on the GI tract, FDA concludes that the GI symptoms associated with ingestion of olestra-containing foods are material fact information within the meaning of 201(n) of the act. Disclosing this information on food labels will enable consumers to associate olestra with any GI effects that it may cause. Consequently, FDA is requiring that such information be disclosed on the label of foods containing olestra to preclude consumers from being misled about consequences which may result from the consumption of the olestra-containing foods. Therefore, in the final rule, FDA concludes that foods containing olestra should bear an appropriate label statement.

In summary, FDA concludes that all safety issues have been addressed adequately and that based upon the currently available evidence, the use of olestra in savory snacks will be safe when used in accordance with the final rule.

FDA's determination will permit the use of olestra in savory snacks. In order for olestra to be lawfully used in other foods (e.g., cakes and pies), a new food additive petition would need to be filed and approved. In conjunction with that review, the agency would then conduct a separate and independent safety evaluation of the additional proposed uses.

Procter and Gamble has notified FDA that the company will be conducting additional studies of olestra exposure (both amounts consumed and patterns of consumption) and the effects of olestra consumption (Ref. 103).

FDA believes that Procter and Gamble's plans to continue to study the consumption and effects of olestra are both prudent and responsible. It is likewise prudent and responsible for FDA to evaluate the results of such studies as it monitors the on-going marketing and distribution of olestra. Only with data from the broader marketing of olestra can the agency, be in the position to evaluate in the future whether there continues to be reasonable certainty of no harm from the use of olestra in savory snacks.

Therefore, as a condition of approval, Procter and Gamble is to conduct the studies that it has identified in its letter to FDA (Ref. 103), consistent with the timetables identified in that letter.

Furthermore, consistent with the terms of that letter, Procter and Gamble is to provide the Food and Drug Administration with access to all data, information, and reports of those studies as such information becomes available.

It is the agency's responsibility as a public health agency to review and evaluate the data generated by Procter and Gamble's studies, as well as any new data that bear on the safety of olestra (such as data and information on the health significance of carotenoids)⁹⁴ to determine whether there continues to be a basis for a reasonable certainty that the use of olestra in savory snacks is not harmful. Thus, consistent with the agency's continuing obligation to oversee the safety of the food supply, FDA will, within 30 months of this approval, review and evaluate any new data and information bearing on the safety of olestra and present such information to the agency's Food Advisory Committee (or a working group of the FAC). To the extent that additional data and information bearing on olestra's safety are submitted to and reviewed by the agency, FDA will, in its discretion, hold any additional meetings of the FAC that may be necessary to consider such information.

This future meeting of the FAC (and any subsequent FAC meetings) will be open public meetings with an opportunity for participation by FDA, Procter and Gamble, and interested members of the public, and will provide an opportunity for public discussion and deliberation of the newly developed data regarding olestra.

As an indication of the agency's view of the importance of this review, evaluation, and public discussion by the FAC of future data on olestra, as well as an indication of the depth of the agency's commitment to do so, the final rule established by this decision includes a statement concerning FDA's commitment in this regard. FDA has used the word "will" in § 172.867(f) with respect to the agency's commitment to conduct such review and evaluation. The agency has thus legally bound itself to institute this review and evaluation. (See *CNI v. Young*, 818 F.2d 943 (D.C. Cir. 1987).)

The decision embodied in this document necessarily articulates certain

⁹⁴The record of this proceeding, particularly the meeting of the Olestra Working Group and the FAC, demonstrates that the question of the role of carotenoids in disease prevention or health maintenance is an issue of intense interest and the focus of continuing scientific study and evaluation. It is thus likely that there will be additional scientific data and information that bears on the question of the role of carotenoids in the future.

baseline parameters concerning the safety data for olestra, particularly parameters with respect to the finding of a reasonable certainty of no harm. These parameters include the exposure to olestra (both amount of consumption and patterns of consumption), and the nature, severity, incidence, and prevalence of any effects of olestra consumption, including any effects on fat-soluble nutrients and any gastrointestinal effects. If, as a result of the agency's review and evaluation and its consultation with the FAC, FDA determines that the results reflected in the new data and information are not consistent with the parameters that form the basis of this decision, or the agency otherwise concludes that the available safety evidence for olestra shows that there is no longer reasonable certainty of no harm from the use of this substance, FDA will institute appropriate regulatory proceedings.

