ORIGINAL SUBMISSION

The Procter & Gamble Company
Ivorydale Technical Center
5299 Spring Grove Ave.
Cincinnati, Ohio 45217
www.pg.com

June 15, 2007

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: GRAS Notification for use of Olestra in cookies

Dear Sir or Madam:

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination] published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the notifier, The Procter & Gamble Company, 5299 Spring Grove Ave, Cincinnati, OH 45217, a GRAS notification of olestra for use in pre-packaged ready-to-eat cookies, a GRAS panel report setting forth the basis for the GRAS determination, and *curricula vitae* of the members of the GRAS panel, and a comprehensive summary report supporting the safety of olestra for the intended use, for review by the agency.

Any communication regarding this notification may be directed to me at the address above, by phone at (513) 627-7374 or by email at wilke.dl@pg.com.

Sincerely,

Donald L. Wilke, PhD
Principal Scientist
Product Safety & Regulatory Affairs
The Procter & Gamble Company

Enclosures

RECEIVED
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BY:

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

Olestra, as defined in Appendix I entitled "**EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OLESTRA FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES**", dated March 19, 2007, has been determined to be Generally Recognized As Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of olestra in pre-packaged, ready-to-eat cookies, as described below is exempt from the requirement of premarket approval.

Signed,

June 15, 2007

J. Michael Jensen
Vice President, Corporate Research & Development
The Procter & Gamble Company

Date

B. Name and Address of Notifier

J. Michael Jensen
The Procter & Gamble Company
Beckett Ridge Technical Center
8611 Beckett Road
West Chester, OH 45069

Address for Correspondence:
All correspondence, including official correspondence, inquiries and requests for additional information should be addressed to:

Donald Wilke
The Procter & Gamble Company
5299 Spring Grove Ave,
Cincinnati, OH 45217

C. Common Name of the Notified Substance

Olestra

D. Conditions of Intended Use in Food

P&G proposes to expand the uses of olestra to include use in pre-packaged ready-to-eat cookies, another snack food type product. Current uses of olestra that have been approved by the U.S. Food and Drug Administration (U.S. FDA) include as a fat substitute in pre-packaged ready-to-eat savory snacks (*i.e.*, salty or piquant, but not sweet) and pre-packaged ready-to-heat, unpopped popcorn kernels.

The individual permitted and proposed food-uses and use-levels for olestra are summarized in Tables 1 and 2, respectively. Food codes representative of each of the permitted and proposed food-uses that were specified as “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” were chosen from the CSFII 1994-1996, 1998 (USDA, 2000). All olestra-containing products meet the specific requirements for fat content claims in the U.S. (21 CFR §101.62) and are labeled with the appropriate claim (U.S. FDA, 2006a).

Food codes were grouped in food-use categories according to Title 21, Section §170.3 of the *Code of Federal Regulations* (U.S. FDA, 2006b). Product-specific adjustment factors were developed based on data provided in the standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000).

Table 1 Summary of the Permitted Food Uses and Use-Levels for Olestra in the U.S.

Food Category	Permitted Food-Use	Use-Levels for Olestra
Snack Foods	Pre-packaged Ready-to-Heat, Unpopped Popcorn	100% replacement of fat of a regular product
	Pre-packaged Ready-to-Eat Savory Snacks	100% replacement of fat of a regular product

Table 2 Summary of the Individual Proposed Food Use and Use-Level for Olestra in the U.S.

Food Category	Proposed Food-Use	Use-Level for Olestra
Baked Goods and Baking Mixes	Reduced-Fat, Low-Fat, and Fat-Free Cookies	100% replacement of fat of a regular product

The use-level, 100% replacement of fat, is based on the fat content of an equivalent regular product (*i.e*., fat content has not been modified). This is consistent with the methodology used by Webb *et al.* (1997) for a study on predicted olestra intake from savory snacks, whereby the olestra content of reduced-fat savory snacks was also assumed to be the same as the fat content of their full-fat counterparts. The fat content of the regular products used for this assessment was determined from the USDA National Nutrient Database for Standard Reference, Release 17. The fat content of regular cookies and snacks is variable, ranging from 7.3 – 30.6% and 3.5 – 38.4%, respectively. For cookies, the reference amount customarily consumed (RACC) per eating occasion is 30 g (21 CFR §101.12) (U.S. FDA, 2006c). Thus, a typical serving of chocolate chip cookies has 7.3 g of fat, while a typical serving of chocolate sandwich cookies with cream filling has 5.7 g of fat. For potato chips, the RACC per eating occasion is also 30 g (21 CFR §101.12) (U.S. FDA, 2006c). A typical serving of plain potato chips has 10.4 g of fat, while a typical serving of tortilla chips (nacho flavor) has 7.7 g of fat. Thus, single servings of reduced-fat, low-fat, and fat-free chocolate chip or sandwich cookies may contain up to 7.3 and 5.7 g of olestra, respectively, while single servings of reduced-fat, low-fat, and fat-free plain potato and nacho-flavored tortilla chips may contain up to 10.4 and 7.7 g of olestra, respectively.

Estimated daily chronic intakes of olestra from all permitted and proposed uses, combined, are summarized in Table 3 (values in parentheses represent chronic daily olestra intakes from all permitted and proposed uses, combined, while values outside parentheses represent chronic daily olestra intakes from permitted uses only). Approximately 11.7% of the total U.S. population was identified as consumers of “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” pre-packaged ready-to-eat savory snacks, pre-packaged ready-to-heat unpopped popcorn, and pre-packaged ready-to-eat cookies (2,419 actual users). Consumption of these types of foods by the total U.S. population resulted in an estimated mean all-person chronic intake of 0.40 g/person/day, and mean and 90th percentile all-user chronic intakes of 3.1 and 7.7 g/person/day, respectively (Table 3).

Of the individual population groups, female adults were estimated to comprise the greatest percentage of users at 13.6%. The greatest mean all-person chronic intake of olestra was determined in female adults, at 0.47 g/person/day, while male teenagers had the highest mean all-user intake of olestra at 3.7 g/person/day. Infants had the lowest all-person and all-user mean chronic intakes of olestra, at 0.12 and 1.2 g/person/day, respectively. Male adults had the greatest 90th percentile all-user chronic intake, with a value of 9.3 g/person/day. Infants had the lowest all-user 90th percentile chronic intake on an absolute basis, with a value of 2.8 g/person/ day, respectively.

As presented Table 3, the addition of reduced-fat, low-fat and fat-free cookies to the assessment had only a small impact on total chronic olestra intake. The total population users-only mean chronic intake of olestra increased marginally from 2.6 g/person/day for permitted

uses to 3.1 g/person/ day with the addition of proposed uses. Likewise, the users-only 90th percentile total population chronic olestra intake increased marginally from 7.0 g/person/day for permitted uses to 7.7 g/ person/day with the addition of proposed uses.

Table 3 Summary of the Estimated Daily Chronic Intake of Olestra from Permitted (and Proposed) Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Infant	0-2	7.7 (8.9)	277 (318)	0.09 (0.12)	NA (NA)	1.0 (1.2)	2.0 (2.8)
Child	3-11	11.9 (13.5)	753 (849)	0.20 (0.28)	NA (NA)	1.7 (2.1)	4.1 (4.8)
Female Teenager	12-19	10.1 (12.3)	71 (86)	0.29 (0.45)	NA (NA)	2.7 (3.4)	7.0 (7.4)
Male Teenager	12-19	8.5 (9.8)	59 (68)	0.27 (0.38)	NA (NA)	3.0 (3.7)	7.4 (8.5)
Female Adult	20 and Up	11.0 (13.6)	501 (622)	0.31 (0.47)	NA (NA)	2.6 (3.1)	6.7 (8.0)
Male Adult	20 and Up	8.3 (10.0)	394 (476)	0.29 (0.40)	NA (NA)	3.1 (3.7)	9.3 (9.3)
Total Population	All Ages	10.0 (11.7)	2,055 (2,419)	0.28 (0.40)	NA (NA)	2.6 (3.1)	7.0 (7.7)

NA = Not Available

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, olestra has been determined to be GRAS on the basis of scientific procedures (see Appendix I entitled, **"EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OLESTRA FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES")**.

F. Availability of Information

Any additional data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request to

Donald Wilke
The Procter & Gamble Company
5299 Spring Grove Ave,
Cincinnati, OH 45217

Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, The Procter &Gamble Company, will supply these data and information.

II. Detailed Information About the Identity of the Substance

A. Identity

The common or usual name of this product is “olestra”. Olestra is composed of a mixture of hexa-, hepta-, and octa-esters of sucrose with medium- and long-chain fatty acids. The name of the product is descriptive with the “ol” portion representing olein, an ester of glycerol and oleic acid (*i.e.*, the liquid portion of fat) and “estr” portion making reference to the chemical form of the product (*i.e.*, an ester).

Common or Usual Name: Olestra
Chemical Name: Sucrose Polyester
Chemical Abstracts Service (CAS) Number: 121854-29-3
Empirical Formula and Formula Weight: Not Available. A typical preparation of olestra consists of approximately 77±5% octa-, 23% hepta-, and 1% hexa-ester with an average molecular weight of approximately 2,400 daltons.
Molecular weight: Approximately 2400 Daltons
Structural Formula: The chemical structure of olestra is illustrated in Figure 1.

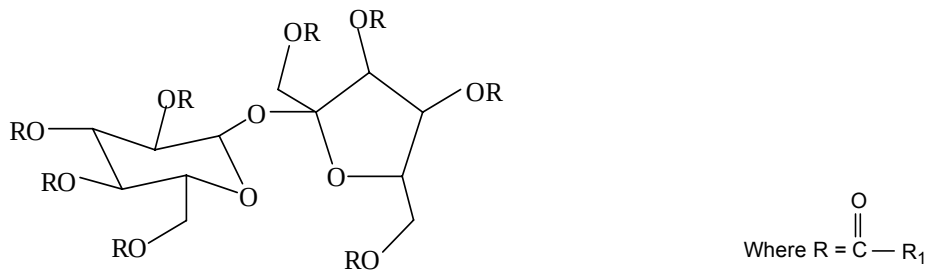

Figure 1 Structural Representation of Olestra

R_1 = fatty acyl groups with carbon chain lengths of C_8 to C_{22}

B. Method of Manufacture

Olestra is principally manufactured from distilled fatty acid methyl esters and sucrose with the quality of the raw materials maintained through various production controls. Other chemicals used in the production of olestra include: dimethylpolysiloxane, hydrochloric acid, methanol, nitrogen, potassium citrate, potassium carbonate, potassium stearate, sodium hydroxide solution, sodium methoxide, synthetic amporphorus silica (silicon dioxide), deionized water, and *DL-α*-tocopheryl acetate (synthetic vitamin E). Refined, bleached, hydrogenated, and deodorized (RBHD) soybean oil; refined, bleached, and hydrogenated cottonseed oil and refined, bleached and hydrogenated rapeseed oil are used as the source of fatty acid methyl

esters for the production of olestra. All the vegetable oils are high purity, edible, and meet food grade specifications of the FCC.

The manufacture of olestra occurs in 2 steps:

Step 1: Preparation of Methyl Esters

Methyl esters used in the production of olestra can be obtained from the methanolysis of fats and oils *via* a number of commercially available techniques. Methyl esters used by P&G in the production of olestra are obtained through the reaction of refined triglyceride oils with methanol at 145°F. The reaction is conducted in the presence of sodium methoxide, a catalyst commonly used in the esterification, interesterification, and transesterification of fats and oils. Following the completion of the reaction the resulting esters are washed with water to remove any residual methanol, dried under vacuum, and distilled at a maximum temperature of 525°F and pressure of 2 to 30 mmHg (absolute).

Step 2: Olestra Synthesis

The preparation of olestra involves the transesterification of sucrose with methyl esters of medium- and long-chain fatty acids.

C. Specifications for Food Grade Material

The official specifications for olestra adopted following its approval by the U.S. FDA as a food additive for use in savory snacks, are published in the Food and Chemicals Codex (FCC, 2003) and are presented below in Table 3. Olestra, as defined by the FCC specifications, is a mixture of sucrose polyesters comprised predominantly of octa-esters, and only small quantities of hexa- or penta-esters of long-chain fatty acids and sucrose. The physical state of the olestra mixture, whether liquid, semi-solid, or solid, is determined by several of the specification parameters including the ester distribution and the length and degree of saturation of the fatty acids. By altering these factors, olestra formulations of variable stiffnesses can be formulated for different purposes. For example, increasing the degree of saturation, fatty acid chain length, or percent of octa-esters will result in an olestra product of greater stiffness. However, since the set of specifications for olestra is not comprised of absolute values, but rather acceptable ranges of values or minimum or maximum levels, it accommodates such variance and allows for a wide range of olestra products, in some cases differing in physical appearance, which comply with the FCC specifications.

Table 3 Chemical Specifications for Olestra		
Specification Parameter	**Specification**	**Method**
Identification		
Fatty Acid Distribution		
C12	≤1%	FCC (2003)
C14	≤1%	FCC (2003)
C16 to C18	≥78%	FCC (2003)
C20	≤20%	FCC (2003)
Unsaturated fatty acids	25-83%	FCC (2003)
Ester Composition		
Octa-ester	≥70%	FCC (2003)
Hexa-ester	≤1%	FCC (2003)
Penta-ester	≤0.5%	FCC (2003)
Purity		
Assay	≥ 97% of combined octa-, hepta-, and hexa-esters of sucrose	FCC (2003)
Free Fatty Acids	≤ 0.5%	FCC (2003)
Lead	≤ 0.1 mg/kg	FCC (2003)
Methanol	≤ 300 mg/kg	FCC (2003)
Peroxide Value	≤ 10 meq/kg	FCC (2003)
Residue on Ignition	≤ 0.5%	FCC (2003)
Thixotropy (Stiffness)*	≥ 50 kPa/s	FCC (2003)
Water	≤ 0.1%	FCC (2003)

Specification values taken from FCC (2003)
* Samples of olestra tested for thixotropy (stiffness) are prepared according to the method detailed in the Food and Chemicals Codex (FCC, 2003).

III. Self-Limiting Levels of Use

Use of olestra as a fat replacement in pre-packaged ready-to-eat cookies will be limited by the fat content of a regular cookie.

IV. Basis for GRAS Determination

Pursuant to 21 CFR § 170.30, olestra intended for use by The Procter & Gamble Company, as defined in Appendix I, has been determined to be GRAS on the basis of scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of olestra as a component of food.

The safety of olestra is supported by numerous published studies on heated and unheated olestra and other sucrose polyesters, including metabolic studies in humans and experimental animals, several short- and long-term animal toxicology studies, and human studies, including post marketing surveillance studies. The toxicology studies available include chronic studies in mice, rats, and dogs and a 2-generation reproductive and developmental toxicity study in rats, a full battery of standard *in vitro* mutagenicity/genotoxicity assays and a short-term *in vivo* genotoxicity study. Studies on gastrointestinal (GI) physiology and function, and olestra's interaction in the digestive tract with lipophilic compounds, as well as effects on appetite regulation and the absorption of nutrients, also support the intended use of olestra as safe.

In addition to the Expert Panel Consensus Statement (Appendix I), a comprehensive summary of the documentation supporting the GRAS status of olestra is included in Appendix II (Entitled: "**SUMMARY OF DATA CONCERNING THE SAFETY OF OLESTRA FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES**").

V. References

FCC. 2003. Food Chemicals Codex (5th Ed.). National Academy Press (NAP); Washington, DC, pp. 356-357, 362-363, 407, 416-417, 455-456.

U.S. FDA. 2006a. Part 101–Food labeling. Section §101.62–Nutrient content claims for fat, fatty acid, and cholesterol content of foods. In: U.S. Code of Federal Regulations Title 21: Food and Drugs. Food and Drug Administration (FDA). U.S. Government Printing Office (GPO); Washington DC, pp. 103-112. Available from: http://a257.g.akamaitech.net/7/257/2422/10apr20061500/edocket.access.gpo.gov/cfr_2006/aprqtr/pdf/21cfr101.62.pdf.

U.S. FDA. 2006b. Part 170–Food additives. Section §170.3–Definitions. In: U.S. Code of Federal Regulations Title 21: Food and Drugs. Food and Drug Administration (FDA). U.S. Government Printing Office (GPO); Washington DC, pp. 5-9. Available from: http://a257.g.akamaitech.net/7/257/2422/10apr20061500/edocket.access.gpo.gov/cfr_2006/aprqtr/pdf/21cfr170.3.pdf.

U.S. FDA. 2006c. Part 101–Food labeling. Section §101.12–Reference amounts customarily consumed per eating occasion. In: U.S. Code of Federal Regulations Title 21: Food and Drugs. Food and Drug Administration (FDA). U.S. Government Printing Office (GPO); Washington DC, pp. 46-56. Available from: http://a257.g.akamaitech.net/7/257/2422/10apr20061500/edocket.access.gpo.gov/cfr_2006/aprqtr/pdf/21cfr101.12.pdf.

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Webb, D.R.; Harrison, G.G.; Lee, M.-J.; Huang, M.-H. 1997. Estimated consumption and eating frequency of olestra from savory snacks using menu census data. J Nutr 127(8, Suppl):1547S-1554S.

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OLESTRA FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES

March 19, 2007

INTRODUCTION

At the request of The Procter and Gamble Company (hereafter P&G), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training, was convened on January 4 & 5, 2007 to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether olestra, under the conditions of intended use as a food ingredient in pre-packaged ready-to-eat cookies intended to be marketed as reduced-fat, low-fat, or fat-free, would be Generally Recognized as Safe (GRAS), based on scientific procedures.

The Panel consisted of the below-signed qualified scientific experts: Dr. G. Harvey Anderson, Ph.D. (Department of Nutritional Sciences, University of Toronto); Dr. Fergus M. Clydesdale, Ph.D. (Department of Food Science, University of Massachusetts Amherst); Dr. Ronald E. Kleinman, M.D. (Pediatric Gastroenterology and Nutrition Unit, Massachusetts General Hospital); Dr. Robert M. Russell, M.D., Ph.D. (Jean Mayer USDA Human Nutrition Research Center, Friedman School of Nutrition, Science and Policy, Tufts University); Dr. William J. Waddell, M.D. (Department of Pharmacology and Toxicology, School of Medicine, University of Louisville). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data on olestra, consisting of over 300 studies, compiled from the literature and other published sources through January 2007. In addition, the Panel evaluated other information deemed appropriate or necessary, including unpublished data and information provided by P&G. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in specified food products, and consumption estimates for all permitted and proposed uses. Metabolic studies in humans and experimental animals were evaluated to determine absorption, metabolism and excretion of olestra and other sucrose polyesters. The assessment of safety involved evaluation of several short- and long-term animal toxicology studies performed with heated and unheated olestra, as well as other sucrose polyesters. The toxicology studies

reviewed included chronic studies in mice, rats, and dogs and a 2-generation reproductive and developmental toxicity study in rats. In addition to the traditional toxicological evaluations, the Panel reviewed data pertaining to the safety of olestra following dietary administration of sucrose polyesters to primates for up to a period of approximately 4 years. A full battery of standard *in vitro* mutagenicity/genotoxicity assays and a short-term *in vivo* genotoxicity study were reviewed by the Panel. The results of studies designed to investigate the safety of olestra in rats with gastric ulcers also were considered. The Panel also evaluated literature on the natural dietary presence of difatty ketones, which occur at low levels in olestra as a result of manufacturing. Data pertaining to the metabolism and safety of difatty ketones also were provided to the Panel for review. The comprehensive evaluation of nutritional issues included review of studies on gastrointestinal (GI) physiology and function, and olestra's interaction in the digestive tract with lipophilic compounds, as well as effects on appetite regulation and the absorption of nutrients. The results of human clinical trials and post-marketing surveillance studies were critically evaluated with particular attention to GI effects and effects on vitamins and lipophilic compounds including carotenoids and pharmaceuticals. In addition to human studies, several nutrition studies conducted in pigs also were evaluated.

The above data were considered in relation to the estimated intakes of olestra from proposed uses in pre-packaged ready-to-eat cookies and from U.S. Food and Drug Administration (FDA)-permitted uses in pre-packaged ready-to-eat savory snacks and pre-packaged ready-to-heat unpopped popcorn. Estimated intakes of olestra from proposed and FDA-permitted uses, combined, were calculated using the USDA 1994 – 1996 Continuing Survey of Food Intakes by Individuals and the 1998 Supplemental Children's Survey, which are based on two 24-hour dietary recalls administered on 2 non-consecutive days. The addition of olestra to pre-packaged ready-to-eat savory snacks, pre-packaged ready-to-heat unpopped popcorn, and pre-packaged ready-to-eat cookies results in products which are intended to be marketed as either low-fat, reduced-fat, or fat-free. Thus, intakes of olestra from proposed and FDA-permitted uses, combined, were estimated using food codes representing reduced-fat, low-fat, and fat-free savory snacks, popcorn, and cookies. This method of intake analysis is conservative, as it is assumed that i) 100% of the fat in the regular fat savory snacks, popcorn, and cookies would be replaced by olestra; and ii) olestra would be incorporated in *all* foods represented by the aforementioned food codes.

Amongst users only, the total population mean and 90th percentile chronic intakes from proposed and FDA-permitted uses combined were estimated to be 3.1 and 7.7 g/day, respectively, compared to estimates of 2.6 and 7.0 g/day, respectively, for FDA-permitted uses only. Thus, the proposed uses increase estimated intakes only marginally, by 0.5 and 0.7 g/day for the mean and 90th percentile, respectively. Mean and 90th percentile acute intakes of 10.4 and 22.8 g/day were estimated from the survey data, based on

individuals who consumed olestra from more than one source on either day of the dietary survey. Intakes were averaged over only the user days as opposed to the total number of dietary survey days, to ensure that estimated acute intakes were not diluted by days on which no olestra was consumed.

Data considered in determining the GRAS status of olestra for use in pre-packaged, ready-to-eat cookies included the following:

CHEMISTRY AND MANUFACTURING

- Olestra is composed of a mixture of primarily (≥97%) hexa-, hepta-, and octa-esters of sucrose with medium- and long-chain fatty acids.
- The manufacturing process of olestra is well established and is in compliance with good manufacturing practices (GMP). It is a two phase process: preparation of methyl esters from refined triglycerides; and, olestra synthesis which involves transesterification of sucrose with methyl esters of medium- and long-chain fatty acids.
- Starting materials and processing chemicals meet food grade specifications, or Code of Federal Regulations (CFR) requirements, or are of high purity.
- Olestra intended for use in pre-packaged, ready-to-eat cookies meets the current Food Chemicals Codex (FCC) specifications.
- Compliance with specifications is supported by analyses for numerous lots of product.
- Fat soluble vitamins A, D, E, and K are added to products containing olestra at concentrations that meet the conditions specified in 21 CFR §172.867(d).
- The chemistry of olestra is well established and stability studies have demonstrated that olestra is as stable as triglycerides under storage, frying and baking conditions.

POST-APPROVAL HUMAN EXPOSURE STUDIES

- Chronic Olestra Intakes: The Olestra Post-Marketing Surveillance Study (OPMSS), conducted after approval of olestra for use in savory snacks, demonstrated that actual chronic olestra intakes from potato chips were much lower than those estimated from intake models (*e.g.,* although the 90th percentile users-only chronic intake of olestra was estimated to be 10.0 g/day for

adolescents, the actual chronic intake was 2.1 g/day. Likewise, for adults, the 90th percentile users-only chronic intake of olestra was estimated to be 8.1 g/day, while the actual intake was 1.8 g/day).

- Acute Olestra Intakes: Randomized, controlled trials conducted after the marketing of olestra in the US demonstrated a wide range of acute olestra intakes.

  - In the 2-hour Movie Theatre Study, which was a randomized double-blind, placebo-controlled study, 1,092 subjects were provided with 13 ounces of regular (triglyceride) or olestra-containing potato chips and asked to consume them freely during a 2-hour movie. The median acute intake of olestra-containing potato chips was 2.1 oz (equivalent to 16.8 g of olestra) while the 90th percentile acute intake was 5.0 oz (equivalent to 40.0 g of olestra). Acute intakes of olestra in this study ranged from 0.8 to 102 g.

  - In the Household Chip Consumption Study, which was a randomized, double-blind, placebo-controlled study, 3,181 subjects were provided with an unlimited supply of either regular (triglyceride) or olestra-containing potato chips for 6 weeks. The median acute intake of olestra-containing potato chips was 1.3 oz (equivalent to 10.4 g of olestra) while the 90th percentile acute intake was 2.3 oz (equivalent to 18.4 g of olestra).

- For pre-packaged ready-to-heat unpopped popcorn, approximately 90% of eating occasions occur as snacks while 10% of eating occasions occur with meals for the total population. For pre-packaged ready-to-eat savory snacks and cookies, approximately 2/3 of eating occasions occur as snacks while approximately 1/3 of eating occasions occur with meals for the total population.

DISPOSITION OF OLESTRA

- *In vitro* studies have shown that hexa-, hepta, and octa-esters of olestra are not hydrolyzed by pure lipase or pancreatic juice preparations. Conversely, sucrose esterified with five or fewer fatty acids (penta- or lower sucrose ester), which accounts for not more than 0.5% of the olestra formulation, is hydrolyzed to sucrose and free fatty acids, with the former hydrolyzed further to glucose and fructose prior to absorption. The hydrolysis products of the smaller sucrose esters (*i.e.*, fatty acids, glucose, and fructose) are subsequently absorbed and processed through common metabolic pathways.

- Recovery studies conducted in humans and experimental animals indicate that greater than 99% of orally administered olestra passes unaltered through the GI tract and is excreted unchanged in the feces.

    - In radiolabel absorption studies in various species, including weanling mini-pigs, considered to be an appropriate model for the potential of olestra absorption in humans, less than 1% of the radioactivity (0.1 to 0.6%) was absorbed following gavage administration of heated or unheated olestra.

    - The distribution of some radiolabel across all tissues and the rapid excretion in expired CO_2 and urine was attributed to the small percentage of the penta- and lower esters that comprise olestra, which are hydrolyzed to fructose, glucose, and fatty acids prior to absorption. More than 99% of the radioactivity was collected in the feces as intact sucrose esters of olestra.

- Olestra is not fermented by human microflora.

- In studies conducted to determine whether the potential for intact absorption of sucrose polyesters would increase in case of damage to the intestinal mucosa, no differences were identified in the percent of absorbed radioactivity in guinea pigs with compromised GI tracts due to pre-treatment with polygeenan compared to animals with histologically normal GI tracts.

TOXICOLOGY STUDIES

- A series of *in vitro* and *in vivo* mutagenicity/genotoxicity assays, subchronic and chronic animal toxicity studies in several different rodent and non-rodent species, and a 2-generation reproductive toxicity study, covering all toxicologically relevant endpoints, have been conducted with olestra and other sucrose polyesters. The results of these studies support the following:

    - Olestra is neither mutagenic nor genotoxic, based on a standard battery of *in vitro* mutagenicity/genotoxicity assays, with and without metabolic activation, even when conducted in the presence of a detergent to increase olestra solubility and cellular uptake in both prokaryotic and eukaryotic test systems. Olestra was not genotoxic in an *in vivo* assay.

    - Olestra does not possess teratogenic properties. No developmental or teratogenic effects were associated with the oral administration of sucrose polyesters in a 2-generation rat study. The lack of teratogenic potential is further confirmed by results of unpublished rat and rabbit teratology studies.

- Olestra is not associated with systemic toxicity. Following short-term (91 days) dietary administration of olestra, no toxicologically significant differences were identified between test and control rats. Absence of olestra-related adverse effects in rats in the published subchronic toxicity studies is additionally supported by results of several unpublished studies in other species including non-rodents.

- Olestra is not carcinogenic nor is it associated with long-term toxicological effects. No treatment-related toxicologically significant findings, including non-neoplastic or neoplastic lesions, were observed in 2-year mouse or rat carcinogenicity assays, or chronic dog studies when olestra was administered in the diet at concentrations of up to 10%. In primates, no adverse effects were observed following treatment with sucrose polyesters for up to 44 months.

- Dietary exposure to olestra is not associated with histological alterations to the GI tract.

The evidence indicates that olestra is not associated with systemic toxicity when administered to experimental animals at dietary levels of up to 10%, the highest dose level tested.

DIFATTY KETONES

- Difatty ketones, while present in olestra in greater concentrations than in conventional fats, are present in other foods (grilled meats, vegetables, and food emulsifiers), the consumption of which results in higher exposures than from olestra-containing foods.

- Difatty ketones are poorly absorbed (less than 20%). The absorption of difatty ketones is further reduced (less than 10%) when they are ingested together with olestra. The small fraction that is absorbed is readily metabolized and excreted in expired air and urine.

- Since difatty ketones are inherent to the olestra formulation, the toxicology studies conducted with olestra also support the safety of difatty ketones at the concentrations found in olestra.

- Human exposure to difatty ketones, per kilogram body weight, from estimated intakes of olestra from permitted and proposed uses combined is several-fold less

than the intake of difatty ketones resulting from the ingestion of olestra in the long-term animal toxicology studies.

NUTRITION STUDIES

- Nutrition studies were conducted in pigs and in humans to determine the impact of olestra on GI function and physiology, GI symptoms, nutrient absorption, drug absorption, and energy balance. These studies used olestra dose levels considerably higher than the expected chronic and acute olestra intakes from proposed and FDA-permitted uses, combined.

Gastrointestinal Function and Physiology

- Several studies demonstrated that olestra is not recognized as a lipid by the GI tract. Unlike digestible fat, olestra does not stimulate the release of hormones such as cholecystokinin, neurotensin, and motilin; consequently, olestra is not associated with GI events typically associated with digestible fat, such as slowing gastric emptying, initiating gallbladder contraction, or inducing gastroesophageal reflux.

    - A reduction in gallbladder contractility is associated with an increased risk of gallstone formation due to stasis of bile and subsequent cholesterol crystallization. However, olestra does not increase the risk of gallstone formation, based on two observations: i) olestra was not associated with gallstone formation in any of the pre-clinical, clinical, and Olestra Post-Marketing Surveillance Studies; and ii) olestra reduces gallbladder bile saturation (*i.e.,* with respect to the amount of cholesterol in bile), most likely because it reduces cholesterol reabsorption from the enterohepatic circulation.

- Olestra is an inert compound and has no osmotic activity. Although olestra reduces stool viscosity, this is an effect of the presence of olestra, a semi-solid material, in the stool, and not due to an alteration in water output. Consequently, olestra, even when consumed in high amounts, does not cause disturbances in water and electrolyte outputs.

- Olestra is resistant to metabolism by intestinal bacteria and does not directly alter several microbiota-associated characteristics. Olestra sequesters cholesterol, bilirubin, and primary bile acids, therefore indirectly reducing the bacterial conversion of cholesterol to coprostanol, bilirubin to urobilinogen, and primary bile acids to secondary bile acids, respectively.

- Fecal short chain fatty acids (SCFAs) are modestly increased following consumption of olestra. Because SCFAs are polar at the pH of fecal contents, they are associated with low octanol/water partition coefficients; thus, olestra is not expected to sequester significant amounts of SCFAs. Observations that the administration of olestra is associated with reductions in breath hydrogen levels support the idea that absorption of fermentative by-products is reduced with the administration of olestra, perhaps due to shorter whole-gut transit times; however, fecal levels of SCFAs following consumption of very large amounts of olestra (*i.e.,* three times the 90th percentile users-only intake from proposed and FDA-permitted uses, combined) were still within the range detected at baseline or in the control groups, indicating that any impact of olestra on SCFAs, at estimated intakes, is expected to be clinically insignificant.

- Several human experimental studies conducted following the FDA approval of olestra for use in savory snacks demonstrated that olestra is well-tolerated:

    - The majority of adverse events reported during the OPMSS were GI disturbances, with loose stools/diarrhea and abdominal cramping being the most commonly reported symptoms. Most GI symptoms were reported to be experienced following a single eating occasion, and following the consumption of less than 2 oz of olestra-containing potato chips (equivalent to less than 16 g of olestra). However, a rechallenge study conducted in 98 subjects who had reported adverse GI symptoms following the consumption of olestra-containing potato chips, demonstrated, under blinded conditions, that the consumption of 1 to 2 oz of olestra-containing potato chips (*i.e.,* 8 to 16 g of olestra) did not result in increased GI symptoms as compared with the consumption of similar amounts of regular triglyceride potato chips.

    - In the Movie Theatre Study, which was a randomized, double-blind, placebo-controlled study, 1,092 subjects were given a 13 oz bag of either triglyceride or olestra-containing potato chips and asked to consume them freely during a 2-hour movie. The median and 90th percentile intakes of olestra-containing potato chips were 2.1 and 5.0 oz, respectively (corresponding to olestra intakes of 16.8 and 40.0 g, respectively). Olestra and triglyceride intakes were divided into quartiles, and no significant differences in the incidence of GI symptoms were observed between the olestra and triglyceride groups.

    - In the 6-week Household Chip Consumption Study, which was a randomized, double-blind, parallel, placebo-controlled trial involving 3,181 subjects, unlimited amounts of olestra or TG-containing potato chips were

provided to study participants, and amounts consumed were recorded in daily diaries. The overall median and 90th percentile intakes of olestra-containing potato chips were 1.3 ounces (equivalent to 10.4 g of olestra) and 2.3 ounces (equivalent to 18.4 g of olestra), respectively. The proportion of subjects reporting GI symptoms in the olestra and triglyceride groups was similar, as was the number of days on which symptoms were reported.

- Two clinical trials compared the GI effects of olestra with wheat bran and with sorbitol.

    - In one study, the consumption of a diet providing either 40 g/day placebo (triglyceride), wheat bran, or olestra was not associated with an increase from baseline in the severity of GI symptoms.

    - In a separate study, the consumption of a diet providing 40 g/day placebo or olestra was not associated with a significant increase from baseline in the severity of any GI symptom; in contrast, the consumption of a diet providing 40 g/day sorbitol resulted in a significant increase from baseline in the severity of several GI symptoms, including cramping, urgency, and nausea. The clinical definition of diarrhea was met on 17 sorbitol treatment days, compared with 0 days during either placebo or olestra treatment.

- Studies conducted in individuals with inflammatory bowel disease indicated no exacerbation of the disease following the consumption of olestra-containing foods.

- A series of studies conducted in human subjects indicated no adverse effects of olestra-containing foods on energy balance.

On the basis of these data, the Panel concluded that olestra does not adversely impact GI function or physiology.

Interactions with Lipophilic Substances

- Data collected from human experimental studies and from the OPMSS indicate that the restoration levels for vitamins A, D, E, and K set forth by the FDA in 21 CFR §172.867(d) are sufficient to offset nutritional imbalances in these vitamins.

- Human experimental studies demonstrate that, like some fibers, phytosterols, and phytostanols, olestra reduces serum carotenoid levels.

- The only known function of carotenoids in humans is that the provitamin A carotenoids (*i.e.,* α-carotene, β-carotene, β-cryptoxanthin) may act as a source of vitamin A in the diet. The Food and Nutrition Board of the National Academies' Institute of Medicine used a conversion factor of 12:1 for dietary β-carotene (*i.e.,* 12 µg of β-carotene from food were equivalent to 1 µg of retinol); however, recent studies conducted in healthy humans demonstrate that the conversion of β-carotene to retinol is even more inefficient, particularly with increasing intakes of β-carotene and in persons with normal vitamin A stores. Although the provitamin A carotenoids can be converted to retinol, there is currently no requirement that a certain fraction of the Recommended Dietary Allowance for vitamin A be met from carotenoids.

- Despite olestra's effects on serum carotenoid levels, markers of oxidative stress, lipid oxidation, protein oxidation, DNA damage, immune function, endothelial function, and macular pigment optical density (MPOD) were not affected following the chronic (one-year) consumption of 7 g/day olestra together with 10 g/day indigestible sucrose polyester. These findings are consistent with the position by the National Academies' Institute of Medicine, that there is currently insufficient data for recommendations regarding the intake of carotenoids.

- Recently the FDA rejected a qualified health claim for lutein and zeaxanthin and a reduced risk of age-related macular degeneration and cataract formation, due to a lack of credible evidence. However, as the science in support of lutein and zeaxanthin in reducing the risks of eye diseases continues to evolve, the Panel considered the effect of olestra on lutein and zeaxanthin and concluded that consumption of olestra from all permitted and proposed uses will not cause clinically meaningful reductions in serum levels of lutein and zeaxanthin based on the following three observations: i) Human experimental studies as well as findings from the OPMSS consistently demonstrated that serum levels of lutein and zeaxanthin are least affected by consumption of olestra, a finding consistent with the lower octanol/water partition coefficients for these hydroxylated carotenoids as compared with other carotenoids; ii) MPOD was not significantly different between olestra consumers and non-consumers; and iii) The one-year intake of up to 7 g/day olestra together with 10 g/day indigestible sucrose polyester (a total amount that is more than 2-fold greater than the total-population users-only 90th percentile chronic intake from proposed and FDA-permitted uses, combined) was not associated with significant alterations in MPOD, despite significant reductions in serum levels of lutein

and zeaxanthin. These observations suggest that MPOD, and therefore the risks of age-related macular degeneration and cataract formation will not be altered in persons consuming olestra from all permitted and proposed uses.

- The regular consumption of olestra from all permitted and proposed uses is unlikely to result in adverse drug interactions in consumers taking various medications:

  - Clinical studies investigating the ability of olestra to affect the absorption of drugs have been conducted for a variety of drugs over a broad lipophilic range. Cyclosporine was the only drug for which a significant olestra-drug interaction was reported [average whole blood cyclosporine area under the curve (AUC) value was reported to be reduced by 18.6% following the consumption of 0.35 g/kg of olestra]; however, because this cross-over study was associated with several limiting factors including small study size (n=7) and lack of appropriate placebo treatment, it cannot be definitively determined that the reported effect was attributable to olestra.

  - In addition, cyclosporine is significantly less lipophilic than oleic acid, and in clinical studies, the consumption of 32 g of olestra in conjunction with radiolabeled triolean only marginally (-1.2%; $P<0.05$) reduced oleic acid absorption.

  - Insights into the potential of olestra to affect drug absorption can also be derived from drug interaction studies with orlistat. Orlistat (a pancreatic lipase inhibitor) therapy results in the presence of significant amounts (~26 g/day) of undigested dietary fat in the GI tract, which is not absorbed prior to excretion in fecal material. The presence of large amounts of undigested fat mimics exposure to olestra, and similar to olestra, orlistat therapy results in the decreased absorption of fat soluble vitamins and carotenoids in a manner that can be offset by supplementation. In addition, it should be noted that the 26 g of undigested fat resulting from orlistat therapy represents an amount that is approximately 3.5 times greater than the estimated, users only, 90th percentile intake of olestra from FDA-permitted and proposed uses, combined, and thus represents a conservative model to evaluate the effects of olestra on drug interactions. The ability of orlistat to alter various drug pharmacokinetic parameters was tested in a number of lipid soluble drugs using well designed bioequivalence methodology in healthy subjects. The only compounds significantly affected by orlistat therapy were amiodarone and cyclosporine.

  - The reported effects of undigested fat on amiodarone and cyclosporine, or olestra and cyclosporine were modest (~18 - 34% decrease in AUC).

Amiodarone displays a highly variable dose-response relationship under normal conditions, and the consumption of food following cyclosporine administration has been reported to decrease the AUC by 13% and C_{max} by 33%. Overall, it is unlikely that clinically meaningful decreases in cyclosporine or amiodarone absorption would be observed with the concomitant use of olestra, since the 90th percentile expected intake levels are approximately 3.5 times below the quantities of undigested fat following orlistat therapy and ~2-fold below the quantity of olestra used in the cyclosporine clinical study.

Following independent, critical evaluation of the above data and information, the Panel unanimously concluded that, olestra, under the conditions of intended use in pre-packaged ready-to-eat cookies, meeting appropriate food-grade specifications, and manufactured and used in accordance with current good manufacturing practice (GMP), is not expected to result in adverse health effects. This conclusion is conditional on the requirement that vitamins A, D, E, and K be added to the olestra-containing cookies at concentrations that meet the conditions specified in 21 CFR §172.867(d).

CONCLUSION

We, the Expert Panel, have independently and collectively, critically evaluated the data and information summarized above and conclude that olestra, meeting appropriate food grade specifications, and produced in accordance with current good manufacturing practice, is Generally Recognized as Safe (GRAS) based on scientific procedures under the conditions of intended use in pre-packaged, ready-to-eat cookies. This conclusion is conditional on the requirement that vitamins A, D, E, and K be added to the olestra-containing cookies at concentrations that meet the conditions specified in 21 CFR §172.867(d).

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University of Toronto

March 21/07
Date

Dr. Fergus M. Clydesdale, Ph.D.
University of Massachusetts

Mar 22/07
Date

Dr. Ronald E. Kleinman, M.D.
Massachusetts General Hospital

March 26, 2007
Date

Dr. Robert M. Russell, M.D., Ph.D.
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March 22, 2007
Date

Dr. William J. Waddell, M.D.
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Dr. G. Harvey Anderson is Professor of Nutritional Sciences, Physiology and Medical Sciences, Faculty of Medicine, University of Toronto. He is Director of the University-Industry Program in Food Safety, Nutrition and Regulatory Affairs. He has served the University in the School of Graduate Studies as Associate Dean, (1996-99), and in the Faculty of Medicine as Dean (Acting Dean with full privileges, 1992) and Associate Dean, Research (1985-88), Chair of the Department of Nutritional Sciences (1981-90), as an elected member of the University's Governing Council (1987-90) and as Regional Director for the Medical Research Council of Canada (1993-94). He initiated and was founding Chair of the Board (1986) of the Canadian National Institute of Nutrition (now the Canadian Council of Food and Nutrition) and has served as a member of its Board of Trustees. He is Chair of the Board of the International Life Sciences Institute, Washington, D.C., and is a member of the Board of the Danone Institute of Canada. He has served as President and Past-President of the Canadian Federation of Biological Societies.

Dr. Anderson received his B. Sc. (Agriculture) and M. Sc. (Animal Nutrition) at the University of Alberta and his Ph.D. (Nutritional Sciences) at the University of Illinois. After postdoctoral experience at the Massachusetts Institute of Technology, he joined the University of Toronto. Dr. Anderson's research on protein and amino acid metabolism, food selection and intake regulation, diet and behavior, infant nutrition, total parenteral nutrition, and diet and chronic disease (with emphasis on sugars and proteins), has led to over 250 publications and the training of more than 80 M.Sc. and Ph.D. students and postdoctoral fellows. His research has received continuous peer-reviewed grant support since 1970.

He has received both the Borden Award (research) and the McHenry Award (leadership) from the Canadian Society for Nutritional Sciences, the Earle W. Crampton Award (McGill University) for Distinguished Service in Nutrition, the Hollington Award for outstanding teaching of medical students in their preclinical years, the University of Toronto Alumni Faculty Award of Excellence for "outstanding academic excellence, service to University and contributions to the community" and a University of Alberta Alumni Honour Award for significant contributions to "the community and beyond". As well he has been the recipient of two Bristol Myers Squibb/Mead Johnson Nutritionals Unrestricted Awards for Nutrition Research (1985-1990 and 2001-2006). He has been elected a Fellow of the American Society of Nutrition.

In addition to serving as a visiting professor at several North American Universities, Dr. Anderson has held academic appointments at many Chinese Universities, including the University of Hong Kong, The Chinese University of Hong Kong, Sun Yat-sen University of Medical Sciences and Beijing Children's Hospital. He was selected as a Ministry of Health Scholar of China in 1987 and from 1986-1992 led the development of the Department of Clinical Nutrition at Sun Yat-sen University of Medical Sciences, Guangzhou, PRC.

Dr. Anderson has served on several editorial boards and research grant committees and as a consultant to governments, universities and members of the food and pharmaceutical industries.

G. Harvey Anderson

1. Most Significant Contributions to Research:

I have been fortunate to stimulate research in several areas including:

1. I formulated and directed testing of the first defined amino acid mixture utilized for total parenteral nutrition in North America. Baxter-Travenol Laboratories produced this amino-acid mixture, Travasol. This work, conducted with Dr. K.N. Jeejeebhoy, Department of Medicine, was at the forefront of development of total parenteral nutrition during the 1970s. (J. Clin. Invest. 1974:53:904-912). Similar studies were conducted in premature infants with Dr. Heather Bryan, Department of Pediatrics, which led to refinements of amino acid formulations (Am. J. Clin. Nutr. 1977:30:1110-1121). With Dr. Stan Zlotkin, then a PhD student, we identified the limited conversion of methionine to cysteine in the premature infant (Am. J. Clin. Nutr. 1981:34:914-923) leading to modification of pediatric solutions.

2. I provided the first report that the milk of mothers giving birth prematurely was higher in nitrogen content than that of full-term mothers (Am. J. Clin. Nutr. 1980:33:811-815). This observation, along with our series of reports on milk nutrient content and nutrient balances in premature infants fed their own mother's milk, provided an impetus for the practice of feeding premature infants their own mother's milk (J. Pedr. Gastroenterol. Nutr. 1982:1:157-159). This work was conducted with Dr. Heather Bryan and Dr. Stephanie Atkinson, who was a Ph.D student under my direction.

3. I was the first to show that rats given food choice regulate their protein intake (J. Nutr. 1974:104:563-572). This led to investigations of macronutrient-specific appetites and the regulatory mechanisms involved. One significant contribution was the observation that brain serotonin, under precursor control by dietary tryptophan, was a regulator of both macronutrient choice and total food intake (Can. J. Physiol. Pharmacol. 1979:57:1043-1057).

4. I formulated the concept that the satiety cascade after protein ingestion begins in the gut either through peptides released in protein digestion or through mechanisms involving gut-derived satiety peptide hormones (e.g. CCK) (Am. J. Physiol. 1999:276:R323-R330). In the satiety cascade, postabsorptive hormones and free amino acids in the brain are late signals, controlling intermeal intervals and food selection in the next meal (Am. J. Physiol. 1994:266:R1675-R1686). Current research is examining the effect of protein source on food intake in humans and in rats and the mechanisms involved. We have found that the effect on satiety of proteins and the peptides released from them is mediated by opioid (J. Nutr. 2002:132: 2775-2780) as well as by CCK-A receptors (Am. J. Physiol. 1999:276:R323-330), raising new concepts of the functional role of protein-encoded biologically active peptides.

5. We identified GLP-1 to be a hormone regulating the feeding response not only to carbohydrate (J. Nutr. 2001:131:1819-1825) but also to protein (J. Nutr. 2003: 133: 2326-2330) and that Exendin 4, a GLP-1 agonist in clinical trials as a drug for treatment of diabetes, raises blood glucose after protein ingestion (Am J Physiol Regul Intgr Comp Physiol. 289(3):R688-94).

6. We reported that growth faltering in Chinese infants to two years of age is primarily environmental and not a consequence of genetics, a hypothesis promoted by academics at the Chinese University of Hong Kong. This observation is of considerable public health significance as it shows that public health measures that change the environment are needed in economically advanced regions of Asia as well as the less advantaged areas (Nutr. Res. 2001:21:505-516) (J. Paediatr. Child. Health 2001:37:456-464).

7. Most significant will perhaps be my recent discovery that high multivitamin intakes by rats during pregnancy leads to altered food intake control, obesity and insulin resistance in the offspring. This

suggests that epigenetic changes due to nutrition occur in utero and have profound impact on the development of regulatory systems. Publications are being prepared. Supported by CIHR (2005).

2. Activities and Contributions:

I have been active in the promotion of nutrition research. I applied for and received funding for the formation of the Human Nutrition Research Council of Ontario (HNRCO). I was Chair of the Board from 1979-1986. This was the first provincial organization to have a mandate to support nutrition research and training. Because the initiative was limited to Ontario I undertook the formation of the National Institute of Nutrition (NIN) and served as the first Chair of the Board from 1984-1989. The HNRCO funds were placed under the management of NIN. These two organizations have supported several million dollars of research activity. I am a member of the Board of the new version of NIN, the Canadian Council of Food and Nutrition.

I have provided Canadian and international leadership in advocating collaboration among scientists from universities, industry and government. I am Chair of the Board of the International Life Sciences Institute (ILSI) based in Washington DC. ILSI is a nonprofit, worldwide foundation established in 1978 to advance understanding of scientific issues related to nutrition, food safety, toxicology and the environment. By bringing together scientists from academia, government, industry and the public sector, ILSI seeks a balanced approach to solving problems with broad implications for the well-being of the general public. It has branches in many parts of the world and has its own research foundation. The annual budget is nearly $US 20 million. I am the only Canadian on the Board and my appointment as Chair attests to my international stature.

I direct the NSERC University-Industry Program in Food Safety, Nutrition and Regulatory Affairs. The objective of this program is to address the scientific basis of current issues of food, nutrition, health and regulatory activities through collaboration with scientists and health professionals from universities, the food industry, government and nongovernmental associations, to achieve the goal of a healthier Canadian population. This Program's Affiliate Office and an NSERC Chair in nutritional toxicology (recruited Dr. Michael Archer, now Chair of the Department) were initiated through a successful application to NSERC in 1992 after I had secured a commitment of support from several members of the food industry. The program is now in its twelfth year. The program has had several successes of interest to the food industry including securing from Health Canada a commitment to health claims, discretionary nutrient fortification and joint US-Canada membership on committees setting nutrient recommendations (the DRVs). It has brought over $3 million to the Department and receives annual support from a membership of 10-12 food companies. We also teach a graduate course on regulatory affairs. Several students have obtained positions with the food industry as a result of taking this course.

I serve on scientific advisory committees for General Mills Inc (Minneapolis), McDonalds (Chicago), Canadian Sugar Institute (Toronto), Forbes MediTech, (Vancouver), McCain Foods (Toronto) Archer-Daniels-Midland (Decatur Il), and on an ad hoc basis as a consultant to other members of the food and drug industry.

I am a member of the Advisory Group, Agricultural Policy Institute of Canada. This is a new national think-tank on new directions for agriculture. My role is to push for greater involvement of provincial and federal Ministries of Agriculture in human health research.

In November 2005 I chaired an international committee asked by the National Academy of Finland to review food and nutritional sciences research and give direction for the next decade.

In addition I have served as President, Canadian Federation of Biological Societies 2000-2001, Founding Member of the Board, and Science Council, Danone Institute of Canada, 1999 (Chaired by Dr. Peter Jones, the research budget is $500000/yr);. Member of the Dietary Reference Intakes panel

on Tolerable Upper Limits and the Macronutrient panel, Health Canada, Ottawa and National Academy of Sciences, Washington, DC. 1997-2002;. Regional Director (University of Toronto), Medical Research Council of Canada , 1992-94.

Peer-reviewed Journal Publications: (last five years)
Submitted or in Press:

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Bellissimo, N, Pencharz, P, Berall, G.B., Goode, R.C., Thomas, S.G. and G. Harvey Anderson. 2007. Effect of mealtime television viewing on food intake after a glucose load. (Ped. Res. in press).

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Abou Samra, R., Wolever T.M.S, and G. H.Anderson. 2007. Enhanced food intake regulatory responses after a glucose drink in hyperinsulinemic men**.** Int. J. Obesity (on line publication now available)

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Woodend, D and G. H. Anderson. 2001. Effect of sucrose and safflower oil preloads on short-term appetite and food intake of young men. Appetite 37:185-195.

Chapters in Books

Aziz, A and G.Harvey Anderson. (2007, in press) The effects of dairy components on food intake and satiety:mechanisms of action and implications for the development of functional foods. In:Functional Dairy Products, 2nd Edition.. Ed: Maria Saarela. Woodhead Publishing Limited. Cambridge, UK

Anderson, G. H, T. Akhavan and R. Mendelson. (2007, In Press) Food Ingredients Implicated in Obesity: Sugars and Sweeteners. In: Novel Food Ingredients. Ed: Jeya Henry. Woodhead Publishing Limited. Cambridge, UK

Anderson, G. Harvey, Alfred Aziz and Rania Abou Samra. 2006. Physiology of food intake regulation: Interaction with dietary components. In: Nestle Nutrition Series: Pediatric Program. Vol 58, p 133-145.

Abou Samra, R. and G. H. Anderson. 2005. Intense Sweeteners and Sugar Replacers in the Regulation of Food Intake and Body Weight. In: Food, Diet and Obesity. Ed: David Mela.. Woodhead Publishing Limited. Cambridge, UK. P 292-310.

Abou Samra, R. and G. H. Anderson. 2005. Intense Sweeteners and Sugar Replacers in the Regulation of Food Intake and Body Weight. In: Food, Diet and Obesity. Ed: David Mela. Woodhead Publishing Limited. Cambridge, UK. P 292-310.

Aziz, A and G. H. Anderson. 2005. Milk proteins in food-food and food-drug synergy on feeding behavior, energy balance and body-weight regulation. In: Food-Drug Synergy and Safety. Eds. L. U. Thompson and W.E. Ward. CRC Press, Taylor and Francis Group, Boco Raton, Florida . p 347-374.

Aziz, A and G. H. Anderson. 2005. Milk proteins in food-food and food-drug synergy on feeding behavior, energy balance ad body-weight regulation. In: Food-Drug Synergy and Safety. Eds. L. U. Thompson and W.E. Ward. CRC Press (Accepted-publication date is July 2005)

Mendelson, R, H. Anderson, H. Brown, J. Chappell, and V. Tarasuk. 2002. Barriers to Changing Food Selection. In: Food Selection: From Genes to Culture. Eds. G. H. Anderson, J. Blundell and M. Chiva. Danone Institute, Paris,. p117-131.

Anderson, G.H. 2003. Sucrose: Dietary Importance. In: Encyclopedia of Food Science, Food Technology and Nutrition. Eds: Macrae, R., R. Robinson and M. Sadler. London, U.K., Academic Press Limited, p 5641-5645.

Edited Conference Proceedings/Books

Dietary Guidelines: Past Experience and New Approaches. Proceedings of an International Dietary Guidelines Conference University of Toronto. Eds: G. H. Anderson, R. Black and S. Harris. J.Am Diet Assoc 2003: 103: (Supplement 2);12; S1-S59.

Glycemic Carbohydrates and Health: An International Symposium. Eds.G. H Anderson and S. Kimura. Nutrition Reviews 2003: 61(5):11(S1-S99).

Food Selection: From Genes to Culture. Eds. G. H. Anderson, J. Blundell and M. Chiva. Danone Institute, Paris. 2002, pp 207.

Anderson, G. Harvey, and Alison Stephen. An evaluation of Health Canada's consultation document, Standards of evidence for evaluating foods with health claims: a proposed framework: symposium and workshops July 24-25, 2000 final reports. University of Toronto. Program in Food Safety, Nutrition and Regulatory Affairs. National Library of Canada, ISBN 0-7727-8716-6, pp 1-65. 2001.

Papers in Conference Proceedings

Anderson, G. Harvey, Alfred Aziz and Rania Abou Samra. 2006. Physiology of food intake regulation: Interaction with dietary components. In: Protein and Energy Requirements in Infancy and Childhood. Eds: Rigio, J. and E.E. Zeigler. Nestec Ltd, Vevey/S. Karger AG. Basal. Nestle Nutrition Workshop Series Pediatric Program. Vol 58, pp 133-145.

Anderson, G.H., Aziz, A., and R. Abou Samra. 2005. Dietary protein and fibre as determinants of the function of the gastrointestinal tract. In: Proceedings of the 18th International Congress of Nutrition. Eds: Vorster H.H., R. Blaauw, M.A. Dhansay, P.M.N. Kuywayo, T.L.Moeng, and E. Wentzel-Viljoan. S. Karger, New York, p 1-9.

Anderson, G.H., A. Aziz, and F Cho. 2006. Whey Protein: Its Effects on, and Mechanisms of Action in Short-term Food Intake Regulation. Proceedings of the Fourth International Whey Protein Conference, Chicago, September. Eds: Brown, P. and P. Huth. American Dairy Products Institute, Elmhurst, Illinois. (in press)

Anderson, G. H. 2004. How Milk Components Affect Food Intake and The Glycemic Index in Humans. In: Recent Advances in the Function and the Nutritional Role of Lactose in Milk and Dairy Products. Proceedings of the International Symposium. Tokyo, November 29, 2003. p. 25-46. The National Dairy Promotion and Research Association. Tokyo.

G. H. Anderson, R. Black and S. Harris. 2003. Introduction to the .Proceedings of An International Dietary Guidelines Conference, Toronto. J Am Diet Assoc 2003: (Suppl 2) 103; S3-57

Anderson, G. H. and D. Woodend. 2003. Effect of Glycemic Carbohydrate on Short-term Satiety and Food Intake. In: Proceedings of the International Symposium on Glycemic Carbohydrates and Health, Tokyo, November 20-21, 2001. Eds: G. H. Anderson and S. Kimura. Nutr. Rev. 61(5):11(S17-S26)

Anderson, G.H, M. He and L. Singh. 2001. Neonatal Nutrition and Behavioural Development. Proceedings of the 13th International Symposium on Maternal and Infant Nutrition. Ed: Gu. Jingfan. P 70-78. Heinz Institute of Nutritional Sciences, China Focal Point, Yanting, Shahe, Guangzhou, P.R. China 510507

Reports:

Anderson, G.H. 2006. Food Sciences in Finland: Evaluation Report pp 70. Academy of Sciences, Helsinki.

Expert Committee on Health Body Weights, Health Canada. Report Published April 2003 Canadian Guidelines for Weight Classification of Adults. Pp 40. Health Canada Publications Center, Ottawa, Canada.

Mendelson, R., Tarasuk, V., Chappell, J. Brown, H. and G. H. Anderson. 2003. Report of the Ontario Food Survey. PP 58. Program in Food Safety, University of Toronto, and Ryerson University, Toronto.

Letters To the Editor:

Jenkins, D.J.A., C.W.C. Kendall, V. Vuksan and G. H. Anderson. 2001. Reply to GMA van Rosendaal et al. Am. J. Clin. Nutr.73:653.

Abstracts/Student Presentations:

2004: Note: **Of the FASEB submissions two were selected for oral presentation and all for poster presentations. Of the CFBS submissions four of our five were selected for the student award competition of nine presentations and Shannon Moore won the competition.**

Aziz, A. and G.H Anderson. 2004. Peptides released during digestion of proteins interact with GLP-1 receptor activation to produce hyperglycemia in rats. The FASEB J. 18(4): Abstr. 120.1, pA135.

Szeto, I.M-y, Cho, F, and G.H. Anderson. 2004. Effect of multi-vitamin supplementation during pregnancy and lactation on the growth and antioxidant status of newborn rats. The FASEB J. 18(4):Abstr.353.4, pA353.4

Samra, R.A., Smirnakis, F., Anderson, G.H. Wolever, T, Geleva, D, and D. Woodend. 2004. Hyperinsulinemia in men does not impair their caloric compensation in response to a glucose drink. The FASEB J. 18(4):727.3, pA1109.

Aziz, A, Cho, F. and G.H. Anderson. 2004. GLP-1 receptor activation contributes to protein-induced satiety in rats by altering both short- and long-term regulators of food intake The FASEB J. 18(4):Abstr. 727.6, pA1110.

Akhavan, T, and G. H. Anderson. 2004. Ratio of fructose to glucose consumed in solutions affects short-term food intake in young men. CFBS annual meeting, June 17-19, Vancouver.

Szeto, I.M-y, Taha, A., Cho, F, and G.H. Anderson. 2004. Effect of multi-vitamin supplementation of rat diets during pregnancy on glucoregulation and fatty acid composition of the offspring. CFBS annual meeting, June 17-19, Vancouver.

Aziz, A, Cho, F. and G.H. Anderson. 2004. Hyperglycemia after Exendin 4, a GLP-1 receptor agonist, given with protein is associated with altered metabolism of glucose, fat and protein that is indicative of a stress response. CFBS annual meeting, June 17-19, Vancouver

Samra, R.A., Wolever, T., Geleva, D., and G.H.Anderson. 2004. Effect of hyperinsulinemia on food intake and associated food intake regulatory hormones in men. CFBS annual meeting, June 17-19, Vancouver

Bellisimo, N., Desantadina, V., Pencharz, P., Berall, G., Goode, R., and G. H. Anderson. 2004. Food intake of obese and normal weight boys in response to glucose and whey protein beverages. CFBS annual meeting, June 17-19, Vancouver

2005 Abstracts in Press Accepted for Experimental Biology, San Diego, April 2-6.
Again we had three selected for oral presentation and one for the student competition

Ignatius Man-Yau Szeto, Paul J. Das, Ameer Y. Taha, Alfred Aziz, G. Harvey Anderson. 2005. Effect of increased multivitamin intake of rats during pregnancy on food intake and glucose metabolism of male offspring. FASEB J Abstracts 19(5):970.4. (Selected for Oral Presentation)

Ameer Y. Taha, Ignatius Man-Yau Szeto, Paul J. Das, David W.L. Ma and G. Harvey Anderson. 2005 Increased vitamin intake during pregnancy by rats alters fatty acid metabolism in female offspring. FASEB J Abstracts 19(5):LB226.

Paul J. Das, Ignatius Man-Yau Szeto, Ameer Y. Taha, Alfred Aziz, G. Harvey Anderson. 2005. High multivitamin intake by pregnant rats affects growth, body composition and food intake in the offspring. FASEB J Abstracts 19(5):LB278.

Rania Abou Samra, G. Harvey Anderson, Thomas Wolever, Daniela Geleva. Daily consumption of cereal fiber for one month improves satiety hormone responses to a glucose load in hyperinsulinemic men. FASEB J Abstracts 19(5):970.2 (Selected for Oral Presentation)

Tina Akhavan and G. Harvey Anderson The fructose to glucose ratio in solutions consumed by young men alters glycemic response, satiety and food intake. FASEB J Abstracts 19(5):LB246. (Selected for Oral Presentation)

Nicola Bellissimo, Virginia Desantadina, Paul Pencharz, Robert C. Goode, Glen Berall, G.Harvey Anderson. Effect of body composition and physical fitness on food intake regulation in normal and overweight boys. FASEB J Abstracts 19(5):970.1. (Selected for ASNS Graduate Student Travel Award and Presentation in Competition).

Tasleem Zafar, Seok-Young Kim, Harvey Anderson, France Cho, and David Yeung. 2005. Beans as a functional food for the regulation of food intake and glycemic response in human subjects. The 5th Canadian Pulse Research Workshop. London Ontario, Nov 28-30, 2004. P22. Pulse Canada, Ottawa.

Abou Samra, R., Wolever, T., Geleva, D., and G.H. Anderson. 2005. Improved satiety hormone responses in hyperinsulinemic men by daily consumption of insoluble fiber. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract W35. Canadian Federation of Biological Societies, Ottawa.

Das, P.J., Szeto, I.M-Y., Taha, A.Y., Aziz, A., Abou Samra, R., and G.H. Anderson. 2005. Increased multi-vitamin intake during pregnancy in rats affects short-term food intake and satiety hormone response in the male offspring. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract W46. Canadian Federation of Biological Societies, Ottawa.

Taha, A.Y., Szeto, I.M-Y., Das, P.J., Ma, D.W-L., and G.H. Anderson. 2005. Increased vitamin intake during pregnancy by results in changes in fatty acid composition in liver of female offspring. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract W64. Canadian Federation of Biological Societies, Ottawa.

Bellissimo, N., Thomas, S., Goode, R.C., Pencharz, P., and G.H. Anderson. 2005. Subjective appetite is increased after whey protein but not after glucose drinks or after a fitness test at the ventilatory threshold. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract T10. Canadian Federation of Biological Societies, Ottawa.

Akhavan, T., and G. H. Anderson. 2005. Solutions with a high glucose to fructose ratio suppress food intake more than those with a low ratio in young men. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract T17. Canadian Federation of Biological Societies, Ottawa.

Zafar, T.A., Kim, S-Y., and G.H. Anderson. 2005. Relationship among glycemic response to glucose drinks and satiety and food intake in young men. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract T34. Canadian Federation of Biological Societies, Ottawa.

Li, E.T.S., He, M., Yau, Y.C., and G.H. Anderson. 2005. Ethnic specific body mass index cut-off points. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract F63. Canadian Federation of Biological Societies, Ottawa.

Szeto, I.M-Y., Taha, A.Y., Das, P.J., Aziz, A., and G.H. Anderson. 2005. Multi-vitamin supplementation of rats during pregnancy alters body weight, adiposity and glucose regulation in the male offspring. CFBS 48th meeting, June 21-25, Guelph. Program and Proceedings: Abstract S08. Canadian Federation of Biological Societies, Ottawa. **(Student Competition**)

2006

Three abstracts submitted to Experimental Biology, San Francisco, April 1-4. **Again, abstract by I Szeto selected as one of 12 in the ASNS student competition. Two selected for oral presentation in theme sessions of food intake regulation. His abstract at the Canadian Society of Clinical Nutrition and Canadian Society of Nutritional Sciences in Edmonton in May was also selected as one of eight in the student competition. He won third place.**

Das PJ, Szeto IMY, Taha AM, Okubo N, Abou Samra R, and Anderson GH. "Multi-Vitamin Supplementation during Pregnancy in Rats Alters the Development of Food Intake Regulation in the Offspring." Experimental Biology. San Francisco, USA (April 1-5, 2006). FASEB J. 20(5); A1002; Abs. 648.4. **Selected for Oral Presentation**

Szeto, I.M.Y., Das, P.J**.**, Taha, A.Y., and Anderson, G.H. (2006) Multi-vitamin supplementation during pregnancy leads to greater weight gain, impaired glucose tolerance and insulin resistance in rat offspring. FASEB J Abstracts 20 (5):821.7. **Selected for Student Competition and Travel Award.**

Taha, A.Y., Szeto, I.M.Y., Das P.J., Ma, D.W.L., and Anderson, G.H. (2006) Increased vitamin intake during pregnancy by rats alters lipid metabolism in the offspring at 12 weeks post-weaning. FASEB J Abstracts 20 (5):662.11.

Bellissimo, N, Goode R, Pencharz P, Thomas S & Anderson H. Effect of Glucose and Protein Preloads on Subjective Appetite and Food Intake in Boys (2006). Proceedings of the 5th Annual Meeting of the Canadian Society for Clinical Nutrition. J. *Applied Physiology, Nutrition, and Metabolism*. May 25 - 27, 2006, Edmonton, AB, Canada.

Szeto, I.M-Y, Okubo N, Das, P.J., Aziz, A., and G.H. Anderson. 2006. Multi-vitamin supplementation of rats during pregnancy increases blood pressure and weight gain in the offspring. Presented at the annual meeting of the Canadian Society of Clinical Nutrtion, Edmonton, May. **(Selected for Student Competition and Travel Award, Third place winner in presentation**)

EDUCATION:

University of Toronto, Ontario, Canada	B.A. Food Chemistry
University of Toronto, Ontario, Canada	M.A. Food Chemistry
University of Massachusetts, Amherst, MA	Ph.D. Food Science & Technology
University of Massachusetts, Amherst, MA	Post-Doctoral Fellow - Food Science & Technology

HONORS:

- Prince of Wales Gold Medal (1960) Awarded to the top graduating senior at Victoria College, University of Toronto.
- National Research Council of Canada Scholarship (1961).
- IFT - General Foods Fellowship (1964).
- University of Massachusetts Distinguished Teacher Award (1972). (Three awards presented per year on a University-wide basis from among 1500 faculty).
- William V. Cruess Award for Excellence in Teaching - presented by the Institute of Food Technologists, 1976.
- Distinguished Food Scientist Award - co-recipient with F.J. Francis, presented by the New York Section of the IFT, 1978.
- Elected to Fellow of the Institute of Food Technologists, 1979.
- Recipient of the Third Annual Ethel Austin Martin Visiting Professorship in Human Nutrition at South Dakota State University, January 1983.
- Recipient of the Lectureship Award from the Philadelphia Section of the IFT for "Dedicated Service and Outstanding Contributions to Food Science and Technology", 1983.
- Recipient of the 1984 Babcock Hart Award, presented by the Institute of Food Technologists "to honor a person who has distinguished himself/herself by research contributions to food technology which have resulted in improved public health through some aspect of nutrition or more nutritious foods".
- Named the F.W. Tanner Lecturer by the Chicago Section of the Institute of Food Technologists, 1985.
- Donald K. Tressler Award for Outstanding Contributions to Food Science and Technology and their Communication to both Scientific Peers and the Public. Presented by the Institute of Food Technologists 1986.
- Named the Ethel Austin Martin Distinguished Lecturer for 1986. South Dakota State University.
- Elected to an Honorary Fellow of the Australian Institute of Food Science and Technology. 1987.
- Recipient of the 1989 Nicholas Appert Award presented by the Institute of Food Technologists to honor a person for preeminence in and contributions to the field of food technology.
- Elected to President of Phi Tau Sigma, the National Food Science Honors Society, 1992.
- Recipient of the 1993 Charles A. Black Award for scientific accomplishment and communication presented by the Council for Agricultural Science and Technology (CAST).

- Named the G. Malcolm Trout Visiting Scholar at Michigan State University, 1993.
- Named the 1993 Centennial Visiting Professor by the Tokyo University of Fisheries.
- Recipient of the Carl R. Fellers Award for bringing honor and recognition to the profession of Food Science. Presented by the Institute of Food Technologists, 1995.
- Named a Fellow of the American College of Nutrition, 1996.
- Named the Ernest Newberry Memorial Lecturer for the 14th International SAAFoST Congress in Pretoria, South Africa, 1997.
- Named a member of the IFT Chief Research Officer's Food Council, 1997-present.
- Inducted as an Honorary Member in "L'Association Internationale Nicolas Appert", 1999.
- Elected Chair of the Board of Trustees of ILSINA (2001-present).
- University of Massachusetts endowed the F.M. Clydesdale Professorship (2001) with funds raised by the Food Science Alumni and friends of the Department.
- Reappointed for a third time as Chair of NAS, IOM, Food Forum through December 31, 2002.
- Named a University of Massachusetts Distinguished Professor by the Board of Trustees, May, 2003.
- Designated a National Associate of the National Academy of Sciences, December, 2003.
- Named Chair of the IFT Expert Committee on Functional Foods (2004-05)
- Appointed to the HHS/USDA 2005 Dietary Guidelines Committee
- Appointed to an NIH Advisory Panel, 2005
- Elected, as a Fellow, to the International Academy of Food Science and Technology, 2006
- Awarded a University Leadership in Action Grant, 2006
- Appointed to the Keystone Food and Nutrition Roundtable, 2007
- Recipient of the Distinguished Faculty Award by the University of Massachusetts Alumni Association, 2007

HONORARY SOCIETIES:

Sigma Xi, Phi Kappa Phi, Phi Tau Sigma. (President, 1992)
President University of Massachusetts Chapter of Sigma X, 1986-1987.

PROFESSIONAL SOCIETIES:

American College of Nutrition (Fellow)
Institute of Food Technologists (Fellow)
American Society for Nutritional Sciences
American Chemical Society
American Association for the Advancement of Science
International Association for Food Protection

ACADEMIC EXPERIENCE:

Distinguished University Professor and Head May 2003 – present.
Professor and Head July 1, 1989 – May 2003. Department of Food Science.
Director of the University of Massachusetts Amherst Food Science Strategic Research Alliance 1996 – present
Director of the University of Massachusetts Amherst Food Science Strategic Policy Alliance, 2004-present.

Chair Search Committee for Dean of the Isenberg School of Management, 2005-2007
Chair Chancellor's Inaugural Academic Events Planning Committee 2002, 2003.
Chair Provost's Committee on Revenue Development, 2001
Co-chair of the University Life Sciences Steering Committee 1996 - 1998.
Acting Head - Sept. 1988-June 30, 1989. Department of Food Science and Nutrition, University of Massachusetts.
Adjunct Professor - Sept. 1, 1988 - 1993. Department of Human Nutrition, Universite Laval, Quebec, Canada.
Professor - September 1976 to September, 1988, Department of Food Science and Nutrition, University of Massachusetts.
Visiting Food Scientist - January 1976 to July 1976. Department of Food Science Technology, University of California, Davis, California.

Associate Professor - February 1972 to September 1976, Department of Food Science and Nutrition, University of Massachusetts.
Assistant Professor - April 1967 to February 1972, Department of Food Science, University of Massachusetts.
Post Doctoral Appointment - 1966-67, Department of Food Science, University of Massachusetts.
Research Associate - 1962-66, Department of Food Science, University of Massachusetts.
Instructor - 1961-62, Department of Food Chemistry, University of Toronto, Toronto, Canada.
Research Associate - 1960-61, Department of Food Chemistry, University of Toronto, Toronto, Canada.

INDUSTRIAL AND GOVERNMENT EXPERIENCE:

Chemist, Canadian Industries Limited, Paint Research and Development Laboratories Carried out product development of automotive and retail paints. Followed this by conducting storage studies, stability tests and complete quality testing of products developed which were deemed to have a marketable value.
Physiological Chemist, Defense Research Medical Laboratories, Canadian Department of National Defense. Investigated the effect of high pressure oxygen on the metabolic pathways of gamma-amino butyric acid in rats.