It is important to recognize that to institute a proceeding to limit or revoke the approval of olestra, FDA would not be required to show that olestra is unsafe. Rather, the agency would only need to show that based upon new evidence, FDA is no longer able to conclude that the approved use of olestra is safe, i.e., that there is no longer a reasonable certainty of no harm from the use of the additive. Further, in any proceeding to withdrawal or limit the approval of olestra, Procter and Gamble would have the burden to establish the safety of the additive. 21 CFR 12.87(c).

Imposing a condition of approval such as this is not without precedent in the area of food additive approvals. At the time that FDA reinstated the approval of the artificial sweetener, aspartame, the Commissioner of Food and Drugs required that the petitioner for aspartame (G.D. Searle & Co.) develop data and other information on the actual use levels of the additive so that the estimated use levels of aspartame that formed the basis of the agency's safety decision could be compared with levels of actual use. (46 FR 38283, 38303; July 24, 1981).

This condition of approval is not, and should not be interpreted as, an indication that FDA has somehow not determined that there is a reasonable certainty that no harm will result from the use of olestra in savory snacks. As discussed in great detail above, the agency has determined, based upon a fair evaluation of the evidence in the record at this time, that such certainty exists. Having so concluded, however, the agency cannot responsibly ignore its continuing obligation to monitor the safety of the food supply and hence, has

imposed the condition of approval set forth above.

As noted, olestra presents several new challenges. It is a macro-ingredient that it not metabolized, one of the first of its type to be subject to FDA review. In addition, olestra's effects on nutrient absorption are not routinely presented by food additives reviewed by FDA. The safety decision for olestra is in large part based on the data from human studies. These studies are more than sufficient to provide a basis to conclude that olestra is safe. The agency recognizes, however, that olestra has the potential to be consumed by the bulk of the U.S. population of 250 million. In these circumstances, FDA believes that it is not only consistent with the agency's mandate under the act to protect the public health to condition the approval of olestra on the conduct of future studies, see *United States v. Bacto-Unidisk*, 394 U.S. 784 (1969), but it is also the most responsible course for the agency to take in these circumstances.

The Procter and Gamble Co. has made a commitment to the agency that it will conduct the studies outlined in the letter to FDA (Ref. 103), and FDA doubts neither the company's independent interest in conducting these studies nor the good faith of its commitment to the agency to do so. Nevertheless, FDA believes that it is important to articulate here the agency's view of the consequences of a failure of the company to adhere to its commitment. That is, if Procter and Gamble does not conduct the identified studies and does not conduct them according to the articulated timetable, FDA will consider the approval set forth in this document to be void *ab initio* and will institute appropriate proceedings, judicial or otherwise, consistent with that view.

XI. Administrative Record and Inspection of Documents

The administrative record for this final rule consists of the food additive petition (FAP 7A3997), all documents filed in that petition, and any items cited in this preamble.

In accordance with §§ 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the CFSAN (address above) by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

XII. Objections

Any person who will be adversely affected by this regulation may at any time on or before February 29, 1996 file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to ¶ the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

XIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m. Monday through Friday.

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11. Memorandum from M. DiNovi, FDA to F. O. Fields, FDA, February 5, 1993.
12. Memorandum from M. DiNovi, FDA to H. Thorsheim, FDA, March 13, 1995.
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22. Memorandum from L. S. Pellicore, FDA, to F. O. Fields, FDA, July 28, 1995.
23. Memorandum from E. J. Matthews, FDA to F. O. Fields, FDA, December 16, 1993.
24. Memorandum from T. F. X. Collins, FDA, to F. O. Fields, FDA, October 23, 1993.
25. Memorandum from J. J. Welsh, FDA, to L. S. Pellicore, FDA, March 1, 1994.
26. Memorandum from M. J. Bleiberg, FDA, to F. O. Fields, FDA, February 8, 1993.
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28. Memorandum from F. S. D. Lin, FDA, to R. Lorentzen, FDA, February 4, 1988.
29. Memorandum from R. W. Moch, FDA, to F. O. Fields, FDA, April 5, 1993.
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List of Subjects in 21 CFR 172

Food additives, Incorporation by reference, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: Secs. 201, 401, 402, 409, 701, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 342, 348, 371, 379e).