SELECTED PROFESSIONAL EXPERIENCE IN ACADEMICS:

a. Research:
Director of research grants in color and appearance of foods and the chemical changes involved in processing, with emphasis on minerals, pigments, and dietary fiber. Have graduated over 20 Ph.D. candidates and a similar number of M.S. candidates.
b. Teaching:
Food Science and Nutrition FS&N 850, Colorimetry and Appearance (graduate course).
FS&N 860, Pigment Chemistry (graduate course).
FS&N 101, The Struggle for Food (average enrollment is 250 students per semester). Total overall responsibility, teach 50%.
FS&N 391A, Senior Seminar in Product Development.
FS&N 385, Special Problems in Food Science.
FS&N 872, Graduate seminar.
Organized short courses in Food Color Measurement and Thermal Processing as well as Symposia.
c. Administration and Counseling (Selected Responsibilities):

Director and Coordinator of the Undergraduate resident instruction program in the Department of Food Science during the 1970's.
Past Chairman of the College of Food and Natural Resources Educational Policies Committee.
Past Member of the College of Food and Natural Resources Educational Policies Committee.
Have served as both a member and chairman of the Food Science Personnel Committee which makes recommendations on salary, promotion and tenure.
Overall responsibility for counseling undergraduate majors in Food Science during the 1980's.
Past Chairman of the Food Science Undergraduate-Faculty Liaison Committee.
Past member of the Food Science Graduate-Faculty Liaison Committee.
Actively involved with University summer student and parent counseling program.
Past Chairman of the Food Science Undergraduate Curriculum Committee.
Member of the University Standing Advisory Committee to the Center for Instructional Resources and Improvement.
Chairman of the University Distinguished Teacher Award Committee (1974).
Member of the Search Committee for a Director of the University Center for Instructional Resources and Improvement (1974).
Member of the Search Committee for a Dean of the College of Food and Natural Resources (1976).
Member of the Search Committee for a Department Head in the Department of Food Science and Nutrition (1978).
Chairman of the Food Science and Nutrition Departmental Research Coordination Committee (1979).
Past Member of the Food Science and Nutrition Graduate Policies Committee in Food Science and Nutrition.
Invited participant in a University Workshop sponsored by the Provost and Vice Chancellor for Deans and Department Heads on Working with the Media, 1985 and on University Outreach in 1996.
Member of the University Employee Assistance Program Board, 1982-1986.
Member of the College of Food and Natural Resources Committee on Teaching Improvement 1989-1991.
Member, University Life Sciences Steering Committee, 1995-present.
Co-Chair, University Life Sciences Steering Committee, 1996-1998.
Member, University Committee on Science and Technology Advancement, 1996-present.
Chair,University Committee on Revenue Development, 2001.
Member of the University Search Committee for a CFNR Development Officer, 2002.
Chair of the University Affairs Inauguration Committee for Chancellor Lombardi, 2003
University Homecoming Weekend Academic Planning Committee, 2004
Search Committee for the Provost and Senior Vice Chancellor, 2004
University Task Force on the Journalism/Communications Departments Merger, 2004
Served as a faculty leader at Commencement,2004
Chaired the University Committee to evaluate Dean Thomas O’Brien of ISOM, 2005
Member of the Provost’s First Fall Convocation planning and selection group, 2005
Faculty leader during Commencement, 2005
Chaired the Search Committee for the Dean of ISOM, 2006, 2007

PROFESSIONAL SOCIETY OFFICES:

- Past Chairman of the Education Committee of the North East Section of the Institute of Food Technologists.
- Inter-Society Color Council Delegate to the National Institute of Food Technologists.
- Chairman of the IFT Communications Committee on Food Safety and Nutrition from its inception in 1972 to 1978.
- Member of the IFT Sub-committee on Nutrition Education (1973).
- Member of the Graduate Jury Awards Committee of the IFT (1975-76).
- Member of the IFT Committee on Graduate Education (1974).
- Member of the North East Section IFT Professional Relations Committee (1974-76).
- Nominated to the Board of Directors of the Inter-Society Color Council of America (1976).
- Member of the William V. Cruess Awards Committee of the IFT (1976-79).
- Member of the Program Committee of the IFT (1976-79).
- Chairman of the Program Committee for the 1981 Annual Meeting of IFT.
- Member of the IFT Communications Committee on Food Safety and Nutrition. 1972 to present.
- Chairman of the Expert Panel on Scientific Affairs of the IFT, 1986 to 1994.
- Elected to Membership on the IFT Executive Committee 1987-90.
- Member of the IFT Policy Board of the Office of Scientific Public, Affairs. 1986-1993.
- Elected to the IFT Council (1989-92).
- Elected as a member and Secretary of the Board of Trustees of the North American Division of the International Life Sciences Institute (1990-present). Elected to Chair of the Board, 2001-2003.
- Elected as a member of the Board of Trustees of the International Life Sciences Institute (1990-present).
- Scientific Advisor to the Food Nutrition and Safety Committee of the International Life Sciences Institute - Nutrition Foundation (1986-1990).
- Chair of the Scientific Advisors of the Food Nutrition and Safety Committee of the International Life Sciences Institute (1990-present).
- Member of the IFT Consumer Task Force, 2001-2002.
- Member of the IFT Committee on Science, Communications and Government Relations, 2000-2003
- Member of the American Dietetic Association Task Force on National Health, Food and Nutrition Policy, 2001-2002.

EDITORIAL BOARDS:

Editor of Critical Reviews in Food Science and Nutrition, CRC Press.
Editor of the CRC Book Series in Food Science and Nutrition.
M***ember*** of the Editorial Board of in Nutraceuticals World.
Associate Editor of the Encyclopedia of Food Science and Nutrition, John Wiley and Sons.
Member of the Editorial Board of Trends in Food Science and Technology, Elsevier Publishing Company.
Member of the Editorial Board of the Journal of Food Protection.
Member of the Editorial Board of Food Research International.
Member of the Editorial Board of Ciencia y Tecnologia Alimentaria.

PUBLICATIONS:

360 Technical Publications (see attached).
20 Books and Monographs
250 Invited Presentations to technical societies, industrial groups consumer groups, radio and TV (past 5 years).

GRANTS AND DEVELOPMENT:

Have been a co-principal investigator or principle investigator of grants from NIH, USDA, the Department of Defense, Industry, Trade Associations, Institutes and Foundations, as well as participating in regional Hatch projects over the past 35 years.

Over the last 5 years Grants have included: Coca Cola Foundation, PI, Food Science/Policy Consumer Acceptance 98-02, $95,500. USDA, CoPI with 5 others and a PI, Seafood Safety 99-02, $871,616. Strategic Research Alliance, Director 98-02, $650,000.

Since 1989, during my tenure as Department Head we have received over $1.8 million in non endowment gifts and over $2.5 million in endowment gifts for a total of over $4.5 million dollars.

Total gifts increased 180 times from FY 1990 to FY 2001. Endowment giving increased from zero to over $2.5 million and non endowment gifts increased 80 times.

We have just initiated our fifth endowment campaign. This campaign will be for one million dollars in support of graduate student scholarships.

CONSULTANTSHIPS (selected)

Have acted and am acting as a consultant to several major U.S. and international food companies.

Serve on or chair Scientific and Technical Advisory Boards and Committees for a number of major food companies, government agencies and the National Academies.

Served as a consultant to the University of Florida Agricultural Research and Education Center, Lake Alfred, Florida, in color chemistry to the National Science Foundation as a member of overview committees and to the National Academies and FOA.

Consulted for the Institute of Nutrition, University of North Carolina, Chapel Hill, North Carolina and Purdue University, Harvard University and Tufts in the area of curriculum design.

APPOINTMENTS AND PRESENTATIONS (selected)

Appointed to the Keystone Round Table on Food Nutrition and Health 2006

Appointed to an NIH Advisory Panel,2005.

Appointed to the committee to review and establish the 2005 Dietary Guidelines for Americans by the Department of Health and Human Services.

Appointed to the National Academy, IOM Committee on the Use of Dietary Reference Intakes on Nutrition Labeling, 2002-2003.

Appointed as a special consultant to FDA 1998-2002.

Elected Chair of the Board of Trustees of ILSI-NA 2001-2003.

Appointed to Chair the Food Forum of the Food and Nutrition Board of the Institute of Medicine National Academy of Science, 1996-1999. Reappointed 1999-2001. Reappointed 2001-2002.

Elected to the Board of the IFIC Foundation 1996-present.

Chaired the FDA Working Panel to evaluate Olestra, November 14-17, 1995.

Appointment to the Food Advisory Committee of the Food and Drug Administration, 1994-1998. Reappointed as an ad hoc non voting member, 1999-present.

Appointed to the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences 1994-1997. Reappointed 1997-2000.

Appointed to the Keystone Committee on National Policy Dialogue on Food, Nutrition and Health 1993-1996.

Appointed to the National Academy of Sciences, Institute of Medicine Committee on Research Opportunities in Nutrition and Food Science 1990-1993.

Appointed to the Oversight Committee of the Designer Foods Program, in the National Cancer Institute, 1991.

Appointed to the Expert Panel on "Emerging Issues in Food Safety and Quality During the Next Decade". This was a panel of the Life Sciences Research Office of the Federation of American Societies for Experimental Biology to advise the Food and Drug Administration for the 1990's. (1989)

Appointed to the United States Senate Select Committee on Nutrition and Human Needs as a member of the panel on Nutrition and the Consumer. (1974).

Appointed to the National Academy of Sciences - National Research Council Board on Agriculture Committee "Scientific and Regulatory Issues Underlying Pesticide Use Patterns and Agricultural Innovations". 1985-87.

Appointed to the National Academy of Sciences - National Research Council General Committee on the DOD Food Program. 1974-77. 1978-81.

Appointed to the National Academy of Sciences - National Research Council Committee on Food Service Systems. 1974-77. Reappointed 1978-81.

Appointed to the Committee on General Nutrition Education of the Pennsylvania State University Nutrition Education Conference Workshop. 1974.

Elected to the Board of Governors of Food Update of the Food and Drug Law Institute, (1984-87).

Appointed to the Board of Advisors of Brigham Young University Ezra Taft

Benson Agricultural Institute, (1983-1991).

Invited to present a paper at the 4th International Congress of Food Science and Technology, Madrid, Spain. 1974.

Invited to present papers at the Gordon Research Conference on Food and Nutrition, in 1974 and 1975.

Invited to testify at the Federal Trade Commission Hearings on Food Advertising, in 1976 and 1977.

Invited to submit testimony to Subcommittees on both the House and Senate on several occasions.

Invited to present an address to the Royal Canadian Institute (Canada's oldest scientific society), 1979.

Invited to present the Annual Lecture to the British Nutrition Foundation, London, England. (1979).

Invited to present a paper at the 6th Annual Congress of the International Nutritional Anemia Consultative Group in Santiago, Chile, 1981, sponsored by AID.

Invited to present a paper to a joint meeting of the British Nutrition Foundation and the Soc. Chem. Ind. London, England, 1986.

Keynote speaker at the annual meeting of the Australian IFST, 1987. Albury, Australia.

Ellen Park, 14th Annual Memorial Lecture. Univ. of Toronto, 1987.

Invited to present one of four Plenary Papers at the Opening Session of the 50th Anniversary Annual Meeting of the Institute of Food Technologists, Chicago, IL, 1989.

Invited as the Foreign Speaker to present the main lecture at the 50th Anniversary of the Finnish Meat Research Institute in Hameenlinna, Finland. August, 1990.

Invited to present a Plenary Paper at the 8th World Congress of Food Science and Technology, Toronto, Canada, October 1991.

Invited to present a paper at the International Congress of Nutrition in Adelaide, Australia, October 1993.

Invited to present the Centennial Lecture at the Tokyo University of Fisheries, 1993.

Invited to present a paper at the Unilever Research Center, Celebratory Symposium at Colworth House, Bedford, England. 1995.

Invited to present a paper at the 16th International Congress of Nutrition in Montreal Canada, 1997.

Invited to present the Ernest Newbury Memorial Lecture at the 14th South

African Institute of Food Science and Technology International Congress, Pretoria, South Africa, 1997.

Invited to present the opening address at the Celebratory Scientific Symposium, of 25th Anniversary" Euro R&D Center, CPC Europe 35th Anniversary" Institute for Research and Development, CPC Germany, 1997.

Invited to present a paper on Research Priorities for Functional Foods to the USDA Advisory Committee, March 13, 2000.

Organized and Chaired a Symposium on Food Science and Health: Towards a National Rational Health Policy, Amherst, MA, November 7, 8, 2001.

Organized and Chaired a Symposium on Future Directions in Food Safety Research sponsored by the Food forum of the Institute of Medicine, National Academy of Science, Washington, DC, February 27, 2002.

Invited to moderate a session on Metabonomics in a Symposium on Food, Nutrition and Health sponsored by the Food Forum of the Institute of Medicine, National Academies of Science, Washington, DC, May 6, 2003.

OUTREACH:

Initiated, organized and serve as Director of the new University of Massachusetts Food Science Strategic Research Alliance which has 20 member Companies.

Formalized the utilization of our Pilot Plant by State Industries.

Began a series of seminars which led to an off campus MS program at Company Headquarters within the State.

Began a certification program for scientific personnel in a Connecticut Company.

Actively involved in teaching short courses to industry as a means of updating current techniques.

Informal counseling to several major food industries, on regulatory issues, health, nutrition and technology.

Work in close cooperation with the State Food Industry and with local groups and organizations.

Presented some 120 interviews to public interest groups and the press in the past five years.

PERSONAL PUBLICATIONS

Original Research:

Wood, J.D., W.J. Watson and F.M. Clydesdale. 1963. Gamma-Amino-butyric Acid and Oxygen Poisoning. Journal of Neurochemistry, 10:625-633.

Clydesdale, F.M. and C.H. Podlesney, Jr. 1968. A Computer Program for the Interconversion of Color Data. Color Engineering, 6(3):55-56.

Clydesdale, F.M. and F.J. Francis. 1968. A study of chlorophyll changes in thermally processed spinach as influenced by enzyme conversion and pH adjustment. Food Technol., 22(6):135-138.

Clydesdale, F.M. and F.J. Francis. 1969. Color Measurement in Foods: Correlation of Raw, Transformed and Reduced Data with Visual Ratings for Spinach Puree. Food Sci., 34:349-352.

Clydesdale, F.M. and C.H. Podlesny, Jr. 1968. Addition to a Computer Program for the Interconversion of Color Data. Color Engineering, (6),24.

Lin, Yi-Do, F.M. Clydesdale and F.J. Francis. 1970. Organic Acid Profiles of Thermally Processed Spinach. J. Food Sci., 35:641-644.

Huang, I-Lo, F.J. Francis and F.M. Clydesdale. 1970. Colorimetry of Foods: Color measurement of squash using the Kubelka-Munk concept. J. Food Sci., 35:315-317.

Huang, I-Lo, F.J. Francis and F.M. Clydesdale. 1970. Colorimetry of Foods: Carrot puree. J. Food Sci., 35:771-773.

Fleischmann, D.L., F.M. Clydesdale and F.J. Francis. 1970. Effect of magnesium carbonate and sodium phosphate on the extraction of chlorophyll-like pigments after thermal processing of spinach puree. J. Milk and Food Technol., 33:456-459.

Lin, Yi-Do, F.M. Clydesdale and F.J. Francis. 1971. Organic Acid Profiles of Thermally Processed, Stored Spinach Puree. J. Food Sci., 36:240-242.

Clydesdale, F.M., D.L. Fleischmann and F.J. Francis. 1970. Maintenance of Color in Processed Green Vegetables. Food Product Development, 4(5):127-138.

Clydesdale, F.M., A.W. Goodman and F.J. Francis. 1971. The effect of a phosphate buffer and magnesium carbonate of quality attributes of cooked green vegetables. J. Milk and Food Technol., 34:78-81.

Clydesdale, F.M., Y.D. Lin and F.J. Francis. 1972. Formation of 2-pyrolidone-5-carboxylic acid from glutamine during processing and storage of spinach puree. J. Food Sci., 37:45-47.

Lin, Y.D., F.M. Clydesdale and F.J. Francis. 1972. A simplified method for the analysis of glutamine. J. Food Sci., 37:488-489.

Ehmann, E.P., R.A. Ageloff and F.M. Clydesdale. 1972. A multipurpose colorimetric computer program. Food Product Development, 6:111-112.

Gullett, E.A., F.J. Francis and F.M. Clydesdale. 1972. Colorimetry of Foods: 5. An orange beverage - Tang. Can. Inst. Fd. Sci. Tech. J., 5(1):32-36.

Gullett, E.A., F.J. Francis and F.M. Clydesdale. 1972. Colorimetry of Foods: 4. Orange Juice. J. Food Sci., 37:389-393.

Driver, M., F.J. Francis and F.M. Clydesdale. 1976. Colorimetry of Dry Breakfast-Type Cereals. J. Food Sci., 41:1353-1356.

Bibeau, T.C., F.M. Clydesdale and F.M. Sawyer. 1974. Glutamine as a predictive measurement in the quality assessment of carrot puree. J. Food Sci., 2:365-367.

Johnson, L., F.M. Clydesdale and F.J. Francis. 1976. The use of colorimetric data to predict chemical and visual changes in solution. 4th International Congress of Food Science and Technology. Vol. II:150-159.

Chu, N.T., F.M. Clydesdale and F.J. Francis. 1973. Isolation and identification of some fluorescent phenolic compounds in cranberries. J. Food Sci., 38:1038-1042.

Eagerman, B.A., F.M. Clydesdale and F.J. Francis. 1973. Comparison of color scales for dark colored beverages. J. Food Sci., 38:1051-1055.

Eagerman, B.A., F.M. Clydesdale and F.J. Francis. 1973. Development of new transmission color scales for dark colored beverages. J. Food Sci., 38:1056-1059.

Bibeau, T.C. and F.M. Clydesdale. 1975. Organic acid profiles of thermally processes carrot puree. J. Milk and Food Technol., 38(9):518-520.

Chu, N.T. and F.M. Clydesdale. 1976. Decomposition of organic acids during processing and storage. J. Milk and Food Technol., 39:477-480.

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Chu, N.T. and F.M. Clydesdale. 1976. Reactions between amino acids and organic acids. Reaction of tryptophan and pyruvic acid. J. Food Sci., 41:891-894.

Chu, N. and F.M. Clydesdale. 1975. The effect of concentration, thermal processing, and storage temperature on the interaction between alpha-ketoglutaric acid and tryptophan. J. Milk and Food Technol. 38(10):573-580.

Johnson, J., F.M. Clydesdale and F.J. Francis. 1975. Use of expanded color scales to predict chemical and visual changes in solutions. J. Food Sci., 41:74-77.

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Bibeau, T.C. and F.M. Clydesdale. 1978. Thermal Stability of Subsidiary Dyes Associated with FD&C Yellow No. 6. J. Food Sci., 43(2):521-523.

Eagerman, B.A., F.M. Clydesdale and F.J. Francis. 1977. Determination of fresh meat color by objective methods. J. Food Sci., 42:707-710.

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Anderson, N.E. and F.M. Clydesdale. 1978. Analysis of tryptophan utilizing its reaction with alpha-ketoglutaric acid. J. Food Sci., 43:1595-1599.

Eagerman, B.A., F.M. Clydesdale and F.J. Francis. 1978. A rapid method for following changes in myoglobin in beef muscle. J. Food Sci., 43:468-469.

Main, J.H., F.M. Clydesdale and F.J. Francis. 1978. Spray drying anthocyanin concentrates for use as food colorants. J. Food Sci., 43:1693-1694.

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Lee, K. and F.M. Clydesdale. 1979. Quantitative determination of the elemental, ferrous, ferric, soluble and complexed iron in foods. J. Food Sci., 44:540-554.

Kostyla, A.S. and F.M. Clydesdale. 1979. Psychophysical relationships between color, flavor, aroma, sourness and sweetness in a red cherry flavored beverage. Presented at IFT meeting, Dallas, 1978.

Clydesdale, F.M., J.H. Main, F.J. Francis and R.H. Damon. 1978. Concord grape pigments as colorants for beverages and desserts. J. Food Sci., 43:1687-1692, 1697.

Clydesdale, F.M., J.H. Main and F.J. Francis. 1978. Cranberry pigments as colorants for beverages and gelatin desserts. J. Food Prot., 42:196-201.

Clydesdale, F.M., J.H. Main and F.J. Francis. 1978. Roselle, Hibiscus Sabdariffa L, anthocyanins as colorants for beverages and gelatin desserts. J. Food Prot., 42:204-207.

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Anderson, N.E. and F.M. Clydesdale. 1980. An analysis of the dietary fiber content of corn bran. J. Food Prot., 43:760-762.

Lee, K. and F.M. Clydesdale. 1980. Effect of baking on the forms of iron in iron-enriched flour. J. Food Sci., 45:1500-1504.

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Camire, A.L. and F.M. Clydesdale. 1981. The effect of pH on the binding of Ca, Mg, Zn, and Fe to wheat bran and fractions of a dietary fiber. J. Food Sci., 46:548-551.

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Nojeim, S.J., F.M. Clydesdale and O.T. Zajicek, 1981. Effect of redox potential on iron valence in model systems and food. J. Food Sci., 46:1265-1268.

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Camire, A.L. and F.M. Clydesdale. Interactions of soluble iron with wheat bran. J. Food Sci., 47:1296-1297.

Clydesdale, F.M. 1982. Potential chemical determinants of iron bioavailability in foods. Proceedings of the 6th Annual Meeting of the International Nutritional Anemia Consultative Group. XI. f, 1-2.

Johnson, J.L., E. Dzendolet, R. Damon, M. Sawyer, and F.M. Clydesdale, 1982. Psychophysical relationships between perceived sweetness and color in cherry flavored beverages. J. Food Prot., 45:606-610.

Moore, A.B., F.M. Clydesdale, and F.M. Clydesdale. 1982. Changes in chromatographic profile of anthocyanins of red onion during extraction. J. Food Prot., 45:738-743.

Glorman, J.E. and F.M. Clydesdale, 1983. The behaviour and stability of iron-ascorbate complexes in solution. J. Food Sci., 48:1217-1220, 1225.

Clydesdale, F.M. and A.L. Camire. 1983. Effect of pH and heat on the binding of iron, calcium, magnesium, and zinc, and the loss of phytic acid in soy flour. J. Food Sci., 48:1272-1274, 1283.

Johnson, J.L., E. Dzendolet, and F.M. Clydesdale, 1983. Psychophysical relationship between sweetness and redness in strawberry flavored drinks. J. Food Prot., 46:21-25, 28.

DiNardo, M., E.M. Buck, and F.M. Clydesdale, 1983. Effect of extended cook times on certain physical and chemical characteristics of waterbath prepared beef. J. Food Sci., 49:844-848.

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Rizk, S.W. and F.M. Clydesdale, 1983. Effect of iron sources and ascorbic acid on the chemical profile of iron in a soy protein isolate. J. Food Sci., 48:1431-1435.

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Gorman, J.E. and F.M. Clydesdale, 1984. Thermodynamic and kinetic stability constants of selected carboxylic acids and iron. J. Food Sci., 49:500-503.

Clydesdale, F.M. 1983. Physicochemical determinants of iron bioavailability. Food Technol. 37(10):133-138, 144.

Rizk, S.W. and F.M. Clydesdale. 1984. Effectiveness of organic acids to solubilize iron from a wheat soy drink. J. Food Prot., 48:648-652,658.

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Clydesdale, F.M. and Nadeau, D.B. 1985. Effect of acid pretreatment on the stability of ascorbic acid iron complexes with various iron sources in a wheat flake cereal. J. Food Sci., 50:1342-1347.

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Eyerman, L., F.M. Clydesdale, R. Hueginin, and O.T. Zajicek. 1987. Characterization of solution properties of four iron sources in model systems. J. Food Sci., 52:197-201,209.

Nadeau, D.B. and F.M. Clydesdale, 1987. Effect of acid pretreatment on the stability of EDTA, cysteine, lactic and succinic acid complexes of various iron sources in a wheat flake cereal. J. Food Prot., 50:587-597.

Platt, S.R. and F.M. Clydesdale. 1987. Mineral binding characteristics of lignin, guar gum, cellulose, pectin and neutral detergent fiber under simulated duodenal pH conditions. J. Food Sci., 52:1414-1419.

Nadeau, D.B. and Clydesdale, F.M. 1987. Effect of sucrose, fructose, and aspartame on fortificant iron solubility in a wheat flake cereal. J. Food Prot., 50:21-24.

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Education Review Articles:

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Clydesdale, F.M. 1978. Book Review. The New Nuts Among the Berries, by R.M. Deutsch. J. Food Technol. 32(1):103-104.

Clydesdale, F.M. 1978. Book Review. Nutrition and Food Choices, by K.W. McNutt. J. Food Technol. 32(9):127.

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Clydesdale, F.M. 1979. Book Review. Technology and Social Shock. E.W. Lawless. J. Food Technol. 33(1):117.

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Clydesdale, F.M. 1984. A review of the book "Developments in Sweetness- 2. Ed. I.H. Grenby, K.J. Parker, and M.G. Lindley. Applied Science Publ. Ltd. Eng. and Elsevier Science Publ. Co., NY. Fd. Technol. 38(3):137.

Clydesdale, F.M. 1984. A review of the book "Alterations in Food Production". Ed. D.W. Knorr and T.R. Watkins. Van Nostrand Reinhold Co. NY. Food Technol. 38(11):138.

Clydesdale, F.M. 1985. A review of the book "Fancy Eating That!" A Closer Look at Food Additives and Contaminants. K.T. Farrer. Melbourne Univ. Press, Australia Food Technol. 39(6):142-143.

Clydesdale, F.M. 1986. A review of the book "Sex and Your Diet". Candy Cummings. Leisure Press, Champaign, IL. Food Technol. 40(12):154.

Clydesdale, F.M. 1987. A review of the book "How to Live Longer and Feel Better" Linus Pauling. W.H. Freeman and Co., New York. Food Technol. 41(3):152-154.

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Clydesdale, F.M. 1987. Letter to the Editor in answer to a letter from Dr. Linus Pauling concerning my review of his book "How to Live Longer and Feel Better". Food Technol. 41(11):28.

Clydesdale, F.M. 1990. A review of the book "The Healing Foods: The Ultimate Authority on the Curative Powers of Nutrition", by P. Hausman and J.B. Hurley. Rodale Press Inc., Emmaus, P.A. Food Technol. 44(2):134.

Clydesdale, F.M. 1991. A review of the book "Foods for the 90's." Edited by G.G. Birch, G. Campbell-Platt and M.G. Lindley. Elsevier App. Sci. Publ. Food Technol. 45(1):179.

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Clydesdale, F.M. 1992. A review of the book "Improving America's Diet and Health, From Recommendations to Action." Edited by Paul R. Thomas. Food and Nutrition Board, Inst. of Med., National Academy of Sciences, National Academy Press, Washington, D.C. Food Technol. 46(4),132.

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Clydesdale, F.M. 1992. A review of the book "Nutrition and the Consumer" Eds. A.F. Walker and B.A. Roll's. Elsevier Appl. Sci. Publ., N.Y. Trends Food Sci. Tech. 4:235.

Clydesdale, F. M. 2003. A review of the book “Expectations and the Food Industry: Impact of Color and Appearance, by John Hutchings.

Books and Monographs:

1) Food Colorimetry: Theory and Applications. F.J. Francis and F.M Clydesdale. 1975. AVI Publishing Co., Westport, CT.
2) Food, Nutrition and You. F.M. Clydesdale and F.J. Francis. 1977. Prentice-Hall, Englewood Cliffs, NJ.
3) Food Science and Nutrition: Critical Issues and Answers. 1979. Edited by F.M. Clydesdale. Prentice-Hall.
4) Human Ecological Issues: A Reader. (with F.J. Francis). Kendall/Hunt, Iowa, 1980. 302 pp.
5) Iron Fortification Technology. Ed. F.M. Clydesdale and K. Wiemer. San Francisco. 1985.
6) Food, Nutrition and Health. (with F.J. Francis) AVI Publishing Co., Westport, CT. 1985.
7) The Effects of Cereals and Legumes on Iron Availability. Committee authored, F.M. Clydesdale committee member. INAG, The Nutrition Foundation, Washington, D.C. 1985.
8) Regulation Pesticides in Food: The Delaney Paradox. Committee on Scientific and Regulatory Issues Underlying Pesticide Use Patterns and Agricultural Innovation (F.M. Clydesdale, Member). Board on Agriculture, Nat. Rev. Council, Nat. Acad. Science. National Academy Press. Washington, D.C. 1987.
9) Clydesdale, F.M. (Editor Chief) 1992. Food Safety - A Monograph Crit. Rev. Food Sci. Nutr. 31(3)163-209.

10) Clydesdale, F.M. (Series Editor) 1993. America's Foods: Health Messages and Claims, Scientific, Regulatory and Legal Issues. Ed. J.E. Tillotson. CRC Press Boca Raton, FL 287 pp.
11) NAS Committee (F.M. Clydesdale a member) 1994. Opportunties in the Nutrition and Food Sciences. Inst. of Med., NAS, National Academy Press, Washington, DC 310 pp.
12) Clydesdale, F.M. (Series Editor) 1994. New Food Product Development. From Concept to Marketplace. G.W. Fuller, CRC Press, Boca Raton, FL, 304 pp.
13) Clydesdale, F.M. (Series Editor) 1995. Food Properties Handbook. Shafiur Rahman. CRC Press, Boca Raton, FL 500 pp.
14) Clydesdale, F.M. (Series Editor) 1996. Aseptic Processing and packaging of Food. David, J.R.D., Graves, R.H. and Carlson, V.R. CRC Press, Boca Raton, FL 256 pp.
15) Clydesdale, F.M. (Series Editor) 1996. The Food Chemistry Laboratory. C. Weaver. CRC Press, Boca Raton, FL. 123 pp.
16) Clydesdale, F.M. (Series Editor) 1996. Handbook of Food Spoilage Yeasts. T. Deak and L. Beuchat. CRC Press, Boca Raton, FL. 210 pp.
17) Clydesdale, F.M. (As part of a 60 member consensus team) 1996. The Final Report of the Keystone National Policy Dialogue on Food, Nutrition and Health. The Keystone Center, Washington, DC, March, 1996, 159 pp.
18) Food Additives: Toxicology, Regulation and Properties. 1997. Ed. F.M. Clydesdale. CD-ROM Format. CRC Press, Boca Raton, FF.
19) Clydesdale, F.M. and Chan, S.H. (Proceedings Editors). 1996. First International Conference on East-West Perspectives on Functional Foods. Nutr. Rev. 57:11,(part 2), 202 pages.
20) Clydesdale, F.M. (Editor). 1996. Special Supplement. Allergenicity of Foods Produced by Genetic Modification. Crit. Rev. Food Sci. Nutr. 36: Supplement.
21) Clydesdale, F.M. (Series Editor) 1998. Antioxidant Status, Diet, Nutrition and Health. Ed. A.M. Papas. CRC Press, Boca Raton, FL 650 pp.
22) Clydesdale, F.M. (Series Editor) 1998. Food Emulsions: Principles, Practice and Technique, by D.J. McClements. CRC Press, Boca Raton, FL 378 pp.
23) Clydesdale, F.M. (Associate Editor). 2000. Wiley Encyclopedia of Food Science and technology, 2nd Edition (F.J. Francis, Editor). 4 Volumes, 2768 pp.
24) Institute of Medicine, National Academy of Science. 2001. Food Forum Workshop Proceedings. Food Safety Policy, Science and Risk Assessment. F. M. Clydesdale, Chair of the Food Forum, 42 pp.
25) Clydesdale, F.M. (Series Editor). 2001. Food Consumers and the Food Industry. Gordon W. Fuller. CRC Press, Boca Raton, FL. 295 pp.
26) Clydesdale, F.M. (Series Editor). 2001. Interdisciplinary Food Safety Research. Eds. Neal H. Hooker and Elsa A. Murano. CRC Press, Boca Raton, FL. 213 pp.
27) Clydesdale, F.M. (Series Editor). 2001. Bread Staling. Eds. Pavinee Chinachoti and Yael Vodovotz. CRC Press, Boca Raton, FL. 177 pp.
28) Clydesdale, F.M. (Series Editor). 2002. Introduction to Food Biotechnology. Peny Johnson-Green. CRC Press, Boca Raton, FL. 293 pp.
29) Clydesdale, F.M. (Series Editor). 2003. Modeling Microbial Responses in Food. Eds. Robin C. McKellar and Xueven Lu. CRC Press, Boca Raton FL. 343pp.
30) Clydesdale, F.M. 2003. The Food Chemistry Laboratory.Connie M. Weaver and James R. Daniel. CRC Press, Boca Raton, FL. 137pp.
31) Clydesdale, F.M. (Series Editor). 2005 Food Microbiology Laboratory. Lynne Mclandsborough. CRC Press, Boca Raton, FL. 179pp.

32) Clydesdale, F.M. (Series Editor). 2005. Food Emulsions. David Julian McClements. CRC Press, Boca Raton, FL. 609pp.

33) Clyesdale, F. M. (Series Editor). 2006. Advanced Quantitative Microbiology for Foods and Biosystems. Micha Peleg, CRC Press, Boca Raton, FL.417pp.

Ronald E. Kleinman
Curriculum Vitae

DATE REVISED: April 9, 2007

Name: Ronald Ellis Kleinman

Office Address: Pediatric Gastroenterology and Nutrition Unit
VBK 107
MassGeneral Hospital *for* Children
Massachusetts General Hospital
55 Fruit Street
Boston, MA 0

Home Address:

EMail:

Place of birth:

Education:

Trinity College, Hartford, Connecticut
New York Medical College, New York
Harvard Medical School, Boston, Massachusetts

Postdoctoral Training:

Internship and Residencies:

Intern in Pediatrics, Montefiore Hospital and Medical College, Albert Einstein College of Medicine, Bronx, New York
Resident in Pediatrics, Montefiore Hospital and Medical Center, Albert Einstein College of Medicine, Bronx, New York
Chief Resident in Pediatrics, Montefiore Hospital and Medical Center, Albert Einstein College of Medicine, Bronx, New York

Clinical and Research Fellowships:

Research Assistant, Institute of Living, Hartford, Connecticut, NIMH Grant #MH08870
Fellow in Human Developmental Biology, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York
Clinical and Research Fellow, Pediatric Gastrointestinal and

Nutrition Unit, Massachusetts General Hospital, Boston, Massachusetts
Research Fellow in Pediatrics, Harvard Medical School, Boston, MA

Licensure and Certification:

National Board of Medical Examiners
Massachusetts License Registration #41023
Diplomat, American Board of Pediatrics
American Board of Pediatrics, Sub-board of Pediatric Gastroenterology
Re-certification, American Board of Pediatrics, Sub-board of Pediatric Gastroenterology
Re-certification, American Board of Pediatrics, Sub-board of Pediatric Gastroenterology

Academic Appointments:

1980-1982	Instructor in Pediatrics, Harvard Medical School, Boston, MA
1982	Assistant Professor of Pediatrics, Harvard Medical School, Boston, Massachusetts
1988	Associate Professor of Pediatrics, Harvard Medical School, Boston, Massachusetts
1998	Professor of Pediatrics, Harvard Medical School, Boston, MA

Hospital Appointments:

1980	Assistant in Pediatrics, Massachusetts General Hospital, Boston, MA
1982	Assistant Pediatrician, Massachusetts General Hospital, Boston, MA
1983-present	Associate in Medicine (Gastroenterology) Children's Hospital, Boston, Massachusetts
1985	Associate Pediatrician, Massachusetts General Hospital, Boston, MA
1987-present	Pediatrician, Massachusetts General Hospital, Boston, MA

Other Professional and Major Visiting Appointments:

1981-present	Visiting Faculty, Cambridge City Hospital, Cambridge, MA
1981-present	Visiting Lecturer, Department of Nutrition and Food Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts
1983	Visiting Consultant, Gorgas Hospital, Panama

Major Committee Assignments (Hospital and Medical School, Representative):

1980-present	Member, Resident Selection Committee, Children's Service, Massachusetts General Hospital, Boston, Massachusetts
1982-1986	Member, Scientific Advisory Committee, Mallinckrodt Clinical Research Center, Massachusetts General Hospital
1983-85	Secretary, Executive Committee, Children's Service, Massachusetts General Hospital, Boston, Massachusetts
1986-1991	Member, IRB, Massachusetts General Hospital
1986-present	Associate, Oliver Wendell Holmes Society, Harvard Medical School, Boston, Massachusetts
1993-present	Chairman, Clinical Practice Management/Quality Improvement Committee, Children's Service Committee, Massachusetts General Hospital, Boston, Massachusetts
1993-1995	Member, Professional Staff Benefits Advisory Committee, Massachusetts General Hospital, Boston, Massachusetts
1994-present	Member, Massachusetts General Hospital Physician's Organization, Practice Committee/Primary Care Council
1995	Chairman, Pediatric Strategy Team for Partner's Community HealthCare, Inc., Boston, Massachusetts
1995	Member, Children's Service Promotion Committee, Massachusetts General Hospital, Boston, Massachusetts
1995-present	Member, Clinical Practice Management/Operations Improvement Committee, Massachusetts General Hospital
1995-present	Member, Physician Information Resource Committee, Massachusetts General Hospital, Boston, Massachusetts
1995	Member, Tertiary/Quaternary Strategic Planning Task Force, Massachusetts General Hospital, Boston, Massachusetts
1995-present	Member, Nutrition Advisory Committee, Harvard Medical School
1996	Chair, Internal Medicine Residency Program Review Committee, Massachusetts General Hospital, Boston, Massachusetts
1996	Member, Physician's Advisory Wayfinding Subcommittee
2000-present	Member, Yawkey Ambulatory Building Steering Committee, Massachusetts General Hospital, Boston, Massachusetts
2005-present	Member, Massachusetts General Physicians Organization Board of Trustees

Major Committee Assignments (National):

1989	Member, Study Section, Liver Transplantation Program Projects, National Institutes of Health
1990	Member, National ORT Project Leadership Committee
1991	Member, Medical Advisory Group on Diet and Nutrition, American Cancer Society

1993	Member, Steering Committee National Cholesterol Education Program, NHLBI, NIH
1993	Consultant, Pediatric Gastroenteritis Patient Outcomes Research Project, Agency for Health Care Policy Research
1994	Member, ACGME Panel on Accreditation of Pediatric Gastroenterology and Nutrition Fellowship Training Programs
1995	Member, WHO Treatment Effects Monitoring Committee
1995	Member, FDA Food Advisory Panel
1995	Member, Scientific Advisory Committee, National Egg Board
1995	Chair, Nutrition Curriculum Development Committee, NASPGN
1995	External Reviewer, Medical Research Council, Canada
1996	Member, American Liver Foundation Children's Liver Council
1996	Member, NIH Program Project Study Section on Dietary Intervention for Prevention of Coronary Vascular Disease
1997	Member, Pediatric Gastroenterology Subboard of the American Board of Pediatrics
2000-2002	Chief Pediatric Consultant, USDA Evaluation of the School Breakfast Program Pilot Project (6/1/2000-2003)
2000	Member, Board of Overseers, Walnut Hill School
2002-2003	Scientific Advisory Committee, Massachusetts Vitamins Litigation Award
2002-Present	Member, Scientific Advisory Board; Institute of Nutrition; Lima, Peru
2003-Present	Member, Infant Formula Subcommittee of the Food Advisory Committee; Department of Health and Human Services; FDA
2005	Member, Committee on the Science of Adolescent Health and Medicine, National Academy of Science
2005	NIH/NICHHD Special Emphasis Panel
2005	Institute of Medicine, Committee on the Synthesis of Research on Adolescent Health and Development
2006	Institute of Medicine, Committee on the Impact of Pregnancy weight on Maternal and Child Health

Memberships, Offices and Committee
Assignments in Professional Societies:

1980-present	Member, American Gastroenterological Association
1981-present	Member, North American Society for Pediatric Gastroenterology
1983-present	Member, Society for Pediatric Research
1983-present	Member, Gastroenterology Research Group
1986-present	Fellow, American Academy of Pediatrics
1986-present	Member, American Association for the Study of Liver Diseases
1988-1989	Member, Committee on Nutrition, American Academy of Pediatrics
1989-1993	Chairman, Committee on Nutrition, American Academy of Pediatrics

1989-present	Member, The American Pediatric Society
1989-present	Member, Society for Mucosal Immunity
1989-present	Member, American Board of Pediatrics
1992-present	Member, Board of Trustees, International Child Health Foundation
1996-present	Member, American Institute of Nutrition
1996-present	Member, American Society for Clinical Nutrition
2000-present	Honorary Fellow, Philippine Pediatric Society
2002-2004	President-Elect, International Society for Behavioral Nutrition and Physical Activity

Editorial Boards:

1990-1994	Member, Editorial Board, Healthy Kids, American Academy of Pediatrics
1991-2002	Member, Editorial Board, Journal of Pediatric Gastroenterology and Nutrition
1993-2000	Member, Editorial Board, Pediatrics
1994-present	Member, Editorial Board, Acta Paediatrica Sinica
1995-2002	Associate Editor, Journal of Pediatric Gastroenterology and Nutrition
1996-present	Member, International Consultative Committee of Pediatric Integral
1998-2002	Senior Associate Editor, Journal of Pediatric Gastroenterology and Nutrition

Major Research Interests:

1. Gastrointestinal Immunology
2. Developmental Gastroenterology
3. Treatment of Acute Diarrheal Disease
4. Psychosocial, Cognitive and Physical Effects of Hunger in Childhood

Research Funding Information:

Project Bread/Cox Foundation
Project title: Community Health Centers Hunger Intervention Project
Primary Investigator: Ronald E. Kleinman, MD
Dates: 1/2003-12/2005 ($285,000)

Project Bread
Project title: Psychosocial, physical and cognitive effects of hunger in school age children.

Primary Investigator: Ronald E. Kleinman, MD
Dates: 6/99-2002; ($55,000)

Abel Foundation
Project title: Maryland meals for achievement evaluation
Primary Investigator: Michael Murphy, EdD and Ronald E. Kleinman, MD
Dates: 6/98-2001; ($5,000)

Novartis
Project title: Health benefits of a cereal supplemented with a prebiotic in free-living infants
Primary Investigator: Ronald E. Kleinman, M.D.
6/28/99-6/30/02; ($850,000)

National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases
Project title: Interaction of antibody and enteric antigen in neonates
Primary Investigator: Ronald E. Kleinman, M.D.
New Investigator Award Grant #AM31079
Dates: 9/1/81-8/31/84

Mead Johnson Nutritional Group
Project title: Determinants of Milk Allergy in Infancy
Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 1/1/86-1/31/89

Mead Johnson Nutritional Group
Project title: Acceptance and tolerance of reformulated Pregestimil
Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 8/1/86-7/31/88

National Institutes of Health
Project title: Maturation of intestinal host defenses
Program Director: W. Allan Walker, M.D.
Project 3: Neonatal immune response to dietary antigen
Primary Investigator: Ronald E. Kleinman, M.D.
Grant #HD 20810
Dates: 8/1/86-3/31/90

Chiles Foundation
Project title: T-cell responses to orally and systemically-administered model dietary protein antigens
Primary Investigator: Ronald E. Kleinman, M.D.

Dates: 12/1/84-1/31/94

Nestec Ltd., Research Center
Project title: Neonatal immune response to milk protein antigens: The role of mucosal T helper cells in the development of oral priming and tolerance
Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 1/1/90-12/31/91

National Institutes of Health
Project title: Helper T cells in mucosal immune response
Primary Investigator: Tien-lan Chang, M.D.
Co-Primary Investigator: Ronald E. Kleinman, M.D.
Grant #A100974
Dates: 5/1/90-4/30/93

International Atomic Energy Agency
Project title: Albumin synthesis and energy metabolism in protein energy malnutrition
Co-Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 9/1/93-8/31/94

Harvard Community Health Plan Foundation
Project title: Access to and utilization of oral rehydration solutions: A prospective study
Co-Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 7/1/93-6/30/96

Middle Atlantic Milk Producers Association
Project title: Nutritional and psychological consequences of hunger: The effect of universal school lunch and breakfast programs
Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 2/1/95-1/30/97

Kellogg Company Foundation
Project title: Nutritional and psychological consequences of hunger
Primary Investigator: Ronald E. Kleinman, M.D.
Dates: 1/1/93-12/31/2000

Principal Clinical and Hospital Service Responsibilities:

1980-present	Attending Physician, Pediatric Gastroenterology and Nutrition Unit
1980-present	Inpatient and ambulatory coverage pediatric bowel/liver transplantation patients

1980-present	General Pediatric Unit Visiting Physician

Major Administrative Responsibilities:

1982-1986	Assistant Program Director, Mallinkcrodt Clinical Research Center, Massachusetts General Hospital, Boston, Massachusetts
1983-1990	Associate Director, Combined Program in Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital and Children's Hospital, Boston, Massachusetts
1985-present	Associate Chief, Children's Service, Massachusetts General Hospital
1986-present	Chief, Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital, Boston, Massachusetts
1995-present	Design Team Leader for Pediatrics; Operations Improvement Program, Massachusetts General Hospital, Boston, Massachusetts
2006-present	Acting Physician In-Chief and Chair, Department of Pediatrics

Teaching Experience:

1978-1983	Lecturer, Gastrointestinal Pathophysiology, Harvard Medical School, Boston, Massachusetts
1981-2002	Visiting Lecturer, Massachusetts Institute of Technology, Cambridge, MA
1983-1986	Board of Tutors, Harvard Medical School, Boston, Massachusetts
1984-2002	Lecturer, HMS Postgraduate Pediatrics Course, Massachusetts General Hospital, Boston, Massachusetts
1984	Lecturer, HMS Postgraduate Pediatrics Course, Children's Hospital, Boston, Massachusetts
1984-2002	Lecturer, Children's Service Core Curriculum Lecture Series
1984-1990	Chairman, Children's Service Research Symposium Committee
1985	Member, New Pathway Course on Matter and Energy
1985	Member, New Pathway Course on Women and Children's Health

Representative Lectures in the Past Ten Years:

1990	Bela Schick Seminar, Brookdale Hospital, Brooklyn, New York
1990	International Food Allergy Symposium, Toronto, Ontario, Canada
1990	Seminar Leader, AAP Seminar, Hynes Auditorium, Boston, MA
1991	Sixth National Conference on Advances in Pediatric GI and Nutrition, Sarasota, Florida
1991	Section Moderator, APS/SPR GI & Nutrition, New Orleans, LA
1991	International Conference on Nutrition and Immunology, St. John's, Newfoundland, Canada

1991	PREP, The Course, Lansdowne Conf Center, Leesburg, Virginia
1992	ASPEN Conference, Orlando, Florida
1992	International Symposium Adverse Reactions to Foods in Infancy and Childhood, Madrid, Spain
1992	International Child Health Conference, Vancouver, BC, Canada
1993	Annual Meeting American Academy of Allergy & Immunology, Chicago, Illinois
1993	VIII International Food Allergy Symposium, American College of Allergy and Immunology, Denver, Colorado
1993	International Symposium "New Perspectives in Infant Nutrition", Murcia, Spain
1994	Children's Memorial Hospital, Chicago, Illinois, Grand Rounds
1994	11th International Conference on Gastronomy, Children's Education: Feeding our future, American Institute of Wine and Food, Monterey, California, Keynote Speaker
1994	33rd Annual Pediatric Postgraduate - Controversies in Pediatrics, Maimonides Medical Center, New York
1994	Grand Rounds, University of Massachusetts Medical Center, Worcester, Massachusetts
1994	National Cholesterol Education Panel Meeting, Bethesda, Maryland
1994	Grand Rounds, Boston City Hospital, Boston, Massachusetts
1994	Annual Meeting, American Dietetic Association, Orlando, Florida
1994	NASPGN Postgraduate Course, Houston, Texas
1994	Food and Nutrition Institute Warsaw, Poland
1994	American Thoracic Society, New York, New York
1995	ILSI Conference on Nutrition, Obesity and Physical Activity, Atlanta, Georgia
1995	FASEB, American Institute of Nutrition
1995	National Cholesterol Education Panel Meeting, Bethesda, Maryland
1995	Tri-state Dietetic Association Annual Meeting (Wyoming, Montana, Idaho), Jackson Hole, Wyoming
1995	Grand Rounds, Massachusetts Institute of Technology Health Center, Cambridge, Massachusetts
1996	Grand Rounds, Cambridge Hospital, Cambridge, Massachusetts
1996	Fifteenth Seminar on Pediatric Gastroenterology and Nutrition, NASPGN, San Diego, California
1996	Chairman, Nutrition Requirements During Infancy Symposium, Taipei, Taiwan
1996	Primary Medicine Today Conference, Hynes Auditorium, Boston, Massachusetts
1996	National Symposium Celebrating 25 Years of ORT Use in the United States, Johns Hopkins School of Public Health, Baltimore, MD
1996	Omaha District Dietetic Association Annual Meeting, Omaha, NB

1996	National Cholesterol Education Panel Meeting, Bethesda, Maryland
1996	Harvard Medical School Postgraduate Course in Primary Care Pediatrics, Boston, Massachusetts
1997	Grand Rounds, Cambridge Hospital, Cambridge, Massachusetts
1997	The Women's Health Lecture Series, North Shore Medical Center, Salem, Massachusetts
1997	Probiotics, Other Nutritional Factors and Intestinal Microflora, 42nd Nestle Nutrition Workshop, Beijing, China
1997	National Maternal Nutrition Intensive Course, University of Minnesota, Minneapolis, Minnesota
1997	Annual Meeting Canadian Pediatric Society, Halifax, NS, Canada
1997	How to Grow a Healthy Child Conference, Pennsylvania State University
2001	Hand in Hand: Making a Difference Together Conference, Phoenix, Arizona
2001	National Institutes of Health Conference: Dietary Supplement Use in Children: Who, What, Why and Where Do We Go From Here?
2002	World Food Program; Childhood Hunger and School Feeding Programs Copenhagen, Denmark
2002	Topics in Primary Care Pediatrics, Cambridge, Massachusetts
2004	Resident Core Curriculum
2004	Topics in Primary Care Pediatrics, Cambridge, Massachusetts
2005	Topics in Primary Care Pediatrics, Cambridge, Massachusetts
2005	Workshop On The Science Of Adolescence, Washington, DC
2005	Failure to Thrive Lecture, Boston, MA
2005	NIH/ODS Workshop on Diet, Nutr., Supplements and Autism, Bethesda, MD
2005	American Academy of Pediatrics Annual Conference, Washington, DC
2005	American Academy of Pediatrics GMO Food Safety, Hawaii
2005	Issues in Primary Care, Boston, MA
2005	Primary Care Pediatric Conference, Boston, MA
2006	Issues In Primary Care, Ft. Lauderdale, FL

Representative Visiting Professorships:

1990	Visiting Professor, University of Arizona, Tucson, Arizona, and Phoenix, Arizona
1989	Visiting Professor, Schneider Children's Hospital, Albert Einstein College of Medicine, Long Island, New York
1990	Visiting Professor, SUNY Health Science Center, Brooklyn, NY
1990	Visiting Professor, SUNY Stony Brook, New York

1990	Visiting Professor, Veteran's General Hospital, Taipei, Taiwan
1991	Visiting Professor, Children's Medical Center, Cincinnati, Ohio
1991	Visiting Professor, Children's Hospital, St. Petersburg, Florida
1992	Visiting Professor, St. Joseph's Hospital, Paterson, New Jersey
1992	Visiting Professor, Cornell University Medical Center, New York
1992	Visiting Professor, National Taiwan University, Taipei, Taiwan
1993	Visiting Professor, Children's Hospital, Denver, Colorado
1993	Visiting Professor, Children's Hospital, Dalhousie University, Halifax, Nova Scotia, Canada
1994	Visiting Professor, Children's Memorial Hospital, Chicago, Illinois
1994	Visiting Professor, Seton Hall University, School of Graduate Medical Education, South Orange, New Jersey
1994	Visiting Professor, Kroc Professorship, University of Massachusetts Medical Center, Worcester, Massachusetts
1995	Visiting Professor, Milton & Pearl Grand Lectureship, Albert Einstein College of Medicine, Bronx, New York
1995	Visiting Professor, 27th Annual Kenneth C. Haltalin Pediatric Center Seminar, University of Texas Southwestern Medical Center, Dallas, Texas
1995	Visiting Professor, North Shore University Hospital, Cornell University Medical School, Manhasset, New York
1995	Visiting Professor, Tulane University Medical School, New Orleans, Louisiana
1996	Visiting Professor, Children's Hospital, Omaha, Nebraska
1997	Visiting Professor, Children's Hospital, Columbus, Ohio
1998	Visiting Professor, University of Vermont, Montpelier, Vermont
2000	Visiting Professor, Philippine Pediatric Society, Manila, The Philippines
2001	Visiting Professor, Robert Wood Johnson Medical School, Piscataway, New Jersey
2002	Barnett Lectureship, Albert Einstein College of Medicine, New York, New York
2001	Medearis Lectureship, Massachusetts General Hospital, Boston, MA

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Original Publications:

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11. Stern M, Harmatz PR, Kleinman RE, Walker WA. Food proteins and gut mucosal barrier. III. The influence of lactation and prolactin on the *in vitro* binding and uptake of bovine serum albumin in the rat jejunum. *Pediatr Res* 1985; 19:320-324

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91. Kleinman RE, Garcia RJ, Ng S, Cleghorn G, Devane S, Sanabria MC, Berseth C, Castillo-Duran C. Perinatal Nutritional Gastrointestinal Disease Working Group Report of the Second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastro and Nutr* 2004 Jun;39 Suppl 2:S703-10.

92. Kleinman RE, Kamin, DS. Hepatitis: Acute and Chronic. In: *Gellis and Kagan's Current Pediatric Therapy* 18. Eds. Burg FD, Ingelfinger JR, Polin RA, Gershon S. W. B. Sauders, Inc., Philadelphia. 2004 (in press)

93. Kleinman RE. Chronic Nonspecific Diarrhea of Childhood. In: *Feeding during Late*

Infancy and Early Childhood: Impact on Health. Ed. Schmitz, HO. Nestle Nutrition Workshop Series Pediatric Program. 2005; 56:73-84.

94. Kleinman RE, Kamin DS. Gastrointestinal Development. In: *Pediatric Nutrition Support Handbook.* Eds. Baker SS, Baker RD, Davis AM. Jones and Bartlett Publishers, Inc. Boston. 2006 (in press)

95. Kleinman, RE. Murphy MJ. Wieneke KM. Desmond, MS. Schiff A. Gapinski, JA. Use of a single-question screening tool to detect hunger in families attending a neighborhood health center. *Ambulatory Pediatrics.* 2007 (in press).

Books and Monographs:

1. Kleinman RE and Jellinek MS. *The pediatrician's guide to safe and healthy food and growth.* Villard Books/Ballantyne Books, New York, NY, October, 1994:292

2. Ghraf R, Falkner F, Kleinman R, Koletzko B, Moran J. Eds. *International Symposium: New Perspectives in Infant Nutrition.* Ediciones Ergon, S.A. C/ Antonio Lopez Aguado, 1 - Madrid, Spain, 1994

3. Kleinman RE, Finegold MJ, Gilger MA, Hawkins EP, Wagner ML, Klish WJ. Eds. *Atlas of pediatric gastrointestinal disease.* Hamilton, Ontario, Canada: Decker Publishing Co.1997

4. Editor, *AAP Pediatric Nutrition Handbook.* 4th Edition. American Academy of Pediatrics, 1998

5. Editor, Pediatric Gastrointestinal Disease. In *Ambulatory Pediatrics*. Dershewitz, Ed 1997

6. Editor, Pediatric Gastrointestinal Disease. In *Saunders Manual of Pediatric Practice.* L. Finberg, Editor 1997

7. Editor, Finberg L and Kleinman RE. *Saunders Manual of Pediatric Practice* 2nd Edition. Philadelphia, W.B. Saunders, 2003

8. Editor, *AAP Pediatric Nutrition Handbook* 5th Edition. American Academy of Pediatrics, 2003.

9. Editor, Walker WA, Goulet O, Kleinman RE, Sanderson IR, Sherman P, Shneider B.*Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management* (4th Edition). BC Decker Publishers Inc., Ontario, Canada, 2004

10. Editor, Kleinman RE, Goulet O, Sanderson IR, Sherman P, Shneider B. Mieli-Vergani, G. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management* (5th

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Abstracts:

1. Kleinman RE, Harmatz PR, Bunnell BW, Bloch JK, Walker WA. The effect of bile duct obstruction on clearance of circulating IgA immune complexes. *Hepatology* 1981; 3:523A

2. Ford WA, Kleinman RE, deVries J, King W, Beolhower R, Malt R. Decrease of bovine serum albumin absorption and increases in sucrase specific activity and in cell size following mid-small bowel resection in the neonatal rat. *Australian Ped Journal* 1981;17(3):236

3. Harmatz PR, Kleinman RE, Bloch KJ, Walker WA. Hepatobiliary secretion of IgA immune complexes. *Gastroenterology* 1981;80:1169

4. Kleinman RE, Bloch KJ, Walker WA. Gut induced anaphylaxis and uptake of bystander protein. An amplification of anaphylactic sensitivity. *Pediatric Research* 1981;15:598

5. Kleinman RE, Harmatz PR, Walker WA. Antigen clearance from newborn circulation by transplacental antibodies: Important defense mechanism against pathologic antigen uptake. *Pediatric Research* 1981;15:525

6. Bloch KJ, Kleinman RE, Walker WA. Effect of local intestinal anaphylaxis on antigen uptake. *J Allergy and Clin Immunology* 1981;67S:64

7. Kleinman RE, Harmatz PR, McClenathan D, Bunnell BW, Bloch KJ, Walker WA. Serum polymeric IgA: A source of pIgA in tears. *Pediatric Research* 1982;16:225A

8. McClenathan D, Kleinman RE, Harmatz PR, Bunnell BW, Walker WA. The effect of barbiturate stimulated choleresis on IgA immune complex excretion in rat bile. *Gastroenterology* 1982; 82:1127

9. Harmatz PR, Kleinman RE, McClenathan D, Bunnell BW, Bloch KJ, Walker WA. Immune complex clearance during pregnancy: Effect on hormonal environment on hepatobiliary transport of polymeric IgA (pIgA). *Pediatric Research* 1982;16:165A

10. Harmatz PR, Kleinman RE, Bunnell BW, McClenathan DT, Bloch KJ, Walker WA. The effect of circulating maternal antibody on transfer of antigen in breast milk. *Pediatric Research* 1983;17:251A

11. Harmatz PR, Kleinman RE, Bunnell BW, Cristello MA, Walker WA, Bloch KJ. The effect of maternal antibodies and enteric challenge with antigen on the uptake of bystander protein in neonatal rabbits. *Pediatric Research* 1984; 18:198A

12. Ford WSA, Harmatz PR, Kleinman RE. Intestinal resection in the neonatal rat: Stimulus for precocious intestinal maturation. *Gastroenterology* 1984; 86:1079

13. Stern M, Bunnell B, Harmatz PR, Kleinman RE, Walker WA. Lactation and prolactation modify local intestinal host defense mechanisms. *Gastroenterology* 1984; 86:1266

14. Walsh M, Harmatz P, Carter E, Breazeale E, Sullivan D, Kleinman R, Walker WA. Acute alcohol intoxication alters secretary IgA (sIgA) clearance into rat bile. *Hepatology* 1984;1050A

15. Breazeale E, Harmatz P, Carter E, Walsh M, Sullivan D, Kleinman R, Walker WA. The effect of acute burn trauma on secretory IgA clearance into rat bile: A compromise of the enteric mucosal barrier. *Hepatology* 1984;1049A

16. Harmatz PR, Walsh MK, Sullivan D, Kleinman RE, Walker WA. The effect of lactation on biliary IgA protein secretion in the rat. *Pediatric Research* 1986; 20:249A

17. Harmatz PR, Hanson DG, Brown M, Kleinman RE, Bloch KJ, Walker WA. *Maternal food proteins in milk.* International meeting on human lactation. Konstance, Germany, September, 1986

18. Lencer WI, Klein KE, Kleinman RE. Tuberculosis or Crohn's disease: A decision analysis. *Gastroenterology* 1986;90;5:1516

19. Harmatz PR, Hanson DG, Hickey K, Lipson A, Walker WA, Bloch KJ, Kleinman RE. Intestinal adaptation in the lactating mouse: Possible mechanisms for the enhanced uptake of dietary protein antigen. *Gastroenterology* 1987;92;5:1426

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23. Harmatz PR, Hughes A, Kleinman RE, Bloch KJ. Differential patterns of protein digestion

within the intestine. *Journal of Allergy and Clinical Immunology* 1988; 81:189:85A

24. Chang T, Harmatz PR, Bloch KJ, Kleinman RE. Passively acquired antibody enhances antigen presentation in the neonate. Pediatric Research 1988; 23;4(2):176A

25. Hatz RA, Harmatz PR, Ariniello PD, Bloch KJ, Walker WA, Kleinman RE. *Enhanced macromolecular uptake from the stomach during gastrointestinal anaphylaxis.* International Convocation on Immunology and Immunopathology of the Alimentary Canal, Buffalo, New York, 1988

26. Hatz RA, Harmatz PR, Bloch KJ, Walker WA, Kramling H-J, Enders G, Kleinman RE. *Gastric mucosal barrier dysfunction during local and systemic anaphylaxis.* Congress of Mucosal Immunology. London, 1989

27. Schreiber RA, Manganaro T, Donahoe PK, Kleinman RE. Experimental rejection injury of extrahepatic bile ducts mimics biliary atresia. *Hepatology* 1988;8,(5):1250:A128

28. Sandler RH, Maller ES, Meyers AF, Snyder JD, Kleinman RE. Use of ursodeoxycholic acid (UDCA) for children with severe liver disease from total parenteral nutrition (TPN): Report of three cases. *Pediatric Research* 1989;25,4:726:124A

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31. Hendricks KM, Stoker T, Cunningham J, Schoenfeld DA, Caballero B, Kleinman RE. Zinc nutriture and growth failure in adolescents with Crohn's disease. *American Journal of Clinical Nutrition* 1990;51:515

32. Schreiber RA, Wang JQ, Kleinman RE. Isolation and culture of biliary epithelial cells from murine extrahepatic bile ducts. *Gastroenterology* 1992;102:A333

33. Hendricks KM, Williams E, Stoker T, Kleinman RE, Walker WA. Comparison of dietary intake in adolescent inflammatory bowel disease with and without growth failure. *Journal of the American Dietetic Association* 1993

34. Hardy SC, Young VR, Castillo L, Nurko S, Garcia-Aranda JA, Worona DL, Atkinson A, Kleinman RE. Measurement of albumin synthesis rates employing the flooding technique of stable isotope infusion in healthy young children and adults. *FASEB Journal* 1995;9;3 (Part 1), abstract 3383:A584

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36. Kleinman RE, Murphy JM, Pagano ME, Wehler CA, Little M. *Hunger and psychosocial dysfunction in low-income American children.* Massachusetts General Hospital Research Symposium, January 1996

37. Duggan C, Penny ME, Hibberd P, Gil AI, Huapaya A, Coletta F, Emenhiser C, Kleinman RE. The effects of infant cereal supplemented with oligofructose in Peruvian Infants: a randomized, double blind trial. *J Pediatr Gastroenterol Nutr* 2001; 33:396

38. Duggan C, Penny ME, Hibberd P, Gil A, Huapaya A, Coletta F, Emenhiser C, Kleinman RE. *The effects of infant cereal supplemented with oligofructose in Peruvian Infants: A randomized double-blind trial.* ASPEN, 2002

39. Penny ME, Huapaya AR, Gil A, Duggan C, Hibberd P, Kleinman RE. Iron supplementation and morbidity among toddlers in Lima, Peru. *FASEB Journal* 2002

40. Murphy M, Kleinman RE. Childhood hunger and universal school breakfast feeding Programs. *ISBNPA Journal* 2002

41. Murphy M, Anderson E, Brown J, Collins J, Agent M, Kleinman R. Five-a-day, Annual Meeting, ISBNPA, Quebec, 2003

42. Murphy JM, Lee H, Kleinman RE. Breakfast eating is related to better child health and functioning; Findings from six US school districts. International Society of Behavioral Nutrition and Physical Activity Annual meeting, Washington, DC June 10-13, 2004

43. Miller E, Canenguez K, Wieneke K, Kleinman RE, Murphy M. Screening families for hunger in community based clinics: Implementation of a hunger screening and outreach program. J Am Pub Health Assn. 2006 (in press)

44. O'Neil CE, Nicklas TA, Kleinman RE. The Relationship Among 100% Juice Consumption, Nutrient Intake, and Weight of Children 2-11 years. Pediatric Research. 2006 (in press)

Curriculum Vitae
Robert Mitchell Russell, M.D.

Address:
Place of Birt

tion:

B.A. Harvard University, cum laude, Government
M.D. Columbia University, College of Physicians and Surgeons

Postdoctoral Training and Residency:

Internship - Medicine, University of Chicago
Junior Assistant Resident - Medicine, University of Chicago
Senior Assistant Resident - Medicine, University of Chicago

NIH Fellow in Gastroenterology, University of Chicago
Summer Program - "International Food and Nutrition Policies" Massachusetts Institute of Technology

vice:

Preventive Medicine Orientation, Brooke Army Medical Center, San Antonio, Texas
Global Medicine, Walter Reed Army Institute of Research, Washington, DC.
Epidemiologist, 20th Preventive Medicine Unit, Long Binh, Vietnam, Rank of Major

(b)

Illinois #036-041801
Maryland #D18096
Massachusetts #47547
Diplomate National Board of Medical Examiners
Diplomate American Board of Internal Medicine
Diplomate American Board of Gastroenterology
Massachusettts Board of Nutritionists #595

Academic Appointments:

1974-1975	Visiting Assistant Professor of Medicine, Shiraz University, Shiraz, Iran
1975-1977	Assistant Professor of Medicine, University of Maryland School of Medicine
1977-1981	Associate Professor of Medicine, University of Maryland School of Medicine
1981-1988	Associate Professor of Medicine, Tufts University School of Medicine
1982-1988	Adjunct Associate Professor of Nutrition,Tufts University School of Nutrition
1988-	Professor of Medicine and Professor of Nutrition, Tufts University

Hospital and Research Appointments:

1975-1981	Staff Physician, Department of Medicine, Section of Gastroenterology, University of Maryland Hospital, and Veterans Administration Hospital, Baltimore, MD
l98l-	Director of Human Studies, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA
1981	Staff Physician Department of Medicine, Sections of Gastroenterology and Clinical Nutrition, New England Medical Center, Boston, MA
1983-2001	Associate Director, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA (Acting Director 12/83-3/84) (1/85-10/86)
1987-	Senior Scientist, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA
1988-	Staff Physician, Nutrition Support Service, New England Medical Center, Boston, MA
1997-	Clinical Laboratory Director, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA
2001-	Director, USDA Human Nutrition Research Center on Aging, Tufts University

Awards and Honors:

1971	Association of United States Army Award, Global Medicine
1974	Chicago Society of Gastroenterology, Research Award
l979-1981	Clinical Investigatorship, Veterans Administration Career Development Program
1991-1992	United States Department of Agriculture-Agriculture Research Service Outstanding paper of the year
1994	Grace A. Goldsmith Award, American College of Nutrition
1995	Ethyl Austin Martin Distinguished Lecturer in Human Nutrition
1997	George Randolph and Patricia Scott Award, Mayo Clinic
1997	Willard Visek Award, University of Illinois
1999	Robert H. Herman Award, American Society of Clinical Nutrition
1999	Distinguished Lecturer - American College of Physicians, “Nutrition Update”
1999	Charles Brown Award in Geriatrics, Temple University
1999	Oliver Smith Award, New England Medical Center
2005	DSM Human Nutrition Award for accomplishments in the field of retinoid and carotenoid metabolism, Durban, So. Africa
2007	Fellow, American Societies of Nutrition

National and International Committee Appointments:

l974-l979	Consultant, Food and Drug Administration, Panel on Review of Vitamin, Mineral and Hematinic Drug Products
l978	Consultant, National Iranian Cancer Foundation, Tehran, Iran
l980-1984	Member, Committee on Nutrition Research, American Society for Clinical Nutrition
l980-1984	Chairman, Council on Nutrition and Gastroenterology, American College of Nutrition
l98l-1989	Secretary-Treasurer, American College of Nutrition
l981-1995	Board of Directors, American College of Nutrition
1982	Ad hoc Member, National Digestive Diseases Advisory Board
1983-1988	Member, Council on Aging, American Gastroenterological Association
1984	Member, U.S./Japan Malnutrition Panel, ad hoc Advisory Committee
1984-1985	Chairman, Program Committee, American Society of Clinical Nutrition
1984-1985	Chairman, Council of Gerontology, American College of Nutrition.
1985	Ad hoc Member, Federation of American Societies for Experimental Biology Expert Panel on Vitamin A Nutriture
1985	Member, Advisory Panel on Nutrition and Electrolytes, United States Pharmacopeia Convention, Inc
1985-1994	Member, International Advisory/Technical Board, Center for Studies of Sensory Impairment, Aging, and Metabolism, Guatemala City, Guatemala
1986-1989	Governing Board, GI Gerontology Research Group, American Gastroenterology Association (Chairman 1989)
1987-1991	National Dairy Council Scientific Advisory Board (Chairman 1990)
1987	Ad hoc Member, Committee on Parenteral and Enteral Nutrition Standards for Long Term Nutrition Care. American Society of Parenteral and Enteral Nutrition
1987	Member, American Institute of Nutrition Nominating Committee
1988-1994	Chairman, Agriculture Research Service, US Department of Agriculture, Human Subjects Research Committee
1989	Member, NIH Consensus Development Panel on Therapeutic Endoscopy and Bleeding Ulcers
1989	Advisory Board, Post Center for Nutrition and Health Education
1989-1992	Member, Graduate Nutrition Education Committee, American Institute of Nutrition (AIN)
1989-1999	Speakers Bureau, National Dairy Council Visiting Professorship Program in Nutrition
1990	Nominating Committee, American Gastroenterology Association-Growth, Development and Nutrition Section
1990-1992	Pretest Committee, American Board of Internal Medicine
1991	UNICEF Consulting Team-Southern Iraq
1992-1994	The American Society for Clinical Nutrition, Council Liaison to the Publications Management Committee
1992-1995	Councilor to the American Society for Clinical Nutrition
1994	Consultant, Biosphere 2
1995	Program-Chair, American Society for Clinical Nutrition Annual Meeting

1995-2000	Member, Steering Committee and Meeting Chairman (1997), Carotene Research Interaction Group (CARIG)
1995-1998	Councilor to the American College of Nutrition
1996	Consultant on Nutrition Fraud - Federal Trade Commission
1996	Committee on Dietary Guidelines, American Cancer Society
1996-1998	American Dietetic Association - Older Americans Campaign Expert Advisory Committee
1996-2001	Board Member, External Advisory Committee, University of Illinois at Urbana-Champaign, University of Nutritional Sciences
1996-1997	FANSA Ad Hoc Working Group on Dietary Supplements. American Institute of Nutrition
1996-1998	Panel Member on Folate and other B Vitamins, Food and Nutrition Board - Institute of Medicine, National Academy of Sciences.
1996-1999	United States Department of Agriculture Scientific Review Board for the Lower Mississippi Delta Nutrition Intervention Research Initiative (Delta NIRI)
1997-1999	International Scientific Committee (ISC) - Auvergne Human Nutrition Research Center. Clermont-Ferrand, France
1997-1999	Advisory Board - Genetic Studies on Vitamin A: Metabolism and Function, Columbia University College of Physicians & Surgeons
1998	Member, Joint WHO/Tufts University Consultation on Nutrition Guidelines for the Elderly
1998-2003	Member, Awards Committee, American College of Nutrition
1998-2000	Chairman, Steering Committee, Carotene Interaction Group (CARIG)
1998-2000	Chairman of Panel on Micronutrients, Food and Nutrition Board, Institute of Medicine, National Academy of Science
1998	Consultant National Technology Transfer Committee, Boston, 1998
1999-2005	Member, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Vice Chair (2000-2005)
1999	Member, U. S. Administration on Aging, Nutrition 2030 Expert Advisory Council
1999-2001	Member, AGA Task Force on Geriatrics
1999-2003	Member, Food and Drug Administration Center for Food Safety and Applied Nutrition's Food Advisory Committee
2001-2002	Vice-President, American Society of Clinical Nutrition
2000-2004	Member, Board of Directors, Life Sciences Research Office, Inc.
2000-2004	Chairman, Expert Committee on Nutrition and Electrolytes, U.S. Pharmacopeia, and Member Council of Experts
2002-2005	American Gastroenterology Asssociation Committee on Public Affairs and Advocacy
2001-	Golden Rice Humanitarian Advisory Board
2001-2005	DRI Standing Committee, IOM, NAS
2002	NIH (NIDDK) Boundary Team member
2002-2004	Board Member, Sight and Life Research Institute, Johns Hopkins School of Medicine
2002-2003	President, American Society of Clinical Nutrition
2003-	Councilor, International Carotenoid Society
2003-2004	ASNS/ASCN/SINR Guiding Coalition

2004-2005	Member, Long Range Planning Committee, American Society of Clinical Nutrition
2004-2006	Trustee, International Life Science Institute
2004-2006	Chair, United States National Committee to the International Union of Nutritional Sciences. Food & Nutrition Board, IOM
2004	Member, Department of Defense Committee on Optimization of Nutrient Composition of Assault Rations. Food & Nutrition Board, IOM
2004	Scientific Review Panel for the 2005 Dietary Guidelines for Americans
2005-	Member, External Advisory Committee for the Harvard Clinical Nutrition Reasearch Center
2005-2006	Chair, Committee on Mineral Requirements for Cognitive & Physical Performance of Military Personnel. Food & Nutrition Board, IOM
2005-2006	Chair, Food and Nutrition Board, IOM, National Academy of Science
2007	Member, Planning Committee for Revisions to the Dietary Reference Intakes, IOM National Academy of Science

University/Local Committee Appointments:

l972-l974	Hyde Park Kenwood Community Conference, Chicago, IL
1976-l980	Member, Committee on Human Nutrition Education, University of Maryland School of Medicine, Baltimore, MD (Chairman, 1980-1981)
l976-l98l	Member, Nutrition Care Committees,VA Medical Center and University of Maryland Hospital, Baltimore, MD.
l980-l98l	Course Director, Basic Human Nutrition,University of Maryland School of Medicine, Baltimore, MD
l98l-1988	Member, Committee on Human Nutrition Education, Tufts University School of Medicine, Boston, MA.
l98l-1988	Member, Tufts New England Medical Center Clinical Study Unit Advisory Committee, Boston, MA
l983-1988	Member, Board of Advisors, Georgia Institute of Human Nutrition
l983	Co-Director, Clinical Nutrition Course, Tufts University School of Medicine, Boston, MA, and School of Nutrition Science and Policy, Medford, MA
1985-1988	Member, Famine Policy Center Committee, Tufts University School of Nutrition Science and Policy.
1985-1988	Member, Health Sciences Campus Planning Committee, Tufts University School of Nutrition Science and Policy
1985-1987	Board of Directors, Frances Stern Nutrition Center, Tufts New England Medical Center Hospitals, Boston, MA
1985-2001	Chairman, Human Studies Committee, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA
1991	Chairman, Task Force on Nutrition Organization at Tufts University School of Nutrition Science and Policy, Medford, MA
1993	Chairman, Scientific Appointments and Promotions Committee, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA and Tufts University School of Nutrition Science and Policy Medford, MA
1994-	Member, Finance and Fund Raising Committee, Tufts University School of Nutrition Science and Policy, Medford, MA. Chairman, 2000-2003

1994-1999	Chairman, Committee on Committees, Tufts University School of Nutrition Science and Policy, Medford, MA., Member, 2000
1999-	Chairman, Brenda and Mathew Ross Aging Initiative, Tufts University
2000-2002	Faculty Representative, Tufts University Trustees' Development Committee
2003-2004	Chairman, Search Committee for Dean, Friedman School of Nutrition Science and Policy, Tufts University
2004-	Member, General Clinical Research Center Advisory Committee of Tufts-New England Medical Center
2004-2005	External Scientific and Program Advisory Committee of Tufts University School of Dental Medicine

Editorial Boards:

1973-	Contributing Editor - Nutrition Reviews (*Associate Editor* 1985-2001, Editor in Chief 2001-)
1982-1989	Editorial Board - Journal of the American College of Nutrition
1983-1986	Editorial Board - Tufts University Health Science News
1983-	Editorial Board - Tufts Health and Nutrition News Letter
1986-1991	Advisory Board Member - Contemporary Issues in Clinical Nutrition
1989-1993	Editorial Board - Rx Nutrition (Physician Continuing Education Program) 1989- Editorial Board - Age and Nutrition
1997-2003	Editor-in-Chief - Nutrition and Clinical Care
1997-	Editorial Board - Nutrition Today
1998-	Editorial Board - American Journal of Clinical Nutrition
1998-2003	Editorial Board - Cyberounds Nutrition Website
1998-2003	Editorial Board - Nutrition Commentator Website
1998-	Editorial Board - European Journal of Nutrition
1998-2004	Associate Editor – Digestive Health and Nutrition
1999	Co-Editor - Present Knowledge in Nutrition, 8th Edition
2001-2007	Associate Editor- American Journal of Clinical Nutrition
2001-	Editor-in-Chief – Nutrition Reviews
2006	Co-Editor- Present Knowledge in Nutrition, 9th Edition
2007-	Associate Editor- Molecular Aspects of Medicine

Memberships:

1978-	American College of Nutrition (Fellow)
1978-2006	American Society of Clinical Nutrition
1979-1983	International Association for the Study of the Liver
1979-	American Society of Nutrition (Formerly AIN, ASNS, ASCN)
1981-2005	American Gastroenterological Association
1982-1986	Massachusetts Medical Society
1982-2003	American College of Physicians (Fellow)
1990-2006	Society for International Nutrition Research
1999-2004	American Aging Association
2002-2004	Association for Patient-Oriented Research

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Publications – Original Journal Articles

1. Sowell JM, Russell RM, Ionata VJ. Tuberculin tine test conversion among United States Army enlisted personnel in Vietnam. Military Medicine l973;l38(2):96-98.