2. New § 172.867 is added to subpart I to read as follows:

§ 172.867 Olestra.

Olestra, as identified in this section, may be safely used in accordance with the following conditions:

(a) Olestra is a mixture of octa-, hepta-, and hexa-esters of sucrose with fatty acids derived from edible fats and oils or fatty acid sources that are generally recognized as safe or approved for use as food ingredients. The chain lengths of the fatty acids are no less than 12 carbon atoms.

(b) Olestra meets the following specifications:

(1) The total content of octa-, hepta-, and hexa-esters is not less than 97 percent as determined by a method entitled "Determination of Olestra by Size Exclusion Chromatography," dated December 19, 1995, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Premarket Approval, Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 200 C St. SW., Washington, DC, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(2) The content of octa-ester is not less than 70 percent as determined by a method entitled "Measurement of the Relative Ester Distribution of Olestra Test Material" dated December 19, 1995, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Premarket Approval, Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 200 C St. SW., Washington, DC, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(3) The content of hexa-ester is not more than 1 percent as determined by the method listed in paragraph (b)(2) of this section.

(4) The content of penta-ester is not more than 0.5 percent as determined by the method listed in paragraph (b)(2) of this section.

(5) The unsaturated fatty acid content is not less than 25 percent (thus not more than 75 percent saturated fatty acid) and not more than 83 percent as determined by a method entitled "Measurement of the Fatty Acid Composition of Olestra Test Material," dated December 19, 1995, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Premarket Approval, Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 200 C St. SW., Washington, DC, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(6) The content of C12 and C14 fatty acids is each not more than 1 percent, and total C20 and longer fatty acids is not more than 20 percent. C16 and C18 fatty acids make up the remainder with total content not less than 78 percent as determined by the method listed in paragraph (b)(5) of this section.

(7) The free fatty acid content is not more than 0.5 percent as determined by a method entitled "Free Fatty Acids" published in the *Official Methods and Recommended Practices of the American Oil Chemists' Society*, 3d Ed. (1985) vol. 1, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the American Oil Chemists Society, 1608 Broadmoor Dr., Champaign, IL 61821, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(8) The residue on ignition (sulfated ash) is not more than 0.5 percent.

(9) Total methanol content is not more than 300 parts per million as determined by the "Total Available Methanol Method," dated December 19, 1995, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Premarket Approval, Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 200 C St. SW., Washington, DC or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North

Capitol Street, NW., suite 700, Washington, DC.

(10) The total heavy metal content (as Pb) is not more than 10 parts per million.

(11) Lead is not more than 0.1 part per million, as determined by a method entitled "Atomic Absorption Spectrophotometric Graphite Furnace Method," Food Chemicals Codex, 3d Ed. 3d Supp. p. 168 (1992), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the National Research Council Press, 2101 Constitution Ave. NW., Washington, DC, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(12) Water is not more than 0.1 percent, as determined by a method entitled "Moisture," *Official Methods and Recommended Practices of the American Oil Chemists' Society*, 4th Ed. (1989), vol. 1, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the American Oil Chemists Society, 1608 Broadmoor Dr., Champaign, IL 61821, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(13) Peroxide value is not more than 10 meq/kg as determined by a method entitled "Peroxide Value," *Official Methods and Recommended Practices*

of the American Oil Chemists' Society, 4th Ed. (1989) vol. 1, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the American Oil Chemists Society, 1608 Broadmoor Dr., Champaign, IL 61821, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC.

(14) The stiffness is not less than 50 kiloPascals/second, as determined by a method entitled "Method for Measurement of the Stiffness of Olestra," dated December 19, 1995, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Premarket Approval, Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 200 C St. SW., Washington, DC, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(c) Olestra may be used in place of fats and oils in prepackaged ready-to-eat savory (i.e., salty or piquant but not sweet) snacks. In such foods, the additive may be used in place of fats and oils for frying or baking, in dough conditioners, in sprays, in filling ingredients, or in flavors.