2. Russell RM, Multack R, Smith V, Krill A, Rosenberg IH. The use of dark adaptation as a reversible indicator of subclinical vitamin A deficiency in patients with chronic small intestinal disease. Lancet l973;2:ll6l-ll64.

3. Neumann H, Moran E, Russell RM. The appearance of a distinct alkaline phosphatase in the serum of patients with lymphatic leukemia and infectious mononucleosis. Science l974;l86:l5l-l53.

4. Russell RM, Boyer JL Bagheri S, Hruban Z. Hepatic toxicity from chronic hyper-vitaminosis A unique morphologic lesion resulting in portal hypertension and ascites. N Eng J Med 1974;29l:435-440.

5. Hruban Z, Russell RM, Boyer JL, Glagov S, Bagheri SA. Ultrastructural changes in livers of two patients with hypervitaminosis A. Am J Pathol l974;76:45l-46l.

6. Russell RM, Ismail-Beigi F, Afrasiabi K, Rahimifar M, Pourkamal D, Ronaghy H. Folate levels among various populations in central Iran. Am J Clin Nutr l976;29:794-798.

7. Russell RM, Ismail-Beigi F, Reinhold J. Folate content of Iranian breads and the effect of their fiber content on the intestinal absorption of folic acid. Am J Clin Nutr l976;29:799-802.

8. Russell RM, Abadi P, Ismail-Beigi F. Role of bacterial overgrowth in malabsorption syndrome of primary small intestinal lymphoma. Cancer l977;39(6):2579-2583.

9. Morrison SA, Russell RM, Carney EA, Oaks EV. Zinc deficiency: A cause of abnormal dark adaptation in cirrhotics. Am J Clin Nutr l978;3l(2):276-28l.

10. Posner D, Russell RM, Absood S, Connor T, Norris A, David C, Martin L. Effective hydroxylation of vitamin D2 in alcoholic cirrhosis. Gastroenterology 1978;74:866-870.

11. Russell RM, Morrison SA, Smith FR, Oaks EV, Carney EA. Vitamin A reversal of abnormal dark adaptation in cirrhosis. Study of effects on the plasma retinol transport system. Annals Int Med l978;88(5):622-626.

12. Russell RM, Dahr JD, Dutta SK, Rosenberg IH. Influence of intraluminal pH on folate absorption: Studies in control subjects and in patients with pancreatic insufficiency. J Lab Clin Med l979;93:428-436.

13. Williams RB, Russell RM, Dutta SK, Giovetti AC. Alcoholic pancreatitis - patients at high risk of acute zinc-deficiency. Am J Med l979;66:889-893.

14. Neumann H, Russell RM, Klein E, Epstein S. N-phosphatase: A disease marker for lymphoproliferative disorders. Brit J Haematology l979;4l:5l9-532.

15. Dutta SK, Russell RM, Iber FL. Influence of exocrine pancreatic insufficiency on the intraluminal pH of the proximal small intestine. Dig Dis Sci l979;24(l0):529-534.

16. Dutta SK, Russell RM, Iber FL. Impaired acid neutralization in the duodenum in pancreatic insufficiency. Dig Dis Sci l979;24(l0):775-780.

17. Nalin DR, Russell RM, Levine MM, Garrett M. Reduced vitamin A (vA) absorption after enteric infections. Current Chemotherapy and Infectious Disease (Proceedings of the llth International Congress of Chemotherapy and the l9th Interscience Conference on Antimicrobial and Chemotherapy) l979;ll:947-948.

18. Russell RM, Dutta SK, Rosenberg IH, Giovetti AC. Impairment of folic acid absorption by pancreatic enzymes. Dig Dis Sci l980;25(5):369-373.

19. Dutta SK, Russell RM, Chowhury B, Oaks EV. Folate content of North Indian breads. Nutr Rep International l980;2l(2):25l-256.

20. Rogers EL, Douglass W, Russell RM, Bushman L, Hubbard TB, Iber FL. Fat soluble vitamins after jejunoileal bypass surgery for morbid obesity. Am J Clin Nutr. l980;33(6):1208-1214.

21. Bushman L, Russell RM, Warfield RD, Curry G, Iber F. Malnutrition among patients in an acute care veterans' facility. J Am Dietetic Assoc l980;77:462-465.

22. Russell RM, Carney EA, Feiock K. Acute ethanol administration causes transient blue-yellow color blindness. Alc Clin Exp Res l980;4(4);396-399.

23. Carney EA, Russell RM. Correlation of dark adaptation test results with serum vitamin A levels in diseased adults. J Nutr l980;110(3):552-557.

24. Campbell TB, Sampliner RE, Russell RM, Garrett MS. Night driving (mesopic) visual acuity in sober alcoholics with and without liver disease. Alc Clin Exp Res l98l;5(l):34-37.

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Li L, Rasmussen, H, Qin J, Yin S, Tang G, Russell RM. The correlation between intakes of vitamin A and total-body vitamin A stores assessed by the labeled-retinol-dilution method in American adults. FASEB J 2007 (submitted).

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Education:

A.B., (Chemistry), University of Nor
M.D., University of North Carolina,

Fellowships:

Public Health Service Postdoctoral Research Fellow, Department of Pharmacology, University of North Carolina, 1955-1958
National Institutes of Health Special Fellow, Department of Pharmacology, Royal Veterinary College, Stockholm, Sweden, 1965-1966
Scholar, Sloan Foundation, Health Sciences Consortium, 1974-1975

Academic Appointments:

Assistant Professor of Pharmacology, School of Medicine, University of North Carolina, 1958-1962
Associate Professor of Pharmacology, School of Medicine, University of North Carolina, 1962-1972
Associate Professor of Oral Biology, Dental Research Center, University of North Carolina, 1967-1969
Professor of Oral Biology, Dental Research Center, University of North Carolina, 1969-1972
Professor of Pharmacology, College of Medicine, University of Kentucky, 1972-1976
Professor of Oral Biology, College of Dentistry, University of Kentucky, 1972-1976
Adjunct Professor of Pharmacology, School of Medicine, University of Louisville, 1972-1976
Adjunct Professor of Pharmacology, College of Medicine, University of Kentucky, 1977-
Professor of Pharmacology and Toxicology, School of Medicine, University of Louisville, 1977-1998
Emeritus Professor of Pharmacology and Toxicology, School of Medicine, University of Louisville, 1998-
Visiting Professor of Pharmacology and Toxicology, Schools of Medicine and Pharmaceutical Sciences, Showa University, Tokyo, Japan, November 1983-May 1984

Honors:

Centennial Alumnus Distinguished Visiting Professor, School of Medicine, University of North Carolina, February, 1979

Administrative Appointments:

Associate Division Director, Center for Research in Pharmacology and Toxicology, University of North Carolina, 1966-1967
Associate Director, Dental Research Center, University of North Carolina, 1968-1972
Director of Graduate Studies in Pharmacology, University of Kentucky, 1974-1976
Chairman, Department of Pharmacology and Toxicology, University of Louisville, 1977-1997
Emeritus Chairman, Department of Pharmacology and Toxicology, University of Louisville, 1997-

Society Memberships:

American Physiological Society, 1973-
American Society for Pharmacology and Experimental Therapeutics, 1958-
American Teratology Society, 1968-
Association for Medical School Pharmacology, 1977- (Secretary 1986-1988; President 1988-1990)
Sigma Xi, 1958-
Society for Experimental Biology and Medicine, 1956-
Society of Toxicology, 1978-
Ohio Valley Chapter of Society of Toxicology, 1983- (President 1983-84)
Royal Microscopical Society, 1986-
International Society for the Study of Xenobiotics, 1989-
Fellow, Academy of Toxicological Sciences, 1992-

Consultant:

Research Triangle Institute, 1965-1972
Block Drug Company, 1968-1972
Becton, Dickinson and Company, 1971-1972
Baxter-Travenol Laboratories, 1974-1980
Faculty of Medicine, University of Kuwait, 1977-
Baby Products Company, Johnson and Johnson, 1977-1982
Procter and Gamble, 1978-1998
Allied Chemical, 1978-1982
American Cyanamid, 1981-1987
Dow Chemical, 1981-1986
R. J. Reynolds Industries, Inc., Scientific Advisory Board, 1985-1988 (Chairman 1987-1988)
CA Blockers, Inc., 1987-1989
Grain Processing Corporation, Inc., 1988-
Norwich Eaton Pharmaceuticals, Inc., 1988-1998
Distilled Spirits Council of the United States, Inc., 1989-
National Food Processors Association, 1995-1998

Board of Directors:

Computer Assisted Teaching Systems (CATS) Consortium, 1977-1983
Pharmacon Research Foundation, Inc. (Chairman), 1979-

Editorial Board:

Drug Metabolism and Disposition, 1972-1993
Toxicology and Applied Pharmacology, 1981-1989
Human and Experimental Toxicology, 1993-
Toxicologic Pathology, 1997-

University of Kentucky Committees:

College of Medicine Second Year Curriculum (Chairman), 1973-1975
College of Medicine Second Year Promotions, 1973-1975
College of Medicine Educational Policy, 1972-1976
College of Medicine Pharmacy and Therapeutics, 1972-1976
Student Evaluation and Academic Policy for Second Year (Chairman), 1975-1976
Academic Area Advisory Committee for Biological Sciences, 1974-1976 (Chairman, 1975-1976)
Graduate School Fellowships for Biological Sciences, 1974-1976 (Chairman, 1975-1976)
Ad Hoc Committee to Review College of Pharmacy (Chairman), 1976
Ad Hoc Committee to Review Institute of Environmental Sciences, 1976

University of Louisville Committees:

School of Medicine Biomedical Hazards Committee (Chairman), 1977-1983
School of Medicine Institutional Self-Study Task Force for LCME Accreditation (Chairman), 1979-1980
School of Medicine Radiation Safety Committee (Chairman), 1980-1983
Cancer Center Advisory Committee, 1978-1983
Biological Hazards Committee, 1980-1983

Commonwealth of Kentucky Committees:

Kentucky Drug Formulary, 1977-1981
Kentucky Tobacco and Health Institute Technical Advisory Committee, 1977-1983
Kentucky Medical Assistance Program, 1978-1981
Kentucky Heart Association Research Review Committee, 1980-1981

National Committees:

Guidelines for Detection of Hepatotoxicity Due to Drugs and Chemicals; Fogarty International Center, 1978
Reproductive Effects Assessment Group (Teratology); Environmental Protection Agency, 1980
Educational Affairs Subcommittee of ASPET: New Approaches to Teaching Pharmacology, 1980-1983
ASPET/S0T 1982 Joint meeting in Louisville, Local Committee Chairman
National Committees (cont.):
Educational Affairs Committee of ASPET, Chairman, 1983-1986

Society of Toxicology Committee on Information Handling, 1986-1988
FASEB Education Committee, 1986-1989
Texas Coordinating Board, review of teaching programs, 1983, 1985, 1987, 1990
TLV Committee, American Conference of Governmental Industrial Hygienists, 1995-1998; Chairman, MISCO Subcommittee, 1996-1998.
Chairman, Science Panel, Center for the Study of Environmental Endocrine Effects, 1995-1998.
Epidemiology in Hazard and Risk Assessment: Expert Panel Review of the "London Principles", 1998-1999.
Flavor and Extract Manufacturers' Association of the United States, Expert Panel, 1999-Chairman, 2005-

International Committees:

Alfred Benzon Symposium III, Copenhagen and Lund, Ion Homeostasis of the Brain, May, 1970
International Agency for Research on Cancer, Alcohol Drinking, Lyon, France, October, 1987
International Life Sciences Institute, Ethyl Carbamate, Brussels, Belgium, June, 1989

Invited Lectures:

More than 100 in North America, Europe, Middle East, China, Japan, Korea, Australia, New Zealand, and Thailand

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Publications

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SUMMARY OF DATA CONCERNING THE SAFETY OF OLESTRA FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES

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DOCUMENTATION SUPPORTING THE EVALUATION OF OLESTRA AS GENERALLY RECOGNIZED AS SAFE (GRAS) FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES

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List of Abbreviations

ADME	absorption, distribution, metabolism and excretion
ALT	alanine aminotransferase
AST	apartate aminotransferase
CCK	cholecystokinin
CH_4	Methane, Natural Gas
CHO	chinese hamster ovary
CO_2	Carbon Dioxide
CSFII	Continuing Survey of Food Intakes by Individuals
GD	gestational day
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GRAS	Generally Recognized as Safe
FCC	Food and Chemicals Codex
H^+	Hydrogen ion
MAC_s	microbiota-associated characteristics
MCV	mean corpuscular volume
MRCA	Market Research Corporation of America
NOAEL	no-observed-adverse effect levels
NRC	National Research Council
OA	olestra
OPMSS	Olestra Post-Marketing Surveillance Study
P&G	Procter & Gamble
RBC	red blood cell
RBHD	refined, bleached, hydrogenated, and deodorized
SCFA	short-chain fatty acids
SPE	sucrose polyester
UDS	unscheduled DNA syntesis
USDA	United States Department of Agriculture
U.S. FDA	United States Food & Drug Administration
VO	vegetable oil

DOCUMENTATION SUPPORTING THE EVALUATION OF OLESTRA AS GENERALLY RECOGNIZED AS SAFE (GRAS) FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES

1.0 INTRODUCTION

Olestra is a sucrose polyester (SPE) that has been developed by The Procter & Gamble Company (P&G) for use as a fat replacement. Olestra is formed by the reaction of sucrose with medium- and long-chain fatty acid esters obtained from edible fats and oils. Current uses of olestra that have been approved by the U.S. Food and Drug Administration (U.S. FDA) include as a fat substitute in pre-packaged ready-to-eat savory snacks (*i.e.*, salty or piquant, but not sweet) and pre-packaged ready-to-heat, unpopped popcorn kernels.

P&G proposes to expand the uses of olestra to include use in pre-packaged ready-to-eat cookies. Under U.S. law, this can be achieved through the U.S. FDA Generally Recognized as Safe (GRAS) process. The GRAS status of a substance must be defined as having use in foods prior to January 1, 1958, or must be determined by scientific procedures. As olestra was not common to foods prior to the above date, it is being evaluated through scientific procedures demonstrating technical evidence of safety. For a substance to be determined GRAS by scientific procedures, a panel of experts qualified to assess the safety of food ingredients must evaluate the data and be of the opinion that the ingredient would be safe under this intended use.

The purpose of this dossier is to outline the identity, manufacture, and intended conditions of use of P&G's olestra, to estimate the consumption of olestra through the intended use, to document the literature regarding the safety of olestra (including evaluation of both toxicological and nutritional considerations), and to assess the safety of olestra under the conditions of intended use. To obtain the necessary information to support the safety of olestra, an exhaustive evaluation of the multitude of published and unpublished studies available for olestra was conducted. In addition to studies provided by P&G, detailed searches of published scientific databases including, Medline, Biosis Previews, Toxline and Embase were conducted to identify literature in the public domain. P&G supplied information regarding ingredient composition, product formulation, and the manufacturing process. The U.S. FDA opinions regarding the approved uses of olestra were also reviewed.

1.1 Variations in Physical States of Olestra

SPEs, a broad group of chemically synthesized compounds in which the sucrose molecule has been esterified with up to 8 fatty acids, were first developed by research scientists at P&G in 1968. Olestra is a specific type of a SPE blend with set specifications, which differentiate it from other mixtures of SPEs. The official specifications for olestra adopted following its approval by the U.S. FDA as a food additive for use in savory snacks, are published in the Food and Chemicals Codex (FCC, 2006) and are presented below in Table 1-1. Olestra, as defined by the FCC specifications, is a mixture of SPEs comprised predominantly of octa-esters, and only small quantities of hexa- or penta-esters of long-chain fatty acids and sucrose. The physical state of the olestra mixture, whether liquid, semi-solid, or solid, is determined by several of the specification parameters including the ester distribution and the length and degree of saturation of the fatty acids. By altering these factors, olestra formulations of variable stiffnesses can be formulated for different purposes. For example, increasing the degree of saturation, fatty acid chain length, or percent of octa-esters will result in an olestra product of greater stiffness. However, since the set of specifications for olestra is not comprised of absolute values, but rather acceptable ranges of values or minimum or maximum levels, it accommodates such variance and allows for a wide range of olestra products, in some cases differing in physical appearance, which comply with the FCC specifications.

Table 1-1 Chemical Specifications for Olestra

Specification Parameter	Specification	Method
Identification		
Fatty Acid Distribution		
C12	≤1%	FCC (2003)
C14	≤1%	FCC (2003)
C16 to C18	≥78%	FCC (2003)
C20	≤20%	FCC (2003)
Unsaturated fatty acids	25-83%	FCC (2003)
Ester Composition		
Octa-ester	≥70%	FCC (2003)
Hexa-ester	≤1%	FCC (2003)
Penta-ester	≤0.5%	FCC (2003)
Purity		
Assay	≥ 97% of combined octa-, hepta-, and hexa-esters of sucrose	FCC (2003)
Free Fatty Acids	≤ 0.5%	FCC (2003)
Lead	≤ 0.1 mg/kg	FCC (2003)
Methanol	≤ 300 mg/kg	FCC (2003)
Peroxide Value	≤ 10 meq/kg	FCC (2003)
Residue on Ignition	≤ 0.5%	FCC (2003)

Table 1-1 Chemical Specifications for Olestra		
Specification Parameter	**Specification**	**Method**
Thixotropy (Stiffness)*	≥ 50 kPa/s	FCC (2003)
Water	≤ 0.1%	FCC (2003)

Specification values taken from FCC (2003)
* Samples of olestra tested for thixotropy (stiffness) are prepared according to the method detailed in the Food and Chemicals Codex (FCC, 2003). The analysis of the samples of olestra prepared with soybean or cottonseed oil demonstrated that the manufactured lots adhered to the chemical specifications for olestra described in Table 1-1.

During the course of olestra's development, P&G formulated various mixtures of SPEs with varying ester distributions and fatty acid compositions, some of which do while others do not meet current FCC specifications. In assembling the data related to the safety of olestra, studies conducted with various mixtures of SPEs were identified, including those conducted with mixtures that fall outside the scope of the current FCC specifications. Since P&G developed and tested different blends of SPEs over time, it was critical to determine the appropriateness of including some of these studies in an evaluation of olestra safety particularly when the ester and fatty acid distributions are crucial determinants of the metabolic fate of olestra. Briefly (for further discussion see Section 6.2), highly esterified SPEs (*i.e.*, hexa-, hepta-, and octa-esters) are not hydrolyzed by gastrointestinal (GI) lipases, nor are they absorbed intact in any measurable/quantifiable amounts. Accordingly, given the lack of systemic absorption, these larger SPEs are not expected to induce any toxicity following oral consumption. While the bulkiness of the larger sucrose esters prevents their hydrolysis, less esterified sucrose molecules are hydrolyzed resulting in the release of sucrose and free fatty acids. However, the absence of any adverse effects in studies conducted with materials containing greater proportions of sucrose esters with lower degrees of esterification further supports the safety of olestra, which primarily consists of larger esters. Hence, the results of these studies also were included in the discussion of olestra safety, even though the test material did not always conform to the FCC specifications, as these studies with lower-end esters are representative of worst-cases scenarios with regard to potential absorption and toxicity.

In some of the earlier animal and human studies conducted with liquid mixtures of SPEs, anal leakage was observed following oral administration of the test material. It was subsequently determined that the incidence of anal leakage was significantly attenuated with SPE formulations that were semi-solid, as opposed to liquid, at body temperature. Consequently, in addition to fatty acid composition and ester distribution, thixotropy as a rheological measure of stiffness also was included in the specifications for olestra. Since many of the animal studies and some of the earlier human trials were conducted prior to the adoption of this specification parameter, thixotropy of the test material was often not reported. However, as already discussed, differences in the physical state of olestra are achieved by minor alterations in a combination of different parameters. As such, many of these liquid formulations still meet the existing FCC specification in so far as fatty acid composition and ester distribution. Moreover, distinctions in the composition of olestra, such as fatty acid length, which dictate the physical

properties of a certain blend, are not expected to impact on the overall safety of the test material. In fact, considering that the absence of olestra-related toxicity is in part due to its lack of systemic absorption as a result of the inability of enzymes to hydrolyze the esters, increasing the size of the molecules in an effort to increase stiffness would further enhance the bulkiness of the esters making them all the more difficult for enzymes to digest. Nevertheless, it also should be noted that the pivotal human clinical trials were conducted with test materials that comply with the FCC specifications for olestra in all respects.

An additional complication encountered when compiling the safety data for olestra was related to the nomenclature used to describe a test material. Since olestra as presently defined is a sub-type of the broader class of SPE compounds, some of the earlier studies discussed in this dossier, which were conducted prior to the adoption of the official olestra specifications, referred to the test material as SPEs rather than olestra, *per se*, even though the specifications for the SPE blend comply with those for olestra. Conversely, some studies also were identified where the olestra designation was applied inappropriately in reference to a test material, which does not meet present-day FCC specifications. For consistency with the corresponding publication or unpublished study report, the nomenclature designated by the study authors to describe the test material was retained in the discussion of the studies in this evaluation of olestra safety. However, in cases where it was determined that a test material referred to as SPEs actually meets the FCC specifications for olestra, this has been noted in the summary of the study results and, vice versa, in cases where the test material did not comply with the FCC specifications, but was called olestra by the study authors, this also has been indicated in the dossier.

1.2 Regulatory Requirements for GRAS Determination

The GRAS determination is based upon scientific procedures, which, according to the *Proposed Rule*, requires that information about the substance(s) demonstrates that there is reasonable certainty in the minds of competent scientists that the substance(s) is not harmful under the intended conditions of use. Table 1-2 outlines the applicable sections, subsections, and specific requirements of the *Proposed Rule* published in the *Federal Register, April 17, 1997* (U.S. FDA, 1997).

In accordance with the specific requirements outlined in the *Proposed Rule*, the present report provides the necessary information to support an evaluation of the GRAS status of olestra, based on scientific procedures, by a panel of qualified experts.

Table 1-2 Subset of Requirements for Generally Recognized as Safe (GRAS) Determination by Scientific Procedures	
Proposed Section	**Specific Requirements**
Identity and Specifications: §170.36(c)(2) (U.S. FDA, 2006c)	"…requires that the notice include detailed information about the identity of the notified substance, including, as applicable, chemical name, Chemical Abstract Service (CAS) registry number, empirical formula, structural formula, quantitative composition, method of manufacture (excluding any trade secrets), characteristic properties, any potential human toxicants, and specifications for food-grade material." Source and quantitative composition may appropriately describe a substance for which a chemical formula cannot be used for identification.
Self-Limiting Levels of Use: §170.36(c)(3) (U.S. FDA, 2006c)	"…requires that the notice include any self-limiting levels of use of the substance."
Technical Evidence of Safety: §170.36(c)(4)(i)(A) (U.S. FDA, 2006c)	"…requires that the notice include a detailed summary of the basis for the notifier's determination that a particular use of the substance is GRAS through scientific procedures. This summary would include a comprehensive discussion of, and citations to, generally available and accepted scientific data, information, methods, or principles that the notifier relies on to establish safety…" "…specifies that the discussion in the notice summary include a consideration of the probable consumption of the substance and the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substances in such diet…"
Basis for Concluding Expert consensus: §170.36(c)(4)(i)(C) (U.S. FDA, 2006c)	"…requires that the notice summary of a scientific procedures GRAS determination include the basis for concluding, in light of the data and information described in the notice, that there is a consensus among qualified experts that there is reasonable certainty that the substance is not harmful under the intended conditions of use.

2.0 SUMMARY OF CHEMISTRY

The common or usual name of this product is “olestra”. Olestra (CAS No. 121854-29-3) is composed of a mixture of hexa-, hepta-, and octa-esters of sucrose with medium- and long-chain fatty acids. The name of the product is descriptive with the “ol” portion representing olein, an ester of glycerol and oleic acid (*i.e.*, the liquid portion of fat) and “estr” portion making reference to the chemical form of the product (*i.e.*, an ester). In commerce the product is referred to as “Olean”.

Olestra is formed by the reaction of sucrose with medium- and long-chain fatty acid esters obtained from edible fats and oils. A typical preparation of olestra consists of approximately 75 or 77±5% octa-, 23% hepta-, and 2% hexa-ester with an average molecular weight of approximately 2,400 daltons. The chemical structure of olestra is illustrated in Figure 2-1.

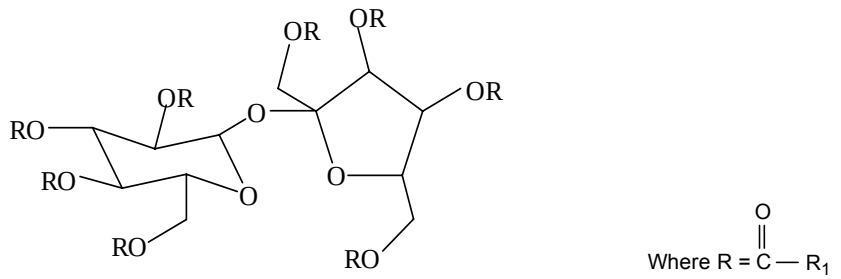


Figure 2-1 Structural Representation of Olestra

R_1 = fatty acyl groups with carbon chain lengths of C_8 to C_{22}

The physical properties of olestra are similar to the fats and oils from which olestra is formed and can be varied based on the selection of the fatty acids used for esterification and through hydrogenation. Olestra is principally formed through the esterification of C_8 to C_{22} fatty acids typically present in edible fats and oils (hydrogenated and unhydrogenated) including, but not limited to caprylic (8:0), capric (10:0), lauric (12:0), myristic (14:0), palmitic (16:0), stearic (18:0), oleic (18:1), linoleic (18:2n-6), linolenic (18:3n-3), arachidic (20:0), and behenic acids (22:0).

The physical properties of sucrose octa-esters in α- and β-like phases were examined and compared to the physical properties of triglycerides with the same fatty acid composition as the sucrose octa-esters. Jandacek and Webb (1978) determined various physical properties (*e.g.*, polymorphism, heat of fusion, melting of binary systems, refractive index, viscosity, density, and interfacial tension) of essentially homogenous sucrose octa-esters of caprylic, capric, lauric, myristic, palmitic, stearic, oleic, elaidic, and linolenic and compared them to the individual triglycerides. The solid phase of the sucrose octa-esters was examined using X-ray diffraction, infrared absorption, and differential scanning calorimetry, which revealed that the sucrose octa-esters had 2 distinct phases, an α-like phase (low melting) and a β-like phase (high melting).

The physical properties of the sucrose octa-esters resembled (*i.e.*, displayed similar trends with respect to changes in density, viscosity, and interfacial tension with increasing fatty acid chain length) those of the analogous triglycerides; however, slight differences were noted including the structure of the sucrose octa-ester β-like phase. The differences between the sucrose octa-esters and the analogous triglycerides were attributed to the larger size of the sucrose octa-ester molecule.

The chemical properties of olestra are essentially equivalent to those of typical triglycerides. In the presence of weak acids the ester linkages are unaffected; however, in the presence of stronger acids the ester linkages are cleaved, resulting in the formation of free fatty acids and the release of free sucrose. The free sucrose is then able to be converted to its component monosaccharides, glucose and fructose *via* acid hydrolysis. Furthermore, the exposure of sucrose to very high temperatures (*i.e.*, approximately 440°F or greater) can result in the hydrolysis of sucrose, even in a neutral environment. Exposure of olestra to alkaline conditions results in the release of its fatty acid constituents through saponification (*i.e.*, analogous to saponification reactions involving triglycerides).

Olestra is resistant to the dilute acidic environment of the stomach and the alkaline conditions of the small intestine and therefore does not undergo chemical hydrolysis within the GI tract of humans.

Olestra is able to undergo oxidative reactions in some of its fatty acid chains, similar to those that occur in triglyceride oils, when exposed to oxygen at elevated temperatures (*i.e.*, >120°F) resulting in the formation of hydroperoxides. The oxidation of olestra can result in rancidity and/or polymerization of 2 molecules of olestra leading to the formation of a dimer. The double bonds present in the constituent fatty acids of olestra would be acted upon by oxidizing agents and result in the formation of oxidized species or fragments similar to those produced by the oxidation of triglycerides composed of similar fatty acids. The degree and type of oxidation is dependent upon the fatty acids present. Furthermore, the types of byproducts formed by the oxidation of the component fatty acids is dependent upon the strength of the oxidizing agent and would be expected to include hydroperoxides, alcohols, aldehydes, and/or ketones, and shorter chain alkyl carboxylic acids.

Similar to triglycerides, olestra is soluble in organic solvents including petroleum ether, halogenated hydrocarbons, and aromatic hydrocarbons, but is insoluble in water. The use of effective emulsifiers permits the partial dispersion of olestra in water. Olestra has been described as a mixture of neutral molecules; however, the pH of olestra solutions has not been measured as olestra is insoluble in water.

3.0 SUMMARY OF MANUFACTURING AND STABILITY

3.1 Manufacturing Summary

Olestra is principally manufactured from distilled fatty acid methyl esters and sucrose with the quality of the raw materials maintained through various production controls. Other chemicals used in the production of olestra include: dimethylpolysiloxane, hydrochloric acid, methanol, nitrogen, potassium citrate, potassium carbonate, potassium stearate, sodium hydroxide solution, sodium methoxide, synthetic amporphorus silica (silicon dioxide), deionized water, and *DL-α*-tocopheryl acetate (synthetic vitamin E). Refined, bleached, hydrogenated, and deodorized (RBHD) soybean oil; refined, bleached, and hydrogenated cottonseed oil and refined, bleached and hydrogenated rapeseed oil are used as the source of fatty acid methyl esters for the production of olestra. All the vegetable oils are high purity, edible, and meet food grade specifications of the FCC.

The manufacture of olestra occurs in 2 steps:

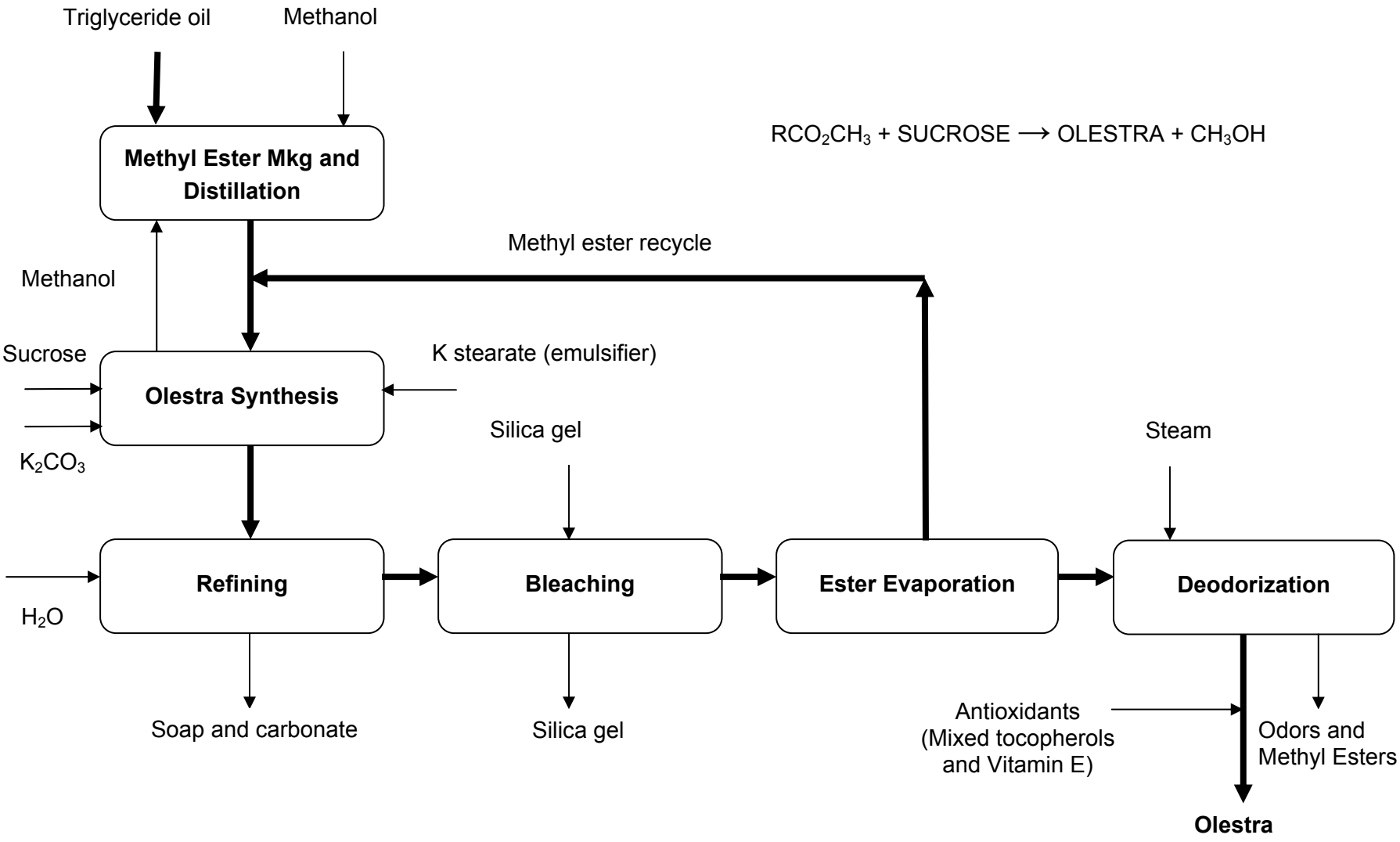
Step 1: Preparation of Methyl Esters

Methyl esters used in the production of olestra can be obtained from the methanolysis of fats and oils *via* a number of commercially available techniques. Methyl esters used by P&G in the production of olestra are obtained through the reaction of refined triglyceride oils with methanol at 145°F. The reaction is conducted in the presence of sodium methoxide, a catalyst commonly used in the esterification, interesterification, and transesterification of fats and oils. Following the completion of the reaction the resulting esters are washed with water to remove any residual methanol, dried under vacuum, and distilled at a maximum temperature of 525°F and pressure of 2 to 30 mmHg (absolute).

Step 2: Olestra Synthesis

The preparation of olestra involves the transesterification of sucrose with methyl esters of medium- and long-chain fatty acids. A schematic representation of the manufacturing process is depicted in Figure 3-1. The chemical specifications for olestra prepared *via* the process illustrated in Figure 3-1 are presented in Table 1-1.

Figure 3-1 Schematic Overview of the Manufacturing Process for Olestra



Typical levels of Vitamin E (mg/g of Vitamin E-tocopherol equivalents) present in olestra prepared with soybean oil or cottonseed oil range from 2.06 to 3.38 mg/g and 2.06 to 2.16 mg/g, respectively. The results of the analysis demonstrate that the Vitamin E level is somewhat variable in lots of olestra prepared with soybean oil; however, the lots prepared with cottonseed oil are consistent with one another. Furthermore, the level of Vitamin E (mg/g of Vitamin E-tocopherol equivalents) present in the samples of olestra is greater than the amount required by the FDA (*i.e.*, 1.9 mg -α-tocopherol equivalents/g of olestra) in all of the samples. The higher levels of α-tocopheryl acetate allow for small amounts of degradation in the processing of specific food products, yet still comply with the regulations concerning Vitamin E levels.

The production of olestra results in the formation of trace amounts of unsaponifiables including aliphatic hydrocarbons, plant sterols, and difatty ketones; however, the level of unsaponifiables in olestra have been reported to be measured at a level lower than in conventional fat with the exception of difatty ketones, which have been reported at higher levels. The formation and composition of unsaponifiables in olestra are due to the components and conditions used in the synthesis of olestra. The hydrocarbons and sterols present in olestra are similar to those present in conventional fats from which the fatty acids used to manufacture olestra are derived. The distillation step used in the manufacture of the fatty acid methyl esters acts as the source of the hydrocarbons and sterols as they are carried over from the production of the fatty acid methyl esters.

Difatty ketones are a family of compounds formed as side reaction products in olestra during the manufacturing process. The analysis of various lots of olestra used in safety studies demonstrated that difatty ketones are present at levels ranging from 36 to 217 ppm (total difatty ketones). Difatty ketones occur naturally in many food matrices including grilled meats, vegetables, and food emulsifiers. The levels of difatty ketones in meats have been reported to range from 0.81 ppm in grilled chicken to 2.73 ppm in grilled steak (Nichols and Holman, 1972). Brassica vegetables have been reported to contain significant quantities of difatty ketones (86 ppm) (Kolattukudy, 1980, 1987) with as much as 3.52 mg/day consumed from the ingestion of 41 g/day broccoli.

The exposure of consumers to difatty ketones present in olestra as a result of the manufacturing process is at or below the level of difatty ketones typically present in the human diet as a result of the consumption of Brassica vegetables. Additionally, heated meat and used frying oils are supplementary sources of difatty ketones, which increase the background exposure of individuals to difatty ketones from sources other than olestra. The consumption of olestra and subsequently the concomitant consumption of difatty ketones does not represent exposure to a novel compound as the general population is exposed to difatty ketones through traditional food sources.

3.2 Summary of the Stability of Olestra and Vitamins Added to Olestra

3.2.1 Olestra Stability

The stability of olestra has been examined under various conditions including: bulk storage at ambient temperatures; high-temperature controlled shelf-storage; high temperature heating/frying; and within crackers during baking. Olestra was demonstrated to be as stable as triglycerides with similar fatty acid compositions and under similar testing conditions.

3.2.2 Vitamin Stability

The stability of vitamin E in 35% olestra shortening was examined under shelf storage at 70°F (~21°C) and 90°F (~32°C) for 1 and 2 months. Additionally, the stability of vitamin E in olestra shortening stored for 1 month at 90°F was further assessed under heated conditions. The examination of the stability of vitamin E in olestra demonstrated that vitamin E is stable in unused olestra shortening, while only minor losses of vitamin E occurred with frying or baking. Minor losses of vitamin E appeared to be due to the cooking conditions rather than storage, since similar levels of vitamin E were present after frying and baking in both fresh samples and samples stored for 1 month at 90°F.

The stability of the other fat soluble vitamins under extreme testing conditions [*e.g.*, temperatures of 130, 150, and 170°F (*i.e.*, ~54, 66, and 77°C, respectively) for up to 6 hours] was examined. The vitamin A concentration was reported to decrease as expected during the stability test with the samples exposed to the high temperature (*i.e.*, 170°C) for 6 hours compared to samples exposed to lower temperatures (*i.e.*, 130°F) over the same time period (~14% *versus* 39% declines in vitamin A in samples held at 130°F and 170°F, respectively). This result was taken into account during the final formulation of the fat soluble vitamin mix.

In addition to the stability of vitamin E in olestra, the stability of other fat soluble vitamins was examined due to the known sequestering effect of olestra on fat-soluble vitamins. The FDA requires that olestra must contain minimum amounts of fat-soluble vitamins prior to shipment (Table 4-1). The stability of supplemental vitamins (*i.e.*, vitamins A, D, E, and K) added to olestra was examined in Reduced-Fat (50%) Ritz, Reduced-Fat Wheat Thins, and Reduced-Fat Triscuit crackers packaged in metallised film or in coex film. The stored samples were tested at 1, 2, and 3 months; however, no changes were reported with regard to the vitamin levels in crackers packaged in the metallized film. Testing was continued with cracker samples packaged in coex film and, at 6 months, actual total loses of approximately 35% were observed, rather than the expected loses of 50%.

4.0 INTENDED USE OF OLESTRA IN FOOD

4.1 Current Regulatory Status

Olestra, meeting the specifications of the *Food Chemicals Codex* (FCC, 2006), is a food additive permitted for use in the United States (U.S.) in place of fats and oils in pre-packaged ready-to-eat savory (*i.e.*, salty or piquant but not sweet) snacks and pre-packaged, unpopped popcorn kernels that are ready to heat (21 CFR §172.867) (U.S. FDA, 2006a). To compensate for any interference with absorption of fat soluble vitamins, it is required that vitamins A, E, D, and K be added to foods containing olestra at the levels specified in Table 4-1.

Table 4-1 Compensation Levels for Vitamins A, D, E, and K

Vitamin	Compensation Level (per gram of olestra)
Vitamin A[1]	51 µg retinol equivalents (as retinyl acetate or retinyl palmitate)
Vitamin E[2]	1.9 mg α-tocopherol equivalents
Vitamin D	12 IU vitamin D
Vitamin K	8 µg vitamin K_1

[1] In the derivation of Dietary Reference Intakes for vitamin A, the units were changed from µg retinol equivalents to µg retinol activity equivalents, to account for vitamin A from the provitamin A carotenoids (α-carotene, β-carotene, and β-cryptoxanthin). Because vitamin A must be added as preformed vitamin A (retinyl acetate or retinyl palmitate), the value does not require correction (Otten *et al.,* 2006).
[2] In the derivation of Dietary Reference Intakes for vitamin E, the units were changed from mg α-tocopherol equivalents to mg α-tocopherol, as only four forms of α-tocopherol, namely *RRR-, RSR-, RRS-, and RSS-*α-tocopherol are biologically active (Otten *et al.,* 2006).

Vitamins A, E, D, and K present in foods containing olestra due to the required addition cannot be considered when determining the nutrient content for the purposes of nutrition labeling or for any nutrient content claims. Olestra is not considered as a source of fat or calories for the purposes of nutrition labeling of food or nutrient content claims.

4.2 Functionality

Olestra may be used as a calorie free replacement for conventional fats and oils for frying or baking, in dough conditioners, in sprays, in filling ingredients, or in flavors. It may be used as a replacement for up to 100% of the conventional fats and oils used to prepare the product.

4.3 Intended Use of Olestra and Levels of Use in Foods

The individual permitted and proposed food-uses and use-levels for olestra are summarized in Tables 4-2 and 4-3, respectively. Food codes representative of each of the permitted and proposed food-uses that were specified as “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” were chosen from the CSFII 1994-1996, 1998 (USDA, 2000). All olestra-containing

products meet the specific requirements for fat content claims in the U.S. (21 CFR §101.62) and are labeled with the appropriate claim (U.S. FDA, 2006b).

Food codes were grouped in food-use categories according to Title 21, Section §170.3 of the *Code of Federal Regulations* (U.S. FDA, 2006c). Product-specific adjustment factors were developed based on data provided in the standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000). All food codes included in the current intake assessment are listed in Appendix A.

Table 4-2 Summary of the Permitted Food Uses and Use-Levels for Olestra in the U.S.

Food Category	Permitted Food-Use	Use-Levels for Olestra
Snack Foods	Pre-packaged Ready-to-Heat, Unpopped Popcorn	100% replacement of fat of a regular product
	Pre-packaged Ready-to-Eat Savory Snacks	100% replacement of fat of a regular product

Table 4-3 Summary of the Individual Proposed Food Use and Use-Level for Olestra in the U.S.

Food Category	Proposed Food-Use	Use-Level for Olestra
Baked Goods and Baking Mixes	Reduced-Fat, Low-Fat, and Fat-Free Cookies	100% replacement of fat of a regular product

The use-level, 100% replacement of fat, is based on the fat content of an equivalent regular product (*i.e.*, fat content has not been modified). This is consistent with the methodology used by Webb *et al.* (1997) for a study on predicted olestra intake from savory snacks, whereby the olestra content of reduced-fat savory snacks was also assumed to be the same as the fat content of their full-fat counterparts. The fat content of the regular products used for this assessment was determined from the USDA National Nutrient Database for Standard Reference, Release 17. The fat content of regular cookies and snacks is variable, ranging from 7.3 – 30.6% and 3.5 – 38.4%, respectively. Thus, for illustrative purposes, the fat content of the more popular cookies and snacks are presented. For cookies, the reference amount customarily consumed (RACC) per eating occasion is 30 g (21 CFR §101.12) (U.S. FDA, 2006d). Thus, a typical serving of chocolate chip cookies has 7.3 g of fat, while a typical serving of chocolate sandwich cookies with cream filling has 5.7 g of fat. For chips, the RACC per eating occasion is also 30 g (21 CFR §101.12) (U.S. FDA, 2006d). A typical serving of plain potato chips has 10.4 g of fat, while a typical serving of tortilla chips (nacho flavor) has 7.7 g of fat. Thus, single servings of reduced-fat, low-fat, and fat-free chocolate chip or sandwich cookies may contain up to 7.3 and 5.7 g of olestra, respectively, while single servings of

reduced-fat, low-fat, and fat-free plain potato and nacho-flavored tortilla chips may contain up to 10.4 and 7.7 g of olestra, respectively.

Although olestra is permitted for use in all pre-packaged ready-to-eat savory snacks and in pre-packaged, ready-to-heat unpopped popcorn, the only olestra-containing products currently available on the U.S. market include potato chips and corn/cornmeal based chips. Food codes for these specific olestra-containing products were identified. However, estimates of intake for this assessment were based on all identified food codes for all pre-packaged ready-to-eat savory snacks (e.g., crackers, puffs, pretzels) and pre-packaged ready-to-heat unpopped popcorn that were “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” in order to derive the most conservative estimates of olestra intakes from permitted uses. Food codes were not identified that were representative of pre-packaged ready-to-heat popcorn; thus, codes for air-popped popcorn and popcorn popped in oil were used.

5.0 ESTIMATED DIETARY INTAKE OF OLESTRA BASED ON PERMITTED AND PROPOSED FOOD USES

5.1 Introduction

The consumption of olestra from all permitted and proposed food-uses was estimated using the USDA 1994 – 1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994 – 1996) and the 1998 Supplemental Children's Survey (USDA CSFII 1988) (USDA, 2000). Details on these surveys are provided in Section 2.1 of Appendix A.

Estimates for the daily intake of olestra represent projected averages over 2 days (day 1 and day 2) of USDA CSFII (1994 – 1996, 1998) data. Individual consumption data were collated by computer and the resulting distributions were analyzed statistically. All-person intake refers to the intake of olestra averaged over all individuals surveyed regardless of whether they consumed food products formulated with olestra, hence the 'all-person' designation. All-user (or users-only) intake refers to the intake of olestra by individuals consuming food products formulated with olestra, hence the 'all-user' (or 'users-only') designation. Individuals were considered users if they consumed 1 or more food products formulated with olestra on either day 1 or day 2 of the survey. Calculations for the mean and 90th percentile all-person and all-user intakes, and percent consuming were performed for various age and population groups, as described in Section 1 of Appendix A.

5.2 Estimated Chronic and Acute Daily Intakes of Olestra from Permitted Food Uses

The estimated chronic intake of olestra from all permitted food-uses is summarized in Section 5.2.1. Previously published studies on estimated chronic and acute intakes of olestra from permitted food uses using Market Research Corporation of America (MRCA) Menu Census Data (Webb *et al*., 1997), data collected as part of the Olestra Post-Marketing Surveillance Study [(OPMSS) (Neuhouser *et al*., 2006)], and data collected during post-marketing human experimental studies (Cheskin *et al.,* 1998; Sandler *et al.,* 1999) are discussed in Section 5.2.2. A complete description of the consumption estimates and further details on previously published studies on estimated olestra intake are presented in Appendix A. A detailed description of the design of the OPMSS is provided in Appendix B.

5.2.1 Estimated Chronic Daily Olestra Intake from All Permitted Food-Uses

The estimated chronic daily intake of olestra from all permitted uses is presented in Table 5-1. In Table 5-1, values in parantheses represent estimated daily chronic intakes of olestra from all permitted and proposed uses, combined.

Table 5-1 Summary of the Estimated Daily Chronic Intake of Olestra from Permitted (and Proposed) Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)							
Population Group	**Age Group (Years)**	**% Users**	**Actual # of Total Users**	**All-Person Consumption**		**All-Users Consumption**	
				Mean (g)	**90th Percentile (g)**	**Mean (g)**	**90th Percentile (g)**
Infant	0-2	7.7 (8.9)	277 (318)	0.09 (0.12)	NA (NA)	1.0 (1.2)	2.0 (2.8)
Child	3-11	11.9 (13.5)	753 (849)	0.20 (0.28)	NA (NA)	1.7 (2.1)	4.1 (4.8)
Female Teenager	12-19	10.1 (12.3)	71 (86)	0.29 (0.45)	NA (NA)	2.7 (3.4)	7.0 (7.4)
Male Teenager	12-19	8.5 (9.8)	59 (68)	0.27 (0.38)	NA (NA)	3.0 (3.7)	7.4 (8.5)
Female Adult	20 and Up	11.0 (13.6)	501 (622)	0.31 (0.47)	NA (NA)	2.6 (3.1)	6.7 (8.0)
Male Adult	20 and Up	8.3 (10.0)	394 (476)	0.29 (0.40)	NA (NA)	3.1 (3.7)	9.3 (9.3)
Total Population	All Ages	10.0 (11.7)	2,055 (2,419)	0.28 (0.40)	NA (NA)	2.6 (3.1)	7.0 (7.7)

NA = Not Available

Approximately 10% of the total U.S. population was identified as consumers of “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” pre-packaged ready-to-eat savory snacks and pre-packaged ready-to-heat unpopped popcorn (2,055 actual users). Consumption of permitted uses of olestra by the total U.S. population resulted in estimated mean all-person chronic intakes of 0.28 g/person/day, and mean and 90th percentile all-user intakes of 2.6 and 7.0 g/person/day, respectively. Of the individual population groups, children were estimated to comprise the greatest percentage of users at 11.9%. The greatest mean all-person chronic intake of olestra was determined to be in female adults at 0.31 g/person/day, while the greatest all-user mean olestra chronic intake occurred in male adults at 3.1 g/person/day. Infants had the lowest mean all-person and all-user chronic intakes of olestra, with values of 0.09 and 1.0 g/person/day, respectively. Male adults were determined to have the greatest 90th percentile intakes on an all-user basis, with a value 9.3 g/person/day. Infants had the lowest 90th percentile all-user chronic intake of olestra from permitted food uses with a value of 2.0 g/person/day.

5.2.2 Market Research Corporation of America (MRCA) Menu Census Study on Intake of Savory Snacks and Post-Marketing Surveillance and Human Experimental Studies of Olestra Intake

Additional data on chronic and acute intakes of olestra from permitted uses may be derived from MRCA estimates, and from Olestra Post-marketing Surveillance (Neuhouser *et al.,* 2006) and human experimental studies (Cheskin *et al.,* 1998; Sandler *et al.,* 1999).

Prior to the introduction of olestra-containing products in the U.S. marketplace, acute and chronic intakes of olestra were estimated by analyzing 14-day Menu Census data collected by MRCA from 4,741 individuals from approximately 2,000 households during 1991-1992 (Webb *et*

al., 1997). This study reported that savory snacks were not consumed on a daily basis; at the 90th percentile consumption level, they were eaten 10 times in 14 days, and on 8 days of the 14-day survey. The users-only mean and 90th percentile chronic intakes of olestra from savory snacks for the total population were estimated to be 3.1 and 6.9 g/day, respectively. The users-only mean and 90th percentile acute intakes of olestra from savory snacks for the total population were estimated to be 10.2 and 18.3 g/day, respectively.

Additional information on chronic intakes of olestra from savory snacks is also available from the Olestra Post-Marketing Surveillance Study (Neuhouser *et al.,* 2006), which was required as a condition of the 1996 U.S. FDA approval of olestra for use in savory snacks. Among users-only, the mean chronic olestra intakes for adults and adolescents were 0.78 and 0.74 g/day, respectively, while the 90th percentile chronic intakes were 1.8 and 2.1 g/day, respectively (Neuhouser *et al*., 2006). The Olestra Post-Marketing Surveillance Study is described in detail in Appendix B.

Two additional post-marketing human experimental studies, the Movie Theatre Study (Cheskin *et al.,* 1998) and the Household Chip Consumption Study (Sandler *et al.,* 1999) are useful in providing further information on the acute intakes of olestra from permitted food uses. The Movie Theatre Study was a randomized, double-blind, placebo-controlled study involving 1,092 subjects, who were provided with 13 ounces of regular (triglyceride) or olestra chips and asked to consume them freely during a 2-hour movie. The median intake of olestra chips was 2.1 ounces (equivalent to 16.8 g of olestra). The 90th percentile intake of olestra chips was 5.0 oz (equivalent to 40 g of olestra).

The Household Chip Consumption Study was a randomized, double-blind, placebo-controlled study involving 3,181 volunteers ages 2 – 89 years. Subjects were provided with unlimited supplies of either regular or olestra chips for 6 weeks (42 days) and asked to record, in daily diet records, the amounts of chips consumed. The median number of days on which olestra chips were consumed was 20 (out of a possible of 42 days), while the 90th percentile number of days on which olestra chips were consumed was 35. The overall median intake of olestra chips was 1.3 ounces per day (equivalent to 10.4 g/day of olestra), while the 90th percentile intake of olestra chips was 2.3 ounces per day (equivalent to 18.4 g/day of olestra). Although this study was 6 weeks long, these intakes represent acute intakes, given that the median overall intakes of olestra were averaged over the number of days on which the chips were consumed, as opposed to the total number of study days (*i.e.,* 42 days).

Because subjects in the Movie Theatre and Household Chip Consumption Studies were given free chips, it is possible that subjects consumed more chips than they normally would or more often than they normally would, and that intakes are exaggerated relative to what would be consumed under real-world conditions. In the MRCA study, the frequency of chip consumption at the 90th percentile was 8 days out of a possible of 14 days, or on 57% of the survey days (Webb *et al.,* 1997); in contrast, in the Household Chip Consumption Study, the frequency of

chip consumption at the 50th percentile was 20 days out of a possible of 42 days (on 48% of the study days), and at the 90th percentile, 35 days out of a possible of 42 days (on 83% of the study days). This observation suggests that in free-living individuals, chip consumption is occasional, and that under experimental conditions in which subjects are provided with unlimited supplies of chips, the frequency of chip consumption increases. It is noteworthy that the Household Chip Consumption Study was designed to select households that were frequent chip consumers; as part of the inclusion criteria (*i.e.,* for households to be eligible for participation), at least half of their members had to have eaten corn or potato chips at least 4 times in the past month, and all eligible members had to participate. Thus, the Household Chip Consumption study involved subjects who were frequent chip consumers, and so chip intakes cannot be extrapolated to the general population. The primary objective of the Movie Theatre and Household Chip Consumption Studies was to assess GI symptoms. The results of these studies, which are discussed in greater detail in section 8.3.2, demonstrated that acute intakes of olestra are well tolerated. Acute and chronic intakes of olestra from permitted uses, as determined by the various studies, are summarized in Table 5-2.

Table 5-2 Acute and Chronic Intakes of Olestra from Permitted Uses

Study	50th Percentile/Median Olestra Intake (g/day)	90th Percentile Olestra Intake (g/day)
Webb *et al.,* 1997 (MRCA Survey)	3.1 (chronic) 10.2 (acute)	6.9 (chronic) 18.3 (acute)
Neuhouser *et al.,* 2006 (OPMSS)	0.78 (chronic, adults) 0.74 (chronic, adolescents)	1.8 (chronic, adults) 2.1 (chronic, adolescents)
1994-1996, 1998 USDA CSFII Data	2.58 (chronic)	7.01 (chronic)
Cheskin *et al.,* 1998 (Movie Theatre Study)	16.8 (acute)	40 (acute)
Sandler *et al.,* 1999 (Household Chip Consumption Study)	10.4 (acute)	18.4 (acute)

Abbreviations: MRCA, Market Research Corporation of America; OPMSS, Olestra Post-marketing Surveillance Study; USDA CSFII, United States Department of Agriculture Continuing Survey of Food Intakes by Individuals.

5.2.3 Impact of Length of Dietary Surveys, and Comparison of Estimated Intakes Derived from USDA CSFII Data with MRCA-derived Intakes and Results from Post-Marketing Surveillance and Human Experimental Studies

It is well established that the length of a dietary survey affects the estimated chronic consumption of individual users. Short-term surveys, such as the typical 1- or 2-day dietary survey, such as that utilized by USDA CSFII 1994 – 1996, 1998, overestimate consumption over longer time periods (greater than 3 months) and are more appropriate to safety assessments (Anderson, 1988). The impact of survey length on the chronic consumption of individual food products by users varies given their frequency of use. For some foods, such as bread, which are typically consumed on a daily basis, short-term surveys likely approximate chronic user consumption. For other foods that are consumed less frequently, longer time

periods are required to establish chronic user consumption. Therefore, the estimated chronic daily intake of olestra in the U.S. derived from USDA CSFII 1994 – 1996, 1998 is likely to greatly overestimate consumption over the long-term given that it is based on two 24-hour recalls and includes food uses that are not typically consumed on a daily basis (Webb *et al*., 1997). Furthermore, conservative assumptions are made when conducting intake assessments that also contribute to an inflated estimate of consumption, such as the assumption that all foods produced by all manufacturers within a food category would contain olestra, and that all foods produced by all manufacturers within a food category would have 100% of their fat content replaced by olestra.

The impact of the length of dietary surveys on the consumption of different types of food products was investigated in a study conducted by the Institute of European Food Studies (IEFS, 1998). In this multi-country study, the consumption of 32 food types, including crisps (*i.e.*, chips) and biscuits (*i.e.*, cookies), was examined in 1,000 males and females aged 10 to 18 years in a food diary study for 1, 3, 5, 7, 10, and 14 days. This study showed that mean and 90th percentile users-only chronic intakes of crisps and biscuits (Table 5-3) based on 1 or 3 days of intake records are substantially higher than intakes based on 14 days of dietary records. This suggests that MRCA-derived chronic intakes, which are based on 14 days of data, are likely to provide more appropriate estimates of chronic intake in comparison to CSFII 1994 – 1996, 1998, which is based on 2 days of intake data.

Table 5-3 Effect of Food Consumption Survey Length on Users-Only Consumption of Biscuits and Crisps: Observations from the Institute of European Food Studies

Food		Users-only intake (g/day)		
		1 day	3 days	14 days
Biscuits	Mean	54	29	16
	90th percentile	100	64	42
Crisps	Mean	49	23	10
	90th percentile	94	48	24

The MRCA-derived chronic intakes presented in Section 5.2.2 were obtained from previously published literature (Webb *et al*., 1997). However, the MRCA data are no longer available publicly for analyses and were presented for comparison purposes only. The results from analyses on the USDA CSFII data (Table 5-1) show that the users-only mean and 90th percentile chronic intakes of olestra from permitted uses (pre-packaged ready-to-eat savory snacks and pre-packaged ready-to-heat popcorn) for the total population were 2.6 and 7.0 g/day, respectively (Table 5-1), which are similar to the MRCA-derived users-only mean and 90th percentile total population chronic intakes of olestra from savory snacks of 3.1 and 6.9 g/day, respectively (Table 5-2). Although there were differences with respect to how the

chronic intakes based on the two different databases were derived, this suggests that the intake estimates derived using the USDA CSFII data are appropriate, while results from the Olestra Post-Marketing Surveillance Study, which found that the 90th percentile intake was as high as 2.1 g/day, suggest that the chronic olestra intakes estimated using USDA CSFII data are, in fact, highly conservative and result in substantial overestimates of chronic intake.

Acute intakes of olestra from permitted food uses estimated from the MRCA data were 10.2 and 18.3 g/day at the 50th and 90th percentiles, respectively (Webb *et al.,* 1997). Sandler *et al.* (1999) demonstrated in the Household Chip Consumption study, that acute intakes of olestra are 10.4 and 18.4 g/day at the median and 90th percentile intakes, respectively (Sandler *et al.,* 1999). Although these intakes are very similar to those estimated in the MRCA survey, the MRCA survey estimates were based on the incorporation of olestra in all savory snacks and not just chips. Likewise, in the Movie Theatre Study, acute olestra intakes were higher, with the median and 90th percentile intakes averaging 16.8 and 40 g/day, respectively (Cheskin *et al.,* 1998).

5.3 Chronic and Acute Intakes of Olestra and Patterns of Consumption from Permitted and Proposed Food-Uses, Combined

Estimates for the chronic daily intake of olestra from permitted plus proposed uses (reduced-fat, low-fat and fat-free cookies) in the U.S. by population group are provided in Section 5.3.1. Estimates for the acute intake of olestra from permitted plus proposed uses in the U.S. population are provided in Section 5.3.2. An examination of patterns of intake at meals *versus* snacking occasions is presented in Section 5.3.3. A complete description of the consumption estimates is provided in Appendix A.

5.3.1 Estimated Daily Chronic Intakes of Olestra from All Permitted and Proposed Food-Uses, Combined

Estimated daily chronic intakes of olestra from all permitted and proposed uses, combined, are summarized in Table 5-1 (values in parantheses represent chronic daily olestra intakes from all permitted and proposed uses, combined, while values outside parantheses repreasent chronic daily olestra intakes from permitted uses only). Approximately 11.7% of the total U.S. population was identified as consumers of “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” pre-packaged ready-to-eat savory snacks, pre-packaged ready-to-heat unpopped popcorn, and pre-packaged ready-to-eat cookies (2,419 actual users). Consumption of these types of foods by the total U.S. population resulted in an estimated mean all-person chronic intake of 0.40 g/person/day, and mean and 90th percentile all-user chronic intakes of 3.1 and 7.7 g/person/day, respectively (Table 5-1).

Of the individual population groups, female adults were estimated to comprise the greatest percentage of users at 13.6%. The greatest mean all-person chronic intake of olestra was

determined in female adults, at 0.47 g/person/day, while male teenagers had the highest mean all-user intake of olestra at 3.7 g/person/day. Infants had the lowest all-person and all-user mean chronic intakes of olestra, at 0.12 and 1.2 g/person/day, respectively. Male adults had the greatest 90th percentile all-user chronic intake, with a value of 9.3 g/person/day. Infants had the lowest all-user 90th percentile chronic intake on an absolute basis, with a value of 2.8 g/person/day, respectively.

In comparison to the results presented in Table 5-1 that show the estimated olestra intakes from permitted uses only, the addition of reduced-fat, low-fat and fat-free cookies to the assessment had a small impact on total chronic olestra intake. The total population users-only mean chronic intake of olestra increased marginally from 2.6 g/person/day for permitted uses to 3.1 g/person/day with the addition of proposed uses. Likewise, the users-only 90th percentile total population chronic olestra intake increased marginally from 7.0 g/person/day for permitted uses to 7.7 g/person/day with the addition of proposed uses.

5.3.2 Estimated Daily Acute Intakes of Olestra from All Permitted and Proposed Uses, Combined

Estimated acute daily intakes of olestra were determined from the CSFII USDA (1994 – 1996, 1998) data by dividing intakes by the total number of user-days as opposed to the total number of dietary survey days. Estimated acute intakes of olestra by olestra users are presented in Table 5-4.

Table 5-4 Summary of the Estimated Acute Daily Intake of Olestra from All Permitted and Proposed Uses by Users-Only in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	Actual # of Users	Actual # of User-Days	All-Users Consumption	
				Mean (g)	90th Percentile (g)
Infant	0-2	318	377	2.1	4.6
Child	3-11	849	995	3.6	8.6
Female Teenager	12-19	86	103	5.5	14.0
Male Teenager	12-19	68	83	6.1	15.3
Female Adult	20 and Up	622	735	5.3	12.1
Male Adult	20 and Up	476	563	6.3	15.2
Total Population	All Ages	2,419	2,856	5.3	12.6

The total population 90th percentile acute intake of olestra is 12.6 g/person/day (Table 5-4), which is higher than the 90th percentile chronic intake for the total population of 7.7 g/person/day (Table 5-1). This would suggest that in general, the intake of permitted and/or proposed uses of olestra did not occur on both days of the survey, which led to a lower chronic intake value in comparison to the acute value. In addition, of the 2,419 users of permitted and/or proposed

uses of olestra, 2,856 days of consumption were recorded (Table 5-4). Thus, 437 of 2,419 individuals, or only 18% of olestra users (represents 2.1% of the total population) consumed a minimum of one permitted or proposed food use of olestra on both days of the survey.

An additional scenario that was considered in estimating the acute consumption of olestra was the consumption of olestra from more than one use (either permitted or proposed) within a single day. Details of the analysis are presented in Table 5.4-2 of Appendix A. For the purposes of this discussion, only individuals who consumed olestra from more than one source on either day of the dietary survey were included; moreover, intakes were averaged over user-days as opposed to the total number of dietary survey days, to ensure that intakes were not diluted by days on which no olestra was consumed. One hundred and ninety user-days (out of a possible of 2,856 user-days) were identified on which olestra was consumed from more than one source. The total-population users-only 90th percentile acute intake of olestra in the subpopulation of individuals who, in one day, consumed olestra from more than one source was 22.8 g/person/day. This methodology provides a more conservative estimate of acute intake and allows for consideration of individuals that may be consuming both low-fat savory snacks and/or popcorn and/or low-fat cookies on the same day. However, given the very small subset of the population consuming olestra from both permitted and proposed uses and the very small number of user-days within each population group, the statistical reliability of these results is questionable.

5.3.3 Intake of Olestra from Permitted and Proposed Uses at Meals *versus* Snacks

Because the pattern of olestra consumption (*i.e.,* with meals *versus* between meals) has an impact on the absorption of lipophilic nutrients such as carotenoids (Daher *et al.,* 1997a), the pattern of olestra consumption was examined by investigating the intake of olestra intake from permitted and proposed food uses at meals *versus* snacks. The results of these analyses for “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light” or “diet” pre-packaged ready-to-heat unpopped popcorn, pre-packaged ready-to-eat savory snacks, and pre-packaged ready-to-eat cookies are presented in Tables 5.5-1, 5.5-2, and 5.5-3, respectively, of Appendix A.

Intake of olestra from all permitted uses occurs primarily as a snack, with 89.6 and 65.5% of eating occasions occurring as a snack for pre-packaged ready-to-heat unpopped popcorn and pre-packaged ready-to-eat savory snacks, respectively, for the total population. Consistent with this, 67.4% of reduced-fat, low-fat and fat-free cookie eating occasions occurred as a snack for the total population. The younger age groups tended to consume a high proportion of cookies as snacks, as opposed to consuming them with main meals, with infants and children consuming olestra from reduced-fat, low-fat and fat-free cookies as snacks during 87.7 and 82.4% of eating occasions, respectively. Though the majority of eating occasions for pre-packaged ready-to-heat unpopped popcorn and pre-packaged ready-to-eat savory snacks occurred as snacks, mean and 90th percentile intakes of olestra from these food-uses tended to be similar at meal and snack occasions, or slightly higher at meals. For reduced-fat, low-fat and

fat-free cookies, intakes of olestra at meals *versus* snacks also tended to be similar, but slightly higher at snack occasions.

5.4 Conclusions

Consumption data and information pertaining to the individual identified food-uses were used to estimate the all-person and all-user intakes of olestra for specific demographic groups and for the total U.S. population. This type of intake methodology is generally considered to be 'worst case' as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate chronic consumption of food products that are consumed relatively infrequently.

In summary, on an all-user basis, the estimated mean chronic intake of olestra from permitted uses in pre-packaged ready-to-eat savory snacks and pre-packaged ready-to-heat unpopped popcorn and proposed uses in pre-packaged ready-to-eat cookies by the total U.S. population was estimated to be 3.1 g/person/day, while the 90th percentile intake was estimated to be 7.7 g/person/day. These chronic intake estimates are only marginally higher than the estimated mean and 90th percentile chronic intakes of olestra by the total population from only permitted uses, 2.6 and 7.0 g/person/day, respectively. Estimates of chronic olestra intakes from permitted uses are similar to previously published estimates based on MRCA data, while the Olestra Post-Marketing Surveillance Study reported substantially lower intakes from olestra-containing products, which demonstrates that the chronic consumption estimates generated using USDA CSFII data are highly conservative.

Estimated acute or daily intakes of olestra are significantly higher than the chronic intakes, with total population 90th percentile intakes of 12.58 g/day (when intakes are divided by user-days as opposed to total number of survey days) and 22.8 g/day (when two or more sources of olestra are consumed during either day of the 2-day survey). Higher intakes were reported when potato chips containing olestra were provided, free of charge, in the Movie Theatre (Cheskin *et al.,* 1998) and Household Chip Consumption (Sandler *et al.,* 1999) studies. The 90th percentile intakes were 40 and 18.4 g/day, respectively. Because olestra is not associated with toxicological effects, acute intakes are not really relevant to the safety assessment of olestra. Olestra interferes with the absorption of fat-soluble nutrients, like the carotenoids. Thus, more applicable to the safety assessment of olestra are: i) The chronic intakes of olestra (which have already been discussed); and ii) The patterns of olestra consumption. Analyses on the patterns of olestra intake from permitted and proposed uses show that the majority of eating occasions occur as snacks, particularly for infants and children.

Although the intakes were determined using the USDA CSFII 1994-1996, 1998 food consumption surveys, a newer food consumption survey was released in the fall of 2006, the NHANES, 2003 – 2004 survey (USDA, 2006). This survey is of similar design as the USDA CSFII food consumption survey and uses the same food code list. Estimation of chronic olestra intakes determined from the NHANES, 2003-2004 survey for the total U.S. population for permitted and proposed olestra uses indicated mean and 90th percentile chronic all-user intakes of 3.2 g and 7.9 g/day, respectively. These estimates are comparable to the data presented above. Only two years of interview data are included in the NHANES 2003 – 2004 survey; in contrast, the CSFII 1994-1996, 1998 surveys provide 4 years of intake data, with double the number of individuals surveyed and a significantly larger proportion of children surveyed. For these reasons, CSFII 1994-1996, 1998 survey data were used to generate estimates for the current intake analysis.

6.0 TOXICOLOGICAL STUDIES OF OLESTRA

6.1 Overview

Olestra is composed of a mixture of primarily (≥97%) hexa-, hepta-, and octa-esters of sucrose with medium- and long-chain fatty acids, which are not hydrolyzed, not fermented by microflora, and not absorbed. Sucrose esterified with five or fewer fatty acids (penta- or lower sucrose ester), which accounts for a very low percentage of the olestra formulation, is hydrolyzed to sucrose and free fatty acids, with the former hydrolyzed further to glucose and fructose prior to absorption. The hydrolysis products of these smaller sucrose esters (*i.e.,* fatty acids, glucose, and fructose) are subsequently absorbed and processed through common metabolic pathways. Studies evaluating the absorption, distribution, metabolism and excretion (ADME) of olestra are summarized in Section 6.2.

Numerous toxicology studies were conducted to support the application of olestra for addition to savory snacks. Specifically, olestra and olestra-like SPE formulations have been evaluated extensively in a standard battery of toxicological studies, including sub-chronic and long-term feeding trials in several different laboratory species, short-term *in vitro* and *in vivo* genotoxicity and mutagenicity assays, and developmental and reproductive studies. No new toxicology studies have been conducted since approval was obtained for use of olestra in savory snacks.

Feeding trials were conducted in mice and rats for a period of 2 years, while in dogs a 20-month study was performed. No treatment-related toxicologically significant findings, including non-neoplastic or neoplastic lesions, were observed in 2-year mouse or rat carcinogenicity assays, or chronic dog studies when olestra was administered in the diet at concentrations of up to 10%. In primates, no adverse effects were observed following treatment with SPEs for up to 44 months. Comparison of the no-observed-adverse effect levels (NOAELs) established under the conditions of the long-term animal toxicity studies (Miller *et al*., 1991; Wood *et al*., 1991a; Lafranconi *et al*., 1994) to estimates of human consumption, indicates that intake of olestra at the 90th percentile is several fold lower than the NOAELs, which were the highest dose levels tested.

The results of a series of *in vitro* genotoxicity and mutagenicity tests conducted in both eukaryotic and prokaryotic test systems, both with and without metabolic activation, unequivocally demonstrated that olestra is non-genotoxic and non-mutagenic (Skare *et al*., 1990; Williams *et al*., 1996). Evaluated following heating and in the presence of a detergent to increase olestra solubility and consequently cellular uptake, olestra also did not induce any mutagenic or genotoxic changes. Similarly, *in vivo*, single- or repeat-dosing with up to 5,000 mg olestra/kg body weight did not result in an increased number of chromosomal aberrations in bone marrow cells of Sprague-Dawley rats compared to controls (Williams *et al*., 1996).

The potential developmental and reproductive toxicity of SPEs was evaluated in a 2-generation study in Sprague-Dawley rats, in which both males and females were fed test diets containing up to 10% of SPEs (approximately 5 g/kg body weight/day) for 91 days prior to mating (Nolen *et al*., 1987). No adverse effects related to mating, conception, embryonic development, fetal and postnatal viability, or postnatal development, were observed in either generation. Likewise, administration of SPEs in the diet at concentrations of up to 15% (approximately 12 g/kg body weight) to female Sprague-Dawley rats during gestational day (GDs) 6 to 13 or 15 did not produce any reproductive or fetal toxicity (Mattson and Hollenbach, 1977; unpublished). The potential teratogenicity of olestra also was assessed in female New Zealand white rabbits, which were administered heated olestra at dose levels equivalent to 10% in the diet *via* gavage for 13 days beginning on GD 6 (Denine and Schroeder, 1993). As in the rat, treatment with olestra did not result in any adverse effects with respect to fetal development. A more detailed summary of the pivotal toxicology studies of olestra and olestra-like SPE formulations is provided in Section 6.3 below.

In conclusion, based on the scientific data available, there is no expectation that intakes of olestra from use in cookies and savory snacks will be associated with any toxicological effects.

6.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

In fat-balance studies, complete excretion of sucrose octaoleate was demonstrated in rats within the limits of sensitivity of this method (Mattson and Nolen, 1972). In humans, an average absorption of 2.3% was calculated based on material-balance analysis; however, as noted by the study authors, incomplete collection of feces during the recovery phase resulting in loss of the SPEs would be incorrectly assumed to be absorbed test material (Fallat *et al*., 1976). Following feeding of rats with radiolabeled SPEs with 6 or more acyl groups for a period of up to 6 weeks, low levels of radioactivity (*i.e*., 10^{-5} to 10^{-3}%) were identified in several organs including the liver and adipose tissue and did not decline following a 3-week wash-out period (Aust *et al*., 1982, 1986). Accordingly, in order to evaluate the potential for olestra to accumulate following longer treatment periods, rats and monkeys were provided radiolabeled olestra in the diet for at least 18 months (Wood *et al*., 1991b). Low levels of radioactivity were occasionally observed in the hepatic tissue of a few rats. In monkeys fed diets containing radiolabeled olestra for a period of 29 months, radioactivity was not detected in the liver. Although radiolabeled test material was recovered from the lungs and the GI tract of monkeys, this was considered to have occurred as a result of aspiration of the radiolabel and the unlikelihood of complete removal of the highly lipophilic test material from the intestinal mucosal surface prior to analysis, respectively.