(d) To compensate for any interference with absorption of fat soluble vitamins, the following vitamins

shall be added to foods containing olestra: 1.9 milligrams alpha-tocopherol equivalents per gram olestra; 51 retinol equivalents per gram olestra (as retinyl acetate or retinyl palmitate); 12 IU vitamin D per gram olestra; and 8 µg vitamin K¹ per gram olestra.

(e)(1) The label of a food containing olestra shall bear the following statement in the manner prescribed in paragraph (e)(2) of this section:

This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added.

(2) The statement required by paragraph (e)(1) of this section shall:

(i) Appear either on the principal display panel or on the information panel of the label;

(ii) Be enclosed by a 0.5 point box rule with 2.5 points of space around the statement.

(iii) Utilize at least one point leading;

(iv) Have type that is kerned so the letters do not touch;

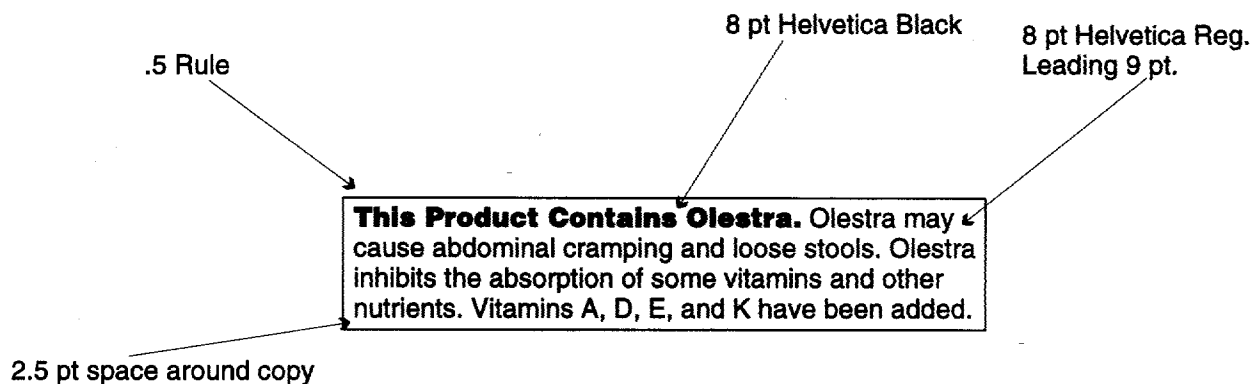
(v) Be all black or one color type, printed on a white or other neutral contrasting background whenever possible;

(vi) Utilize a single easy-to-read type style such as Helvetica Regular and upper and lower case letters; and

(vii) Be in type size no smaller than 8 point.

(3) The sentence "This Product Contains Olestra." shall be highlighted by bold or extra bold type, such as Helvetica Black. The label shall appear as follows:

BILLING CODE 4160-01-F



BILLING CODE 4160-01-C

(4) Vitamins A, D, E, and K present in foods as a result of the requirement in paragraph (d) of this section shall be declared in the listing of ingredients. Such vitamins shall not be considered in determining nutrient content for the nutritional label or for any nutrient claims, express or implied.

(5) Olestra shall not be considered as a source of fat or calories for purposes of §§ 101.9 and 101.13 of this chapter.

(f) Consistent with its obligation to monitor the safety of all additives in the

food supply, including olestra, the Food and Drug Administration will review and evaluate all data and information bearing on the safety of olestra received by the agency after the effective date of this regulation, and will present such data, information, and evaluation to the agency's Food Advisory Committee within 30 months of the effective date of this regulation. The purpose of such presentation will be to receive advice from the Committee on whether there continues to be reasonable certainty that use of olestra in compliance with this

regulation is not harmful. The agency will hold such additional Food Advisory Committee meetings on olestra as the agency determines, in its discretion, to be necessary. Based upon the results of this entire process, the FDA will initiate any appropriate regulatory proceedings.

Dated: January 24, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

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