More recently, 2 extensive gavage studies were conducted to evaluate the disposition of orally administered heated olestra in rats (Miller *et al*., 1995) and weanling mini-pigs (Daher *et al*., 1996). In the rodent study, 2 additional groups of rats received olestra samples with high or low

degrees of fatty acid saturation, and another group was treated with a SPE sample containing 28% short-chain penta- and lower polyesters. In rats, the majority (*i.e*., 99.86 to 99.98%) of the administered radioactivity was recovered in the feces, GI tract and its contents, and rinse solution and, therefore, not more than 0.14% of the administered radioactivity was considered to have been absorbed (Miller *et al*., 1995). The absorbed radiolabel was rapidly eliminated *via* the urine and expired as CO_2. Not more than 0.0008% of the administered radioactivity distributed to the olestra-containing liver lipid fractions of olestra-treated animals. While low levels of radiolabeled sucrose were collected in the urine of groups of rats receiving the SPEs with lower degrees of esterification, analysis of the sucrose-containing fraction of urine samples of olestra- (heated, unsaturated, and saturated test samples) treated rats did not reveal any urinary sucrose. It was therefore concluded that the majority of the absorbed radioactivity was actually representative of the sucrose metabolites, glucose and fructose, taken up systemically following de-esterification of penta- and lower SPEs in the GI tract, rather than absorption of intact olestra. Prior to absorption, sucrose is effectively hydrolyzed to glucose and fructose *via* brush-border enzymes. Thus, the rapid expiration of radioactivity as CO_2 and elimination in the urine support the conclusion that systemic radioactivity detected was associated with the uptake of the sucrose metabolites, fructose and glucose. The radioactivity collected as expired CO_2 was considered to be the result of systemic glucose metabolism rather than an end-product of bacterial fermentation, since, as demonstrated in the *in vitro* studies, olestra is not fermented by intestinal microflora. Moreover, the radioactivity distributed to various organ tissues and analysis of lipid fractions revealed radiolabel in fractions that would contain triglycerides and other lower molecular weight lipids. Collectively, such a broad distribution of radioactivity indicates that the monosaccharides resulting from the hydrolysis of sucrose in the intestinal mucosa were used in normal physiological pathways and consequently incorporated in the *de novo* synthesis of various metabolic products, including lipids.

In the weanling mini-pigs approximately 99.4% of the recovered radioactivity was unabsorbed. As in the rat study, the broad distribution of the radiolabel to various organs including the brain, further supports that the radioactivity was representative of the sucrose hydrolysis products, glucose and fructose. It was noted that the radioactivity observed in the urinary bladders was likely the result of radioactivity in urine, since the bladder was not washed prior to analysis, whereas the excess level of radioactivity in the lungs was due to inadvertent aspiration of the test material by the mini-pigs.

Daher *et al*. (1997b) also conducted a study in guinea pigs to examine whether olestra absorption would increase in the case of a compromised GI tract. Generally, no differences were noted in the absorption of radiolabeled olestra between normal guinea pigs and those with increased permeability of the GI tract as a result of pre-treatment with poligeenan, suggesting that humans with conditions of the GI tract that would increase the permeability of the intestine to larger molecules (*i.e*., inflammatory bowel disease) will not absorb olestra at increased levels.

6.3 Summary of Pivotal Toxicology Studies

The review of the safety of olestra is based on its metabolism, as discussed above, and on a series of short- and long-term animal toxicity studies, reproductive and teratology studies, *in vitro* and *in vivo* assays for mutagenicity/genotoxicity, and human clinical trials. Details of the human clinical trials are provided in the discussion of nutrition.

During the course of the development of olestra, P&G formulated various mixtures of sucrose esters with varying octa-, hepta-, and hexa-ester distributions and fatty acid compositions. Official specifications for olestra adopted following its approval for use as a food additive are published in the Food Chemicals Codex (FCC, 2003) and are presented in Table 1-1.

In assembling the data related to the safety of olestra, studies conducted with various mixtures of sucrose esters were reviewed, including those conducted with mixtures that fall outside the scope of the FCC specifications. Although a slightly greater degree of absorption has been demonstrated for lower sucrose esters than for highly esterified molecules, absence of any adverse effects in studies conducted with materials containing greater proportions of sucrose esters with lower degrees of esterification further supports the safety of olestra and, hence, results of these studies also were included.

6.3.1 Short Term Oral Toxicity Studies

Studies with common cooking oils have demonstrated that frying particularly at very high temperatures and for prolonged periods of time causes chemical changes in the fats. In some cases, heating of cooking oil has been associated with the production of toxic and genotoxic products (Clark and Serbia, 1991). Thus, several studies were conducted to assess whether heating of olestra would alter its potential to induce toxicity. In a 91-day feeding study, male and female Sprague-Dawley rats (10 rats/sex/group) were fed diets containing various blends of heated and unheated olestra and vegetable oil (OA/VO) (Miller and Long, 1990). Specifically, rats were administered diets with added pan-fried (380°F for 30 min) or deep-fried (365°F for 84 hr) OA/VO blends containing olestra and vegetable oil in ratios of 35:65 and 75:25, respectively. With the exception of the unheated OA/VO blend with 75% olestra, in which the olestra fraction consisted of 81.2, 18.2, 0.35, and 0.25% of octa-, hepta-, hexa-, and penta-esters, respectively, the remaining diets contained olestra with an octa- and hepta-ester distribution of approximately 95 to 96% and 4 to 5%, respectively, and less than 0.1% of the two lower-end esters. The exact composition of the vegetable oil, which is typically used to describe a blend of a variety of oils customarily used for cooking, was not specified. The heated blends were added to the diets at concentrations of 5 or 10%. Two other groups of rats were provided the OA/VO blends without heating at a dietary concentration of 10%. Additionally, 4 more groups were administered unheated, pan-fried, or deep-fried vegetable oil (at 10%) or the basal diet (AIN-76). All diets were supplemented with various levels of vitamins A and E. Since the basal diet already contained menadione (vitamin K_3), it was not necessary to supplement diets

with additional vitamin K. Body weights and food consumption of rats were monitored throughout the study. Blood samples were collected at week 13 for hematology and biochemistry. At study end, animals were necropsied and subjected to gross and microscopic evaluations. Absolute and relative weights of the liver, gonads, kidneys, adrenals, heart, spleen, brain, and thymus were determined. Based on reported weekly food consumption, males and females receiving 75/25 OA/VA at a dietary concentration of 10% ingested approximately 4.5 and 3 g olestra/kg body weight/day, respectively, whereas in the 5% group, males and females were exposed to approximately 2 and 1.5 g olestra/kg body weight/day, respectively. Dietary concentrations of 10% of the 35/65 OA/VO blend were equivalent to olestra dose levels of approximately 1.9 and 1.3 g/kg body weight/day for male and female rats, respectively, and 0.8 and 0.6 g/kg body weight/day for males and females, respectively, ingesting the blend at 5% in the diet.

No early deaths and no ocular variations were reported. Overall, OA/VO-treated groups exhibited higher food consumption values (likely due to compensation for caloric dilution). Body weights and weight gains were generally comparable across the treatment groups. While all treatment groups tended to have higher body weights compared to the basal controls, the difference was not statistically significant. No significant differences were observed in food utilization efficiency. Variations in a number of hematological and clinical chemistry endpoints [*i.e.*, differences in red blood cell count (RBC), mean corpuscular hemoglobin (MCH), prothrombin time (PT), and glucose levels in males, and total protein, globulin, and bilirubin levels in females] observed between groups, while statistically significant, were concluded to be due to normal biological variance, since the differences were sporadic, not dose-dependent, and did not cause any morphological effects. Moreover, no consistent differences were noted between groups receiving heated blends and those fed the corresponding unheated blend or vegetable oil. Although differences were observed in the absolute weight of adrenal glands and relative brain and heart weights between males of certain groups, none of these variations occurred between animals fed heated and those fed unheated OA/VO blends. Furthermore, differences in relative organ weights also did not occur between groups receiving heated OA/VO blends and heated vegetable oil, or unheated OA/VO blends and unheated vegetable oil. No treatment related gross or microscopic alterations were observed. It was concluded that heated OA/VO blends were non-toxic and did not differ from unheated OA/VO blends or vegetable oil.

The potential short-term toxicity of heated olestra was evaluated in groups of 40 Fischer 344 rats (20 animals/sex/group) (Williams *et al*., 1996). Olestra was heated under conditions that exceeded those expected in commercial preparation of snacks fried in olestra (*i.e*., olestra heated to 177 to 185°C and used to cook batches of potato slices for a total of 5 hours/day over 5 to 7 days). Heating resulted in elevated peroxide values (8 mEq/kg) and approximately 5- and 18-fold increases in free fatty acids and in polymer content, respectively. Test animals were administered 1, 5, or 10% of heated olestra in the diet for a period of 91 days. All test diets were supplemented with vitamins A, D, and K at levels 5-fold greater than those recommended

by the National Research Council (NRC) for the rat, and with vitamin E at concentrations of 0.87, 4, and 8% in the low-, mid-, and high-dose diets, respectively. Two control groups of rats were provided the basal diet (Purina Certified Rodent Mash-5002) with or without vitamin supplementation. A third control group was maintained on a diet containing 10% heated triglycerides (TG) without added vitamins. Animals were examined twice daily for general appearance and morbidity. Thorough physical examinations were performed on a weekly basis, as were measurements of body weights. Food intake was recorded three times per week. Examinations of the eye were conducted at study beginning and again at study completion. Serum and urine samples were collected for hematology, clinical chemistry, and urinalysis upon study completion. At necropsy, all animals were subjected to a gross examination, and organs (*i.e.*, brain, adrenals, ovaries, testes with epididymides, kidneys, and liver) were excised and weighed. Organ-to-body weight and organ-to-brain weight ratios also were calculated. A full spectrum of major organs was collected from all animals in the 3 control groups and in the high-dose olestra group, as well as from all animals dying prior to study completion in the low- and mid-dose olestra groups, for microscopic evaluation. For low- and mid-dose animals surviving until study termination, histopathology was limited to the lungs, liver, kidneys, and any gross lesions.

No early deaths were observed in any of the groups. Slight to minimal loss of fluid from the anus was noted in olestra-treated rats which was considered by the authors to be related to the high dose levels at which the test material was administered (it was not clear from the study description if this effect was observed in all groups of olestra fed animals, or if it was only observed with the highest dose). Based on average food consumption observed during the study period, male and female rats consumed approximately 0.6 and 0.7, 3 and 4, and 7 and 8 g olestra/kg body weight/day in the low-, mid, and high-dose groups, respectively. Although food intake of rats in the 10% olestra group was approximately 10% greater than that observed in controls, the difference in food consumption was not accompanied by variations in body weight or food utilization efficiency compared to controls. In light of the fact that olestra is not absorbed and is therefore non-caloric, the increase in food consumption was not unexpected. Conversely, rats receiving TG in the diet consumed between 17 and 19% more food than basal diet controls, but exhibited a 12% greater weight gain due to higher food utilization efficiency (22 to 33%) than other groups of rats. All clinical chemistry, hematological, and urinalysis parameters were comparable among animals of different groups, and ophthalmoscopy and macroscopic examinations were unremarkable. Organ weight variations were limited to a small, statistically significant reduction in the absolute and relative weights of the adrenals in high-dose males, but only in comparison to the basal control group, which did not receive additional vitamin supplements in the diet. Furthermore, the variability in adrenal weights was also noted by the authors to fall within the limits of historical ranges. No treatment related histological findings were observed in the adrenals or any other organs. The study results indicate that administration of heated olestra in the diet at concentrations of up to 10% (approximately 7 to 8 g olestra/kg body weight/day) was not associated with any adverse effects in rats.

6.3.2 Chronic Oral Toxicity Tests

Mice

Two studies were performed to assess the potential long-term toxicity of olestra [(98.9% purity; 84% octaester, 16% heptaester, and <0.1% of each hexaester and penta- and lower esters; 51% stearic acid (C_{18}), 29% oleic acid ($C_{18:1}$), 11% palmitic acid (C_{16}), and 9% linoleic acid ($C_{18:2}$)] in Swiss CD-1 mice in which all test diets were supplemented with vitamins A, D, E, and K (10 mg/kg diet) (Lafranconi *et al*., 1994). The test material used in these studies consisted of octa and hepta esters in a ratio of 5:1, which comprised close to 100% of the ester composition. Hexa and lower-esters contributed less than 0.1% to the overall ester distribution. In the first study, groups of 200 mice (100/sex) were provided 2.5, 5, or 10% of olestra in the diet. Additionally, the study included two control groups, one receiving a basal diet with supplemental vitamins and the other without. The second study was conducted in parallel with the first study and was intended to serve as a confirmation of results observed in the first study. In the second study, mice were administered 0 or 10% of olestra in the diet. At each dose level, 50 animals per sex continued on their respective diets for 24 months, whereas 15 mice/sex/ group were necropsied at 12 months for an interim evaluation and 35 mice/sex/group were used for periodic assessment of vitamin status (at months 1, 2, 3, 6, and 9). Animals were observed daily for general health, appearance, and survival. Thorough physical examinations, determinations of body weights, weight gain, and food consumption were performed once a week. Ophthalmoscopy was conducted at study initiation and again at 12 and 24 months. Blood samples for clinical chemistry and hematology were collected from mice at the 12- or 24-month scheduled necropsies. All study animals were subjected to gross examination and the liver, kidneys, brain, spleen, heart, and gonads were weighed and organ-to-body and organ-to-brain ratios determined. Tissue samples from a wide range of organs and any gross lesions and tissue masses also were obtained from all animals including those found to be dead or in a moribund state. Samples from the liver, kidneys, lung, heart, and GI tract were examined histologically at every dose level. All other tissue samples were subjected to histopathological examination only from animals in the control and high-dose groups. In case of any abnormalities observed at the high-dose level, the same tissues were evaluated at every other dose level.

Based on mean food intake values in the first study, low-, mid-, and high-dose male mice ingested between 3 and 4, 6 and 7, and 15 g olestra/kg body weight/day, respectively, whereas low-, mid-, and high-dose females consumed approximately 4, between 8 and 9, and 17 g olestra/kg body weight/day, respectively. In the second study, olestra added to the diet at 10% resulted in dose levels in the range of 16 to 18 g/kg body weight/day in males and 18 to 19 g/kg body weight/day in females based on mean food intake. No overt signs or symptoms of toxicity and no variations in ocular abnormalities among groups were observed throughout the study period. No consistent variations were observed among groups in body weight, weight gain, and

survival rates. Statistically significant increases were observed in food consumption at week 52 in test males and females in the second study, and in high-dose males and females in both studies at week 103. Food consumption also was significantly elevated in females at the mid-dose level compared to controls. Assessment of vitamin status did not reveal any differences in hepatic levels of vitamins A and E in olestra-treated mice compared to the unsupplemented control group. Likewise, vitamin K status was comparable among the groups. While serum 25-hydroxyvitamin D levels were 30 and 15% lower in high-dose males and females, respectively, compared to controls, they were well above the minimum level required to maintain normal vitamin D status. Control mice receiving the vitamin-supplemented basal diet were hypervitaminotic. Compared to controls, clinical chemistry variations were limited to a significant decrease in bilirubin values in mid-dose males and, a not unexpected reduction in cholesterol values in test males in the second study at 12 months. At study termination, clinical chemistry values were comparable among groups in both studies. No statistically significant variations were noted in electrolyte levels. In the first study, evaluation of hematological parameters at 12 months revealed a significant reduction in mean corpuscular hemoglobin (MCH) concentration and red blood cell count (RBC) in mid-dose males and in high-dose females, respectively, compared to controls. At 24 months, MCH values were increased significantly in high-dose females in both studies, as was mean corpuscular volume (MCV), but only in the first study. Additionally, MCH values also were elevated compared to control levels in females administered 2.5% olestra in the diet. Overall, none of the variations observed in the clinical chemistry and hematology parameters were considered to be treatment-related given the lack of a dose-response and persistence of effect throughout the entire study period. Also, results differed from one study to the other. Macroscopic examination of animals whether sacrificed at necropsy, found dead, or sacrificed in a moribund sate, was unremarkable. Absolute and relative brain, heart, kidney, spleen, and testes weights were comparable among test and control groups. In the first study, absolute and relative ovary weights were significantly reduced in high-dose females and relative liver weights were decreased in low-dose females. These organ weight variations were not confirmed in the second study. No treatment related differences in the incidence of neoplastic and non-neoplastic lesions was observed between treated and control groups in either study. Also, no morphological changes of the GI tract were observed in olestra-treated mice compared to control mice.

Rats

Wood *et al*. (1991b) performed two studies in Fischer 344 rats to determine potential chronic toxicity of olestra (99% purity). The test substance consisted of fatty acid esters of sucrose, with an octa:hepta:hexa ester distribution of 60:30:10. Fatty acid composition consisted of 10% palmitic acid (C_{16}), 6% stearic acid (C_{18}), 44% oleic acid ($C_{18:1}$), 35% linoleic acid ($C_{18:2}$), 3% linolenic acid ($C_{18:3}$), and <1.5% other fatty acids. Throughout the study periods, rats were allowed *ad libitum* access to water and food. The diets were supplemented with vitamins A, D, E, and K at 5 times the levels recommended by the NRC. In the first study, male and female

rats (75/sex/group) were administered 0, 0.99, 4.76, or 9.09% of olestra in the diet for up to 24 months. At each dose level, 30 rats (15/sex) were necropsied at 12 months, with 100 rats (50/sex) maintained for the full duration of the study period. The remaining 20 rats (10/sex) were retained for additional investigational studies. In the second study, 50 males and 73 females were provided 0 or 9.09% of olestra in the diet. At 12 months, 15 females in each group were necropsied, whereas the remainder of females and all males were sacrificed at 24 months. Animals were observed daily for general condition and once weekly a detailed physical examination was performed. Body weights and food consumption were measured and body weight changes and intake of the test substance were calculated weekly for the first 12 weeks and monthly thereafter. Food utilization efficiency was determined for the first 12 months in the first study, and an ophthalmoscopic examination was performed on all animals at study beginning and again at scheduled necropsy on all surviving animals. In the second study, animals were subject to ophthalmoscopy at months 9 and 24. At 12 months in the first study, and at 24 months in both studies, urine (first study only) and blood samples for hematology and clinical chemistry were collected from up to 15 animals. In both the first and second study, all animals were examined macroscopically, and in the first study the brain, heart, kidneys, liver, and spleen were weighed and organ-to-body and organ-to-brain ratios calculated for all animals surviving until the scheduled killing. In the second study, livers were weighed from all animals surviving until scheduled necropsy (either 12 or 24 months), whereas spleen and brain weights were obtained only from animals surviving until study termination. Whenever possible, organ-to-body ratios were determined. In both studies, histopathological evaluation was conducted on a wide spectrum of organ tissue samples (including reproductive organs in study 2) from all control and high-dose animals dying during the study period and those surviving until study completion. Additionally, the liver and pituitary glands were examined microscopically from animals at all dose levels. Likewise, tissues from different segments of the GI tract also were examined microscopically from all animals sacrificed at 12, 18, and 24 months. Furthermore, all gross lesions and tissue masses were examined from control rats and high-dose animals, as well as from all animals dying during the study, found and sacrificed in moribund condition, and from all rats sacrificed at 12 months. Liver lobe samples for stereological examination of basophilic foci at 12 and 24 months were collected from 15 test and 15 control females only in the second study.

Based on mean food consumption, low-, mid-, and high-dose male rats in the first study consumed approximately 0.4, 2, and 5 g olestra/kg body weight/day, respectively. Female rats in the low-dose group consumed between 0.5 and 0.6 g olestra/kg body weight/day and approximately 3 and 6 g olestra/kg body weight/day at the mid- and high-dose levels, respectively, during the course of the first study. In the second study, the high-dose male and female rats maintained for 12 months ingested approximately 5 and 6 g olestra/kg body weight/day, respectively, whereas males and females in the 24-month trial consumed approximately 4 and 5 g olestra/kg body weight/day, respectively. No differences were observed in growth, longevity, and general health among animals of different groups in either

study. Likewise, the results of ophthalmoscopy, hematology, clinical chemistry, urinalysis, and the gross examinations were unremarkable. Fecal analyses did not reveal any effects of olestra treatment on fecal water content. In study 1, but not 2, a significant increase in body weight was observed in mid-dose males and in high-dose males and females at 12 months; however, the differences in body weight did not exceed 5% compared to controls. In both studies, food consumption was observed to increase with increasing levels of olestra, reaching statistical significance at the high-dose level, as a result of the low caloric density of the diets containing the test material. This finding was accompanied by fluctuations in food utilization efficiency. Mortality rates of all groups were comparable to control values in this and other studies (*i.e.*, historical values). Isolated absolute organ weight and organ-to-body weight differences were observed in the studies, but none were dose-related or observed consistently across both studies or genders and therefore were not considered to be treatment related. The incidences of all non-neoplastic and neoplastic lesions in treatment groups were comparable to concurrent controls or within historical controls.

Dogs

In order to assess the potential long-term toxicity related to the consumption of olestra in a non-rodent species, Miller *et al*. (1991) conducted a 20-month feeding study in 4- to 6-month-old pure-bred beagle dogs. Groups of 10 male and female dogs (5/sex/group) were administered olestra (99.1% purity) in the diet at a concentration of 0 (Purina Canine Chow), 5, or 10%. Approximately 91% of the olestra test material consisted of octaesters, with the remaining 9% identified to be heptaesters. Lower esters comprised less than 0.1% of the ester composition. Stearic acid (C_{18}) made up more than 50% of the fatty acid composition, with oleic acid ($C_{18:1}$), linoleic acid ($C_{18:2}$), palmitic acid (C_{16}), and other fatty acids accounting for 19.7, 15.0, 9.6, and 2.3% of the distribution, respectively. Prior to the initiation of the 20-month study, a preliminary 91-day study was performed to determine the optimal vitamin A and E supplementation levels required to offset any possible toxicities related to the effect of olestra on vitamin status. In the 91-day study, olestra-treated dogs, at each dose level, received between 1.25 and 2.5-times the NRC requirement for vitamin A, and between 2.5 and 5.0 times the NRC requirement for vitamin E. NRC requirements for vitamin A and E in the dog are 5,000 IU/kg/diet and 50 IU/kg diet, respectively. In the 20-month study, dogs receiving 5% olestra were supplemented with vitamins A and E at 1.5 and 2.5-times the NRC requirements, respectively. Dogs receiving 10% olestra were given 3 and 5 times the NRC requirements for vitamins A and E, respectively. Throughout the study, food consumption was recorded daily, and dogs were observed for any overt signs and symptoms of toxicity. Dogs were weighed once per week. Ophthalmoscopy, hematology, and clinical chemistry examinations were performed at 12 and 20 months. At study completion, dogs also were subjected to a neurological examination and subsequently necropsied and examined for any gross abnormalities. Absolute and relative organ weights were determined and tissue samples were preserved appropriately for histopathological examination.

Low- (*i.e.*, 5%) and high-dose (*i.e.*, 10%) males consumed 1.4 and 2.6 g olestra/kg body weight/day, respectively, whereas low- and high-dose females consumed 1.3 and 2.9 g olestra/kg body weight/day, respectively. All animals survived until study termination and did not exhibit any morbidity, diarrhea, emesis, or loss of appetite. An increase was noted in the incidence of soft-stool formation in olestra-treated animals. Food consumption was observed to increase slightly; however, the increase attained statistical significance only during the early stages of the study and only in females. The somewhat elevated food intakes were accompanied by slight, but non-statistically significant elevations in mean weekly body weights in high-dose dogs compared to control animals. Notably, caloric intakes were comparable among all groups. Both ophthalmoscopic and neurological examinations were unremarkable. Only infrequent and inconsistent variations were noted in the hematological and clinical chemistry parameters, all of which remained within the normal historical control ranges. Absolute and relative organ weights were similar among all groups of dogs. Pathological findings were limited to sporadic lesions, common to this breed of dog. Microscopic findings were typically classified as minimal to mild and occurred with similar incidence and severity in all groups of dogs. Occurrence of mild degeneration of the tubular spermatogenic epithelium in 2 of the 5 high-dose males, in the absence of similar effects in either the low-dose or control group, comprised the only exception; however, as noted by the authors, mild tubular degeneration is frequently encountered in laboratory beagles (Hotterndorf and Hirth, 1974). Overall, the results of the study indicated that olestra provided to dogs at dose levels 20-fold greater than the estimated intake of olestra from its intended conditions of use, did not induce any toxicologically significant adverse effects.

Monkeys

In a study intended to evaluate SPE as a potential hypocholesterolemic agent, male African green monkeys (*Cercopithecus aethiops pygerythrus*) were administered diets containing approximately 10% SPE (ester and fatty acid composition not specified) (Adams *et al.*, 1981). Specifically, following a 2-month control period during which monkeys received 0.7 mg cholesterol/cal to induce a state of hypercholesterolemia, the dietary cholesterol level was lowered to 0.3 mg/cal and monkeys (n = 30) were assigned to 1 of 4 groups to receive (i) the control diet with 50% of fat calories replaced with fiber [low-fat (25%) - no SPE; n = 8], (ii) unchanged control diet [high-fat (40%) - no SPE; n = 8], (iii) control diet with half of the fat replaced with SPE [low-fat-SPE; n = 7), (iv) or the control diet plus the same amount of SPE as in the “low-fat-SPE” diet (high-fat-SPE; n = 7) for 15 consecutive months. The low-fat-SPE and high-fat-SPE diets, which each contained approximately 10% SPE, resulted in daily dose levels of approximately 3.2 and 3.5 g SPE/kg body weight, respectively. Each diet provided a total of 150 kcal/kg body weight per day. Throughout the study, monkeys were examined daily and blood samples for clinical chemistry (*i.e.*, blood urea nitrogen, serum creatinine, fasting blood glucose, total serum protein, and total serum albumin:globulin ratio) and hematology (*i.e.*, hematocrit, hemoglobin, total and differential leukocyte counts, and total erythrocyte count) were

collected on days 28 and 42 of the control period and on days 60, 120, 240, and 300 of the treatment period. Plasma cholesterol levels and body weights were measured on weeks 4, 6, and 8 of the control period, at 2-week intervals during the first 6 months of the treatment period, and monthly thereafter. All animals were reported to gain weight during the study period and no significant differences were observed among different treatment groups in body weight and weight gain. Monkeys were reported to remain in excellent health for the duration of the experimental period. Incidences of loose stools with mucous and blood were reported with similar frequency among all groups. Additionally, 4 monkeys (3/lowfat-SPE and 1/high-fat-SPE) experienced rectal prolapse and an abscessed canine tooth was reported in 1 high-fat-SPE-treated monkey. All clinical chemistry and hematology parameters remained within normal limits and no significant variability was noted among the different treatment groups. Plasma cholesterol concentrations also were similar among all groups at the end of the study period; however, monkeys in the groups receiving SPE in the diet exhibited a greater absolute and percent change in cholesterol levels compared to pre-experimental values. The effect of SPE on cholesterol values was greatest in monkeys exhibiting a high or intermediate sensitivity to dietary cholesterol levels, compared to those exhibiting a low plasma cholesterol response to dietary cholesterol. Conversely, no differences in cholesterol levels were found between the two SPE-treated groups, or between the two non-SPE-treated groups.

Following the 15-month experimental feeding period, monkeys in the Adams *et al*. (1981) study continued on the same diets for an additional 14 months, such that in total monkeys received olestra-containing diets for 29 months. These monkeys also were used in the study conducted by Wood *et al*. (1991a) to assess olestra absorption and distribution following oral administration (see Section 6.1). It was also noted in the Wood *et al*. (1991a) study that 2 months prior to the onset of the 29-month feeding period, the monkeys had been used in a 9-month trial during which olestra also was provided in the diet at a concentration of 10%. Eighteen weeks following completion of the 29-month feeding trial, test and control monkeys were placed on diets containing 0, 2, 4, or 6% olestra for 2 months in random order. Some monkeys were therefore exposed to olestra for a total of 44 months. Since the purpose of the Wood *et al*. (1991a) study was to assess the potential for the accumulation of olestra in the liver, no details were provided regarding toxicological parameters. However, in an unpublished private communication in which the use of the data from the Adams *et al*. (1981) efficacy study to support the safety of olestra was considered, it was reported that administration of olestra for up to 44 months did not adversely affect general health and several clinical chemistry parameters including levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Stitzel, 1984). Furthermore, results of both gross pathology and microscopy of lung and intestinal tissues were unremarkable. Histopathology also did not reveal any proliferative lesions in the hepatic tissue. It was noted that the absence of a control group (*i.e*., all monkeys had been treated with olestra for at least 6 months) precluded any assessment regarding any potential quantitative changes in expected background lesions known to occur in this strain of monkey.

6.3.3 Genotoxicity Assays

In Vitro

The potential mutagenicity and genotoxicity of olestra has been extensively studied in numerous *in vitro* assays in both prokaryotic and eukaryotic test systems. The genetic endpoints evaluated in these studies included induction of reverse mutations, chromosomal aberrations, and unscheduled DNA synthesis (UDS). Furthermore, in order to determine if metabolic activation affected the mutagenic/genotoxic potential of olestra, assays were performed with olestra alone or in the presence of a bioactivation system. The ester and fatty acid composition of the olestra test material used in studies conducted by Williams *et al*. (1996) was previously described in Section 6.3.1. The olestra test material used in assays performed by Skare *et al*. (1990) comprised 56.3% octaesters, 34.3% heptaesters, 9.3% hexaesters, and 0.8% penta- and lower esters. The fatty acid distribution consisted of palmitic (10.6%), stearic (5.4%), oleic (44.6%), linoleic (34.7%), linolenic (2.1%), and other (2.7%) fatty acids.

Evaluated in the Ames assay in several strains of *Salmonella typhimurium* (*i.e.*, TA98, TA100, TA1535, TA1537, and TA1538) with and without metabolic activation (S9) at concentrations of up to 21.6 mg/plate, both heated and unheated olestra consistently tested negative for mutagenic activity (Skare *et al.,* 1990; Williams *et al.,* 1996). The heated olestra was prepared by batch-frying potato slices for 25 to 32 hours over 5 to 7 days (approximately 5 hours/day) at 177 to 185°C. Additionally, the *Salmonella* mutagenesis assays performed by Williams *et al*. (1996) were repeated with a non-ionic surfactant detergent, to increase the transmembrane flux of olestra. Results for samples treated with the surfactant also were negative and showed no differences in comparison to results obtained without the addition of the surfactant (Williams *et al.,* 1996).

The absence of mutagenicity observed in the bacterial test systems was confirmed in eukaryotic organisms. Following incubation of mouse lymphoma cells, Chinese hamster ovary (CHO) cells, and rat hepatocytes with heated or unheated olestra, cells were examined for mutation frequency, chromosomal aberrations, and UDS, respectively (Skare *et al*., 1990; Williams *et al*., 1996). In the mouse lymphoma assays, the highest concentration of olestra tested was 23.4 mg/mL, whereas 5.0 mg/mL was the highest concentration reported in both the chromosomal aberration and UDS assays (Skare *et al.,* 1990; Williams *et al.,* 1996). In the mouse lymphoma assay, no significant increases in mutant frequencies were reported at the *tk* locus in olestra-treated cells with or without metabolic activation in comparison to negative controls (Skare *et al.,* 1990; Williams *et al*., 1996). Likewise, at concentrations of up to 5.0 mg/mL, olestra did not significantly increase UDS in rat hepatocytes without metabolic activation. Similarly, olestra did not increase the number of chromosomal aberrations/cell in CHO cells in comparison to controls, both in the absence and presence of an exogenous source of metabolic activation compared to negative controls. As in to the *Salmonella* mutagenesis assays, experiments conducted by Williams *et al*. (1996) also were performed with a non-ionic

surfactant. The addition of the detergent did not induce any changes with respect to the lack of olestra-related mutagenicity/genotoxicity in mammalian cells.

In Vivo

The potential genotoxicity of heated olestra was evaluated in an *in vivo* bone marrow cytogenetic assay in rats. Heated olestra was administered to male and female Sprague-Dawley rats (5 animals/sex/dose) at dose levels of 0 (control), 500, 1,700, or 5,000 mg/kg body weight/day (Williams *et al*., 1996). Conditions of heating were the same as described for the *in vitro* studies. Rats were administered olestra by gavage, and were divided into single- and repeated-exposure groups, with animals in the latter groups treated for a period of 5 days. Animals were sacrificed at various times post-administration and bone marrow collected from the femurs for analysis of bone marrow cells for chromosome abnormalities. In animals administered olestra at dose levels of up to 5,000 mg/kg body weight/day, the percentage of aberrant cells and the number of chromosomal aberrations/cell were similar in comparison to negative controls. It should be noted that the maximum dose level of olestra tested (*i.e.,* 5,000 mg/kg body weight/day) represents an amount that is 38-fold greater than the 90th percentile user-only intake of olestra by humans from the consumption of olestra-containing foods.

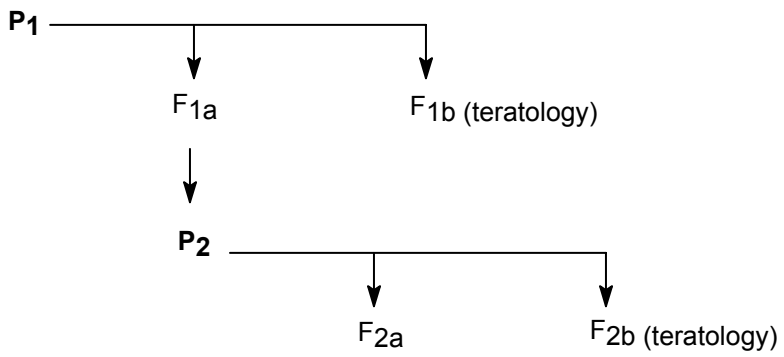
Overall, results of the *in vitro* and *in vivo* experiments indicate that olestra does not exhibit mutagenic or genotoxic activity, even following repeated exposures at relatively high dose levels. Moreover, *in vitro* test results were unaffected by the addition of microsomal enzymes intended to simulate potential *in vivo* bioactivation or by the addition of surfactant detergents, which would be expected to aid in the transmembrane flux of olestra. Since heating of olestra under extreme conditions causes measurable changes in the chemical composition of olestra, such as increasing levels of reactive peroxides (Williams *et al.,* 1996), *in vitro* tests also were conducted with heated samples of the SPE. Excessive heating did not increase the potential of olestra to induce mutagenic or genotoxic responses.

6.3.4 Developmental and Reproductive Studies

To assess the potential for olestra to act as a reproductive or teratogenic toxicant, a two-generation reproduction and developmental study was conducted in Sprague-Dawley CD rats (Nolen *et al*., 1987). SPEs (58.0% octaester, 33.0% heptaester, 8.2% hexaester, and 0.7% penta- and lower esters; fatty acid composition not specified) were administered at dietary concentrations of 0, 1, 5, or 10% [approximately 0 (Purina Lab Chow), 0.5, 2.5, and 5 g/kg body weight/day, respectively (U.S. FDA, 1993)], with the 2 highest dose groups also receiving supplemental vitamins A and E at concentrations of 4.8 and 18.8 g/kg in the diet, respectively. Hydrogenated palm oil also was added to the high-dose diets at a concentration of 2% to control potential anal leakage of the test material. At all other dose levels, including the control group, the oil was added in order to maintain a comparable level of lipids among groups. Test diets

were fed to the parental males (15/group) and females (30/group) (P_1) for 91 days prior to mating (see Figure 6-1 for overview of mating procedure). Lactation and viability indices were recorded for each F_{1A} litter. On post-natal day 29, 15 male and 30 female F_{1A} pups were randomly selected for breeding (P_2). Following weaning of the F_{1a} generation, P_1 dams were rested and then mated again to produce the F_{1b} generation. On gestation day (GD) 20, P_1 dams were sacrificed and the F_{1b} fetuses removed. As in the previous generation, P_2 dams were rested prior to the next mating after having weaned F_{2a} pups and subsequently sacrificed on GD 20. All F_{1b} and F_{2b} fetuses were examined for gross abnormalities. Additionally, 1/3 of the F_{1b} and F_{2b} fetuses were examined for skeletal anomalies, while the rest were sectioned and examined for soft-tissue abnormalities. At weaning, F_{2a} pups were grossly examined but not necropied. With the exception of the F_{2a} pups, necropsy was performed on all rats in the study. The heart, liver, and kidneys were weighed and all major organ tissues from control and high-dose animals were preserved for microscopic examination.

Figure 6-1 Schematic Overview of Mating Procedure



In the first generation (F_{1a}), a slight, but statistically significant increase was noted in the number of pups born dead to rats in the 10% group; however, the actual number of dead pups (*i.e.*, 0.8/litter) was low and not unusual for this species. This effect did not occur in the second generation (F_{2a}). No differences were noted in the conception rate, the number of live pups born, or the sex ratio in either generation. Likewise, the survival of neonates was similar among groups. First generation pups (F_{1A}) in the 10% group had statistically significant higher body weights than controls at birth and on day 4, whereas significantly greater body weights were observed in male and female pups in the second generation (F_{2A}) at weaning (day 22). The authors considered this to be likely related to the increased food consumption of dams during gestation and lactation (resulting in increased intake of other nutrients, particularly protein). While dietary SPEs did not affect the growth of parental rats except for high-dose F_0 dams in which body weights were significantly elevated compared to controls, both sexes of rats at the high-dose level exhibited significantly increased food consumption, accompanied by a dose-related decrease in food conversion efficiency. With respect to any of the teratological indices

evaluated, no statistically significant differences were observed in the first generation (F_{1b}). In the second generation (F_{2b}), a statistically significant increase in the number of corpora lutea and resorptions was reported in 10% females. The elevated incidence of corpora lutea was thought by the authors to have occurred as a result of random variation, whereas the latter finding was a result of unusually low control group values (compared to historical controls). Kyphosis (curvature of the spine) was observed in 8 pups in the second generation (F_{2b}) in the group administered 1% the SPEs in the diet; however, the pups were clustered in 2 litters of dams that were sisters and were sired by the same male. As such, these findings were concluded to be genetic aberrations. Moreover, the occurrence of kyphosis was not confirmed in the first generation and was not dose related. None of the pups examined for skeletal malformations at the mid- and high-dose levels exhibited abnormalities of the spine. Otherwise, no differences in soft-tissue and skeletal abnormalities related to the treatment of parental rats with SPEs were noted. Likewise, no consistent, statistically significant differences were observed in any pathological endpoints (including histopathology). Overall, the results of this study indicated that dietary SPEs did not adversely affect reproduction or development in rats.

The absence of olestra-related teratological effects was confirmed in one unpublished rat study (Mattson and Hollenbach, 1977; unpublished) and in a rabbit study, the results of which have only been published as an abstract (Denine and Schroeder, 1993). In the study conducted by Mattson and Hollenbach (1977; unpublished), 4 groups of 20 female Charles River Sprague-Dawley rats were provided an 80:20 mixture of SPEs and completely hydrogenated palm oil in the diet at concentrations of 0 (soybean oil control), 4, 8, or 15% beginning on GD 6 and continuing until day 13, at which point half of the dams were sacrificed. The mixture of SPE that contributed 80% to the overall test material comprised 69% octaesters, 28% heptaesters, and 3% hexaesters. Palmitic acid (C_{16}), stearic acid (C_{18}), oleic acid ($C_{18:1}$), and linoleic acid ($C_{18:2}$) contributed 7.6, 3.6, 15.3, and 72.4% to the fatty acid composition with the remaining 1.2% accounted for by other unspecified fatty acids. The remaining 10 females per group continued on their respective diets for another 2 days (until GD 15) and were subsequently sacrificed on GD 20. Based on measured maternal food consumption, females sacrificed on GD 13 consumed approximately 3.1, 6.0, and 12.3 g SPEs/kg body weight/day at the low-, mid-, and high-dose levels, respectively. Low-, mid-, and high-dose females treated until GD 15, ingested SPEs at daily dose levels of approximately 2.8, 6.4, and 11.7 g/kg body weight, respectively. A significant increase in food consumption was observed among treated dams. Additionally, statistically significant variations were noted in implantation efficiencies of treated dams sacrificed on GD's 13 or 20; however, the differences were inconsistent between the 2 time periods and as such concluded by the study authors to be incidental. All reproductive parameters (*e.g.*, mean numbers of corpora lutea, live fetuses, implantations, resorptions, *etc.*) and fetal indices (*e.g.*, size, weight, viability, skeletal and soft-tissue malformation, *etc.*) were comparable among groups.

In the study conducted with rabbits, groups of 18 mated female New Zealand white rabbits were administered olestra (76.5% octaesters, 20.4% heptaesters, 3.2% hexaesters, and <0.3% of penta- and lower esters; 0.5% myrisitic acid, 21.4% palmitic acid (C_{16}), 4.3 stearic acid (C_{18}), 29.6 oleic acid ($C_{18:1}$), 38.8 linoleic acid ($C_{18:2}$), 0.1% linolenic acid ($C_{18:3}$), and 5.0% arachidic acid (C_{20})), which had been used for deep frying of potatoes, *via* gavage at dose levels equivalent to 0, 1, 5, or 10% in the diet during GD's 6 to 18 (Denine and Schroeder, 1993). On GD 30, does were necropsied and the fetuses removed. No maternal toxicity was observed at any dose level. The number of external, visceral, and skeletal malformations on a per fetus or per litter basis in olestra-treated groups did not differ significantly from controls. Furthermore, the types of malformations noted were not unusual for this strain of rabbit and the number of fetal malformations was within the historical range. No significant differences were observed in litter sizes, mean fetal weights, sex distribution, and pregnancy rates of treated rabbits compared to controls. It was therefore concluded, based on the results of this study, that heated olestra is neither maternally toxic nor teratogenic at oral doses of up to 10% in the diet.

6.3.5 Comparison of NOAELs to Estimates of Human Consumption

Comparison of the NOAELs established under the conditions of the long-term animal toxicity studies (Miller *et al*., 1991; Wood *et al*., 1991a; Lafranconi *et al*., 1994) to estimates of human consumption, indicates that intake of olestra at the 90th percentile is several fold lower than the NOAELs, which were the highest dose levels tested. As summarized in Table 6-1, the available NOAEL values support margins of safety in the range of 20 to 146 relative to the 90th percentile intake estimates and 47 to 345 when mean intake estimates are considered.

Table 6-1 Comparison of Dose Levels Tested in Animal Studies with Estimates of Human Consumption

Study (reference)	NOAEL (g/kg bw/day)	Mean (g/kg bw/day)	Margin of Safety	90th %centile (g/kg bw/day)	Margin of Safety
2-Year mouse study (Lafranconi *et al*., 1994)	15 to 19	0.055	300-345	0.13	115-146
2-Year rat study (Wood *et al*., 1991a)	4 to 6	0.055	73-109	0.13	31-46
20-Month dog study (Miller *et al*., 1991)	2.6 to 2.9	0.055	47-53	0.13	20-22

NOAEL = no-observed adverse effect level

7.0 INFORMATION TO ESTABLISH THE SAFETY OF OLESTRA – NUTRITION

7.1 Introduction

In this section, the effects of olestra on GI physiology and function, GI symptoms, and the absorption of lipophilic compounds are reviewed.

7.2 Gastrointestinal Physiology and Function

7.2.1 Esophageal Reflux and Gastric Acid

Dietary fat stimulates the the duodenal release of various GI hormones, such as cholecystokinin (CCK) and neurotensin. Lipolysis of fat, as well as chylomicron formation, appear to be essential for the release of these GI hormones (Hildebrand *et al.,* 1998; Meyer *et al.,* 1998; Raybould *et al.,* 1998; Matzinger *et al.,* 2000; Feinle *et al.,* 2001; O'Donovan *et al.,* 2002). Olestra is resistant to digestion by mammalian and bacterial lipases; thus, because olestra is not associated with lipolysis or with chylomicron formation, it is not expected to elicit GI effects typically associated with digestible fat, such as gastroesophageal reflux (GER) and delays in gastric emptying.

Maas *et al.* (1997) demonstrated, in healthy human subjects, that the intraduodenal infusion of digestible fat was associated with a significant reduction in gastrin-stimulated gastric acid secretion and significant increases in plasma CCK levels; in contast, the intraduodenal infusion of SPE did not suppress gastrin-induced gastric acid secretion and was not associated with significant increases in plasma CCK levels. This observation is consistent with the finding that unlike digestible fat, SPE does not cause an increase in peptide YY, an enterogastrone secreted in response to CCK and believed to be involved in the inhibition of gastric acid secretion by ingested fat (Maas *et al.,* 1998b). That CCK and peptide YY are not released in response to the duodenal perfusion of SPE suggests that the duodenum responds to SPE as a non-nutritive ingredient rather than a digestible lipid. This is supported by the observation, in rats, that olestra is not associated with increased secretions of pancreatic lipase (Hager and Schneeman, 1986).

Maas *et al.* (1997) suggested that SPE, by not inhibiting gastrin-stimulated gastric acid secretion, may potentiate the pathogenesis of gastroesophageal reflux disease (GERD). This phenomenon is highly unlikely for several reasons. First, the cumulative minutes of postprandial GER (defined as a pH <4.0) as well as the cumulative episodes of postprandial GER were significantly lower following the consumption of 3.5 ounces olestra-containing chips (approximately 28 g of olestra) than following consumption of 3.5 ounces of triglyceride-containing chips (Just *et al.,* 1993). Second, unlike digestible fat, olestra does not stimulate the

duodenal release of CCK (Kelly and Hunter, 1996; Maas *et al.,* 1997; Maas *et al.,* 1998a). CCK has paradoxical roles with respect to GER. On the one hand, CCK inhibits gastric acid secretion, but on the other hand, it induces transient lower esophageal sphincter relaxations, thereby contributing to acid reflux (Zerbib *et al.*, 1998). Thus, while it can be argued that gastric acid secretion is not inhibited with SPE, it can also be argued that SPE is associated with maintenance of lower esophageal pressure, conducive to reduced regurgitation or reflux of gastric acid. Finally, human experimental studies assessing the GI symptoms associated with the consumption of SPE (Cox and Jackson, 1987) or olestra (Sandler *et al.,* 1999; McRorie *et al.,* 2000a,b) found no significant difference in the incidence of heartburn between the active and placebo groups, even with olestra intakes of 40 g/day. Thus, the totality of evidence suggests that, unlike digestible fat, SPE will not contribute to the pathogenesis of GERD.

7.2.2 Gastric Emptying and GI Transit

Studies in animals (Meyer *et al.,* 1998) and humans (Hildebrand *et al.,* 1998; Matzinger *et al.,* 2000; Feinle *et al.,* 2001; O'Donovan *et al.,* 2002) have shown that the slowing of gastric emptying is dependent on lipolysis of triacylglycerols to monoacylglycerols and free fatty acids. There has been some speculation that the release of CCK and the subsequent slowing of gastric emptying are dependent not only on lipolysis, but also on the formation of chylomicrons (Raybould *et al.,* 1998). That lipolysis of trigacylglycerols is necessary for lipid-mediated reductions in gastric emptying is further supported by observations that gastric emptying is rapid in patients with pancreatic exocrine insufficiency (Carney *et al.,* 1995), and that the pharmacological inhibition of lipases results in a more rapid gastric emptying of fat (Hildebrand *et al.,* 1998; Borovicka *et al.,* 2000; Feinle *et al.,* 2003).

Because olestra is resistant to hydrolysis by mammalian and bacterial lipases, it is not expected to cause delays in gastric emptying. Indeed, several studies demonstrate that while digestible fat delays gastric emptying, SPE does not delay gastric emptying. When SPE was administered as the exclusive source of dietary fat in a mixed meal, it had a gastric emptying rate similar to that of water but significantly less than that of butter (Cortot *et al.,* 1981*,* 1982). Similarly, when SPE was administered as the exclusive source of dietary fat in a milk-based drink, gastric emptying was significantly faster as compared with the administration of the same milk-based drink containing an equivalent amount of digestible triglycerides (Kelly and Hunter, 1996). While solid SPE emptied more slowly than liquid SPE, the gastric emptying rates were significantly faster than equivalent amounts of digestible fat (Meyer *et al.,* 1999). These studies cumulatively suggest that, when administered as the exclusive source of dietary fat, the gastric emptying of SPE is significantly faster than that of a conventional fat. Another interpretation is that while the gastric emptying of conventional fats is delayed, that of SPE is not.

The gram-for-gram substitution of SPE for conventional fat (Cortot *et al.,* 1982; Kelly and Hunter, 1996; Meyer *et al.,* 1999) results in a food product that is lower in caloric content. While dietary fat is known to delay gastric emptying, the caloric content of a meal also affects gastric

emptying. Thus, Aggarwal *et al.* (1993) administered isocaloric and isonitrogenous meals in which the 45-gram fat content was replaced with up to 30 g of olestra. Significant differences in gastric emptying were not detected between the treatment groups. Thus, when olestra is consumed with an appreciable amount of digestible fat, gastric emptying is unaffected. This observation is consistent with the finding, in rats fed a 20% fat diet, that that the addition of hydrogenated palm oil (a digestible fat) to SPE results in a significant delaying in gastric emptying as compared with the native SPE administered alone (Hastings and Braun, 1983 FAP VOLUME 10).

7.2.3 Stool Weight, Composition, and Viscosity

The effects of olestra on stool weight, composition, and viscosity have been compared with the effects on these fecal parameters of wheat bran and sorbitol. Although wheat bran, sorbitol, and olestra traverse through the digestive tract without being hydrolyzed by digestive enzymes, they elicit quite different effects on measures of fecal output. Studies have demonstrated that the laxative efficacy of wheat bran is directly proportional to the coarseness of the bran (Brodribb and Groves, 1978; Heller *et al.,* 1980), and that the laxative effects of wheat bran can be mimicked by non-fermentable, non-osmotic plastic particles cut to match the size of wheat bran (Tomlin and Read, 1988). Thus, the laxative mechanism of wheat bran involves a mechanical stimulatory effect on the bowel mucosa, resulting in an increase in water secretion and/or a decrease in water reabsorption. Although wheat bran is considered an insoluble fiber, it is associated with an increase in fecal water content. Olestra is an inert semi-solid that is not fermented by bacteria. It has no osmotic activity, and is not a mechanically course fiber. Thus, olestra would not be expected to increase stool water content. Sorbitol is a hexahydric alcohol with known osmotic laxative effects. It is a natural constituent in many fruits, and is used, in the food industry, as a sweetener (hard and soft candy, chewing gum) and to improve the quality, texture, and shelf-life of foods. Sorbitol is Generally Recognized as Safe by the U.S. FDA for a multitude of uses, at levels up to 99% in hard candies (21 CFR §184.1835) (U.S. FDA, 2006e). One of the provisions for use of sorbitol in the food industry is that if consumption is expected to exceed 50 g/day, the food is required to have a label stating, “Excess consumption may have a laxative effect” [21 CFR §184.1835(e)] (U.S. FDA, 2006e).

Knowledge of the physical and physiological properties of olestra, sorbitol, and wheat bran is useful in understanding the effects of these non-hydrolyzable substances on parameters of fecal output. In a human experimental study, the administration of 20 or 40 g/day olestra or bran was not associated with a significant increase in mean stool weight (g/bowel movement) relative to the placebo group (McRorie *et al.,* 2000a); in contrast, the administration of 40 g/day sorbitol resulted in a significant increase in mean stool weight as compared with the placebo group (McRorie *et al.,* 2000b). While, compared to the placebo group, mean daily stool output (g/day) was significantly increased with the administration of 20 or 40 g/day bran, the administration of equivalent amounts of olestra had no effects on mean daily stool output relative to the control

group (McRorie *et al.,* 2000a). In contrast, the administration of 40 g/day sorbitol resulted in a marked increase in mean daily stool output (McRorie *et al.,* 2000b). In a human experimental study comparing the effects of a 200 mL test drink containing either 50 g of liquid SPE or 50 g of triacylglyerols on gastric transit, significant differences in fecal weight (collected for 24 hours following administration of the test meal) were not observed (Kelly and Hunter, 1996). Fecal weight was greater in the SPE group (453.33 ± 122.05 g) than in the control group (395.00 ± 107.85), with the difference (55 g) almost identical to the amount of SPE consumed.

Stool weight (output) is a function of both fecal water content and indigestible matter. Thus, when equivalent amounts of indigestible material are administered, differences in stool output result primarily from differences in fecal water output. In a porcine feeding study, McRorie *et al.* (2000c) demonstrated that, compared with the control group, the administration of either 40 or 80 g/day of olestra resulted in a significant reduction in percent stool water content, while the administration of 40 or 80 g/day wheat bran resulted in a significant increase in percent stool water content. In a human study, percent fecal water content was significantly lower with the administration of 20 or 40 g/day olestra as compared with the administration of a placebo or 20 or 40 g/day wheat bran (McRorie *et al.,* 2000a). The decrease in stool water content is not due to an olestra-induced increase in water reabsorption; rather, the decrease in stool water content is secondary to an increase in the relative amount of olestra in the stool, resulting in a calculated smaller percent fecal water content. It is noteworthy that, in humans, olestra feeding has been associated with either no difference in absolute fecal water content (McRorie *et al.,* 2000a) or statistically significant but clinically insignificant increases in absolute fecal water content (McRorie *et al.,* 2000b). In the latter case, the administration of 20 or 40 g/day olestra resulted in a significant increase in mean stool water output as compared with the placebo group; however, when compared with the mean stool water output at baseline, the administration of 20 g/day olestra resulted in an 8.8 ± 8.9 g/day increase in stool water output (less than a tablespoon per day), while the administration of 40 g/day olestra resulted in a 37.4 ± 11.1 g/day increase in stool water output (just over 2 tablespoons) (McRorie *et al.,* 2000b). These marginal increases in stool water output would not adversely affect electrolyte levels. Hence, while the presence of olestra in fecal matter reduces the relative fecal water content, the actual stool water output is not really affected. The finding by McRorie *et al.* (2000b) that stool water outputs with olestra consumption were significantly greater than those observed in the placebo group is confounded by an unexpected decrease in stool water output in the placebo group as compared with baseline. In a human experimental study, the administration of 40 g/day sobitol was found to increase stool water output markedly, by 345.9 ± 47.0 g/day (by over 1 cup/day) from baseline (McRorie *et al.,* 2000b). The effects of olestra on mean stool weight, daily stool output, and fecal water content and output suggest that it generally increases fecal output gram for gram.

Fecal water content and apparent fecal viscosity are related. Stool viscosity was significantly reduced in pigs administered 40 or 80 g/day sorbitol or wheat bran, with sorbitol having more

pronounced effects (Neeley *et al.,* 1998; McRorie *et al.,* 2000c). The administration of 40 g/day olestra to pigs resulted in either insignificant or marginally significant increases in stool viscosity with respect to baseline (Neeley *et al.,* 1998; McRorie *et al.,* 2000c). The administration of 80 g/day olestra to pigs resulted in significant decreases in stool viscosity that were comparable to those attained with 80 g/day wheat bran (Neeley *et al.,* 1998; Greenwood-van Meerveld *et al.,* 1999; McRorie *et al.,* 2000c). Findings from human experimental studies assessing the effects of olestra and wheat bran or olestra and sorbitol on stool viscosity are consistent with findings from animal studies. McRorie *et al.* (2000a) observed that, compared with the placebo group, stool viscosity was significantly reduced only in the olestra 40 g/day treatment group, but not in any of the other treatment groups. Although stool viscosity and fecal water content are related, in this particular study, wheat bran, though associated with an increase in percent fecal water content, was not associated with a significant reduction in stool apparent viscosity. This is most likely because stool water content and stool apparent viscosity are nonlinearly related (McRorie *et al.,* 1998). Small increases in stool water content have gross impacts on stool viscosity only if the initial stool water content is ≤75% (*i.e.,* stools are very dry and hard); for stool water contents ≥80%, modest increases in stool water content have negligible effects on stool viscosity. Baseline stool water content in the wheat bran groups ranged between 80 and 81%; thus, although stool water content increased significantly to 83.9 ± 0.8% and 83.4 ± 0.7% with the consumption of 20 or 40 g/day wheat bran, no significant changes in stool viscosity were observed. Decreases in stool viscosity with the administration of 40 g/day sorbitol were immediate and pronounced, corresponding to a University of Maryland stool descriptor of "runny/loose" (McRorie *et al.,* 2000b). In contrast, decreases in stool viscosity with the administration of 20 or 40 g/day olestra were gradual, moderate, and dose-dependent, corresponding, with either case, to a University of Maryland stool descriptor of "soft/less form" (McRorie *et al.,* 2000b). That olestra's effects on stool viscosity are dose-dependent has been reported by others (Neeley *et al.,* 1998; McRorie *et al.,* 2000b,c).

Despite a significant reduction in stool viscosity with the consumption of 40 g/day olestra daily for 6 days (McRorie *et al.,* 2000a,c), the stool viscosity ratio (highest stool viscosity ÷ lowest stool viscosity within a given day) was less than 3 and similar to the stool viscosity ratio associated with the consumption of similar amounts of bran. In contrast, the stool viscosity ratio with the consumption of 40 g/day sorbitol was 19.5 (McRorie *et al.,* 2000b). The stool viscosity ratio was developed to predict abdominal cramping/pain, and is based on observations that severe abdominal cramping/pain is associated with the passage of formed stool followed by 1 or more loose/liquid stools, resulting in a high stool viscosity ratio (McRorie *et al.,* 2000b). A stool viscosity ratio of <5 has been associated with no or mild cramping, while a stool viscosity of 25 has been associated with severe abdominal cramping (McRorie *et al.,* 2000b).

While supplementation with wheat bran or sorbital was associated with a significant increase in fecal water content, supplementation with olestra was associated with a significant reduction in fecal water content (McRorie *et al.,* 2000a,b,c). Despite these differences in stool water

retention, all treatments were associated with reductions in stool viscosity, with bran's and sorbital's stool softening effects attributable to increased fecal water content, and olestra's stool softening effects attributable to the increased fecal content of olestra, which is semi-solid at body temperature. The levels of olestra and wheat bran that were administered in these studies were very high. One, one-ounce serving of potato chips made with 100% olestra contains approximately 8 g of olestra. Thus, the administration of 20 or 40 g/day olestra everyday for up to 6 days translates to the equivalence of 2.5 and 5, one-ounce servings of potato chips, respectively, per day. The administration of 20 g/day olestra is 6.4-fold and 2.6-fold greater than the 50th and 90th percentile all-user estimated chronic daily intakes of olestra from savory snacks and cookies, while the administration of 40 g/day olestra is 12.9-fold and 5.2-fold greater than the 50th and 90th percentile all-user estimated chronic daily intakes of olestra from savory snacks and cookies. Similarly, a serving of Bran Buds cereal contains approximately 12 g of wheat bran. Thus, the 20, 40, and 80 g/day wheat bran groups were consuming 1.7, 3.3, and 6.6 servings, respectively, of Bran Buds cereal per day everyday for up to 6 days. Clearly, these intakes overestimate the amounts of olestra or wheat bran that would normally be consumed, and consequently, the effects of wheat bran or olestra on stool viscosity and fecal water content would be far less pronounced with intakes that are more representative of actual consumption. In contrast, the amount of sorbitol administered in the study conducted by McRorie *et al.* (2000b) was 40 g/day. Despite the marked increases in fecal water content and decreases in stool viscosity with the administration of this amount of sorbitol, labeling of a product with a sorbitol warning (*i.e.*, excess consumption may have a laxative effect) is mandated only when consumption is expected to exceed 50 g/day. Clearly, olestra's effects on stool viscosity and fecal water (and electrolyte) output are akin to those elicited by equivalent amounts of bran, but far less substantial than those elicited by sorbitol.

7.2.4 Bile Acids

7.2.4.1 Effects on Gallbladder Contraction

The consumption of digestible fat is associated with the duodenal release of CCK, which acts as a powerful stimulus for gallbladder emptying; however, the consumption of SPE is not associated with CCK release and subsequent gallbladder contraction. In a human experimental study, Kelly and Hunter (1996) demonstrated that while the consumption of a 200 mL test drink containing 50 g of triacylglycerols resulted in significant increase in postprandial plasma CCK levels as well as in the gallbladder ejection fraction, the consumption of a 200 mL test drink containing 50 g of SPE was not associated with these outcomes. Likewise, in a crossover study, Maas *et al.* (1998a) demonstrated that the consumption of 60 mL of liquid digestible fat resulted in a significant increase from baseline in plasma CCK levels and a significant decrease, from baseline, in gallbladder volume; in contrast, the consumption of 60 mL of liquid SPE, like the consumption of 60 mL of a saline solution, had no effect on plasma CCK levels or gallbladder volume relative to basline. These observations are supported by another study in

which the intraduodenal perfusion of SPE was found not to stimulate the release of CCK (Maas *et al.,* 1997). Although gallbladder contractility was not evaluated in this latter study, CCK is known to be a potent stimulus for gallbladder contraction, and so it can be reasonably assumed that gallbladder contraction would have been reduced in this study.

Observations that olestra does not stimulate the release of CCK are consistent with the hypothesis that products of lipolysis, such as free fatty acids or monoacylglycerols, are necessary for the duodenal release of CCK. When administered fatty meals, patients with pancreatic insufficiency have diminished gallbladder emptying rates and CCK release; however, the addition of pancreatic enzymes to the meal normalizes the impaired responses (Jansen *et al.,* 1989; Masclee *et al.,* 1989). Likewise, the lipase inhibitor Orlistat has been associated with a reduced release of CCK in humans (Fried *et al.,* 1992; Schwizer *et al.,* 1995).

Concern has been expressed that gallbladder hypomotility may cause stasis of bile in the gallbladder and facilitate cholesterol crystallization, thus increasing the risk of gallstone formation (Hay and Carey, 1990; Busch and Matern, 1991; Paumgartner and Sauerbruch, 1991; Maas *et al.,* 1998a). Obese patients attempting rapid weight loss with very-low-energy, very-low-fat diets appear to be especially at risk (Marzio *et al.,* 1988; Liddle *et al.,* 1989; Maclure *et al.,* 1989; Stone *et al.,* 1992; Everhart, 1993). This latter point is significant, particularly since consumption of low-fat/fat-reduced products made with olestra may be particularly high in subjects attempting to lose weight. In evaluating the clinical implications of an olestra-induced reduction in CCK release, it is imperative that the studies be put into context. Maas *et al.* (1997, 1998a) compared the effects of SPE to a digestible triacylglycerol; the fats were administered either intraduodenally or orally, without other dietary components, and no effects on gallbladder contraction were observed. When SPE was administered as part of a test milk (*i.e.,* other dietary components were consumed in conjunction with SPE), a 22% reduction in gallbladder volume was observed, as compared with the significantly greater 45% reduction observed following the consumption of digestible fat (Kelly and Hunter, 1996). This is in contrast to the observations that SPE, when administered alone, had no effect on gallbladder volume (Maas *et al.,* 1997*,* 1998a). The SPE test milk contained, 58.7%, by weight, skimmed milk; thus, although the digestible fat content in the test milk was negligible, the test milk contained small amounts of protein (approximately 2 grams, calculated using the USDA protein content of 3.37 g/100 g for skimmed milk). CCK release is stimulated by protein and amino acids; thus, when consumed in combination with other nutrients (amino acids or digestible fat), olestra is not expected to completely prevent gallbladder emptying.

In addition to bile stasis or gallbladder hypomotility, an additional factor that increase the predisposition for gallstone formation is the saturation of gallbladder bile (Dowling, 2000). The more saturated the bile, particularly with respect to the cholesterol content, the increased likelihood that the cholesterol may precipitate out of the bile and crystallize, leading to the formation of gallstones. In 11 overweight subjects, the consumption of a 1000 kcal/day diet in

combination with 50 g/day SPE for 6 weeks did not result in a significant increase in the saturation of gallbladder bile; rather, gallbladder bile saturation was decreased in most subjects, thought the reduction was not significant (Crouse and Grundy, 1979). This observation is further evidence that consumption of SPE will not increase gallbladder bile saturation and, hence, the risk of gallstones.

7.2.4.2 Effects on Fecal Bile Acid Excretion and Composition

SPE has either no effects or marginally significant effects on the fecal excretion of bile acids. This observation is consistent with the physical characteristics of bile acids and how these physical characteristics are altered as digesta residue traverses the GI tract. When excreted from the gallbladder, the primary bile acids are conjugated to either glycine or taurine; thus, when released into the duodenum, bile acids are amphipathic, containing both a hydrophobic face (*i.e.,* the cholesterol-derived portion) and a hydrophilic face (*i.e.,* the amino acid conjugate). Conjugated bile acids do not have very high oil-water partition coefficients; consequently, they do not have a high affinity for SPE, which is extremely lipophilic (Jandacek, 1982). The bulk of bile acids are absorbed almost exclusively in the ileum, and mostly in conjugated form (Mayes, 2000). Remaining bile acids enter the large intestine, where they become subject to deconjugation (*i.e.,* removal of the amino acid conjugate) and 7α-dehydroxylation, resulting in the formation of secondary bile acids. Because the amino acid moieties are hydrophilic, their removal results in slightly more hydrophobic bile acids, with chenodeoxycholic acid being the most hydrophobic deconjugated bile acid (Jandacek, 1982). That the total recovery of chenodeoxycholic acid, the most lipohilic deconjugated bile acid, in bile was unaffected by the administration of SPE to male Sprague-Dawley rats is evidence that the fecal excretion of other, less lipohilic bile acids, would most likely not be affected. The finding by Glueck *et al.* (1980) that, in some subjects, the fecal excretion of secondary bile acids was significantly reduced while the fecal excretion of primary bile acids was markedly increased is consistent with the slightly more hydrophobic nature of deconjugated (as opposed to conjugated) bile acids and their slight tendency to partition into the oil phase, thus reducing bacterial 7α-dehydroxylation. This effect is desirable, particularly since secondary bile acids are associated with detergent-like, irritant effects in the colon (Nagengast *et al.,* 1995).

7.2.5 Microflora

Several preliminary unpublished *in vitro* studies reported no metabolic products of olestra following its incubation with either human fecal samples or bacteria isolated from human fecal samples. The shortcoming of these earlier studies, however, is that they were temporally limited (*i.e.,* they did not evaluate the possibility of bacterial adaptation to olestra with repeated or chronic exposure). An *in vitro* study, based on quantification of ^{14}C in fatty acids, CH_4, and CO_2 following 72 hours of anaerobic incubation of ^{14}C olestra with human feces demonstrated, as in the earlier studies, that olestra is not metabolizable by colonic microbes (Nuck *et al.,*

1994). As fecal samples were collected from subjects who had been consuming olestra (9 g/day) daily for 21 to 31 days, the possibility of bacterial adaptation to olestra was ruled out.

In a series of publications, Siigur *et al.* (1994, 1996a,b) assessed the impact of olestra on microbial metabolism. Several metabolic processes, such as the metabolism of cholesterol to coprostanol, the inactivation of tryptic activity, the degradation of mucin, the metabolism of β-aspartylglycine, the conversion of bilirubin to urobilinogen, and the fermentation of carbohydrates and proteins to yield short-chain fatty acids (SCFAs) and other bi-products (H^+, CH^4, CO_2), are dependent on a normal colonic microflora and, in fact, are classified as MACs or microbiota-associated characteristics (Midtvedt *et al.,* 1985). These processes are often disrupted when the colonic microflora is disturbed, as in germ-free animals or following antibiotic administration (Midtvedt *et al.,* 1985).

The effects of 24 g of olestra, administered for 28 days in conjunction with a moderate (7 g/day) or high (24 g/day) fiber breakfast meal on MACs were compared with the effects of 24 g of conventional fat, administered with the same moderate or high fiber breakfast meals (Siigur *et al.,* 1996a). The administration of olestra did not result in a significant alteration, from baseline, in tryptic activity or fecal levels of β-aspartylglycine. While, compared to baseline, conversion of cholesterol to coprastanol and conversion of bilirubin to urobilinogen were unaffected in the placebo groups, significant reductions were observed in both olestra treatment groups. Because cholesterol and bilirubin are highly liophilic, they partition into the olestra (oil) phase in the intestinal lumen, thereby reducing their interaction with relevant intestinal microbes. The administration of olestra was associated with a significant increase from baseline in fecal mucin secretion. This effect, on its own, cannot be considered a deleterious effect, as fecal mucin excretion also increased significantly from baseline in both placebo groups. Dietary fiber is known to either increase fecal mucin levels (Bovee-Oudenhoven *et al.,* 2003) or to reduce fecal mucinase activity (Chau *et al.,* 2005; Chau and Chen, 2006). While a mechanical stimulatory effect cannot be ruled out (*i.e.,* the presence of fiber or olestra in the colon may cause colonic wall distension and a subsequent stimulation in mucin production), the most likely explanation for the olestra-induced increase in fecal mucin content is the concomitant increase in SCFAs. SCFAs are known to stimulate the release of mucin (Scheppach *et al.,* 1992; Sakata and Setoyama, 1995; Shimotoyodome *et al.,* 2000).

The increase in fecal SCFAs with the administration of olestra was almost certainly related to a reduced intestinal absorption of SCFAs, rather than to an increase in the production of SCFAs. Observations that the administration of olestra/SPE is associated with reductions in breath hydrogen levels (Eastwood and Allgood, 1995) support the idea that absorption of fermentative by-products is reduced with the administration of olestra, perhaps due to slightly shorter gut transit times (Kelly and Hunter, 1996; Kelly *et al.,* 1998). While SCFAs may partition out into the olestra phase, this is highly unlikely as SCFAs are not very lipophilic (*i.e.,* they are associated with very low octanol/water partition coefficients). Evidence regarding the physiological

importance of SCFAs is still evolving, and a recent review of the health effects of SCFAs (Wong *et al.,* 2006) indicates that they may reduce the risk of various GI disorders, cancers, and heart disease. Although the long-term effects of olestra on SCFA absorption and metabolism are currently unknown, it is noteworthy that even with very high daily intakes of olestra (24 g/day for 4 weeks), fecal levels of SCFAs remained within the range detected at baseline or in the placebo groups (Siigur *et al.,* 1994; 1996b).

Siigur *et al.* (1994; 1996a) administered 24 g of olestra *together* with either a moderate (7 g/day) or high (24 g/day) breakfast meal. This intake level for olestra is approximately 8-fold greater than the 50th percentile and 3-fold greater than the 90th percentile users-only chronic intakes estimated for permitted and proposed uses of olestra in savory snacks and pre-packaged cookies. Furthermore, that potato chips/cookies made with olestra would be consumed together with a moderate/high fiber breakfast meal is highly unlikely, given that current food usage data indicate that more than two-thirds of savory snacks and cookies are eaten as snacks and not with meals. Thus, even under exaggerated conditions of use, the effects of olestra on microbial metabolism are expected to be nominal.

7.2.6 Allergenicity of Olestra

The allergenic potential of olestra is very low. Most identified allergens are proteins. According to the U.S. FDA, proteins in 8 major foods, including milk, eggs, fish, wheat, tree nuts, peanuts, soybeans, and crustaceans, are estimated to cause 90% of the allergic reactions in the United States (Formanek, 2001). Olestra is not a protein; rather, it is a SPE derived from the esterification of fatty acids from soybean or cottonseed oil with sucrose, using processes common in the fats and oils industry. Moreover, while soy protein is considered a common allergen, there are no detectable levels of protein present in the soybean oil used to make olestra, nor in the final olestra oil. Fat-soluble vitamins (A, D, E, K) are added to snacks made with olestra to compensate for the loss of these vitamins due to their dissolution in olestra and subsequent fecal excretion; however, an allergic reaction to these vitamins is highly unlikely. Acacia gum, the vitamin carrier system used in snacks made with olestra, also seems like an unlikely allergen due to its insignificant protein content. Thus, foods made with olestra are unlikely to elicit an allergic reaction.

P&G implemented a post-market surveillance program following the 1996 U.S. FDA approval of olestra for use in savory snacks. During the almost 4-year surveillance program (which spanned from the initial test market introduction of olestra in April 1996 through February 2000), 564 allergy-like reports were called in to the surveillance toll-free number (Burks *et al.,* 2001). This incidence represented 3.5% of all health effects reported by callers to the surveillance program. Burks *et al.* (2001) conducted allergy testing in 27 subjects previously reporting allergy-like symptoms following consumption of potato chips made with olestra. Each subject underwent a standard skin prick test to the following compounds: acacia gum; snack manufacturer's fat-soluble vitamin mixture; soybean oil, cottonseed oil; soybean olestra;

cottonseed olestra; and histamine and saline controls. No subject elicited a positive response to olestra or its components, with the exception of 1 subject, who had a positive skin prick test to soybean oil, but not to soybean olestra. Following the skin prick testing, subjects participated in a randomized, double-blind, placebo-controlled within-subject crossover food challenge study to assess the allergenicity of olestra snacks. Following an 8-hour fast, subjects ate, in random order, olestra-containing potato chips (Frito-Lay WOW! Lays Potato Chips) and placebo potato chips (Husman's potato chips). The dose of potato chips consumed at each challenge was at least the amount alleged to have caused the symptoms that prompted the consumer to phone the post-market surveillance toll-free number. Consumption of the olestra-containing potato chips was not associated with an allergic reaction in any of the subjects. In contrast, consumption of the regular potato chips was associated with reactions consistent with immediate hypersensitivity in 2 subjects.

When a new food ingredient is introduced into the market, it is not uncommon that allergic reactions are reported. For example, 4% of consumer reports for aspartame were related to food allergy (Butchko and Kotsonis, 1994), even though double-blind, placebo-controlled, randomized, crossover studies found no evidence to indicate that aspartame was a likely allergen (Garriga *et al.,* 1991; Geha *et al.,* 1993). Placebo-controlled testing indicates that the actual prevalence of food allergy is approximately 1.5% of the adult population; nevertheless, as many as 20% of consumers believe they have a food allergy (Sampson, 1997).

That reports of allergic reactions to olestra were not truly allergies is supported by several observations. First, olestra is not a protein. Second, not a single animal or human experimental study has reported an allergic reaction with the administration of olestra. This observation is significant, given that olestra has been administered to subjects with greater degrees of vulnerability, such as children (Cox and Jackson, 1987; Sandler *et al.,* 1999; Allgood *et al.,* 2001) and individuals with compromised GI tracts (ulcerative colitis, Crohn's disease) (Zorich *et al.,* 1997a). Third, the vast majority of allergy-like reports were made following the very first olestra eating occasion, and it is well known that allergic reactions require prior exposure to the allergen. Lastly, many reports of olestra allergy indicated that symptoms began as many as 6 hours following consumption of olestra and that avoidance of olestra or treatment with antihistamines did not alleviate the symptoms. These observations are not consistent with true hypersensitivity reactions. Cumulatively, these observations confirm the findings of Burks *et al.* (2001) that olestra is not allergenic.

7.2.7 Conclusion

Olestra is resistant to digestion by mammalian and bacterial llipases; hence, it is not associated with physiological effects typical of digestible fats. Digestible fats are hydrolyzed in the small intestine, and the products of lipolysis result in the duodenal release of various hormones, a principal 1 being CCK. CCK has a multitude of effects. It causes transient relaxations of the lower esophageal sphincter, resulting in the regurgitation of the acid contents of the stomach;

hence, dietary fat is associated with GER. CCK also delays gastric emptying and is a potent stimulator of gallbladder contraction and bile release. Because olestra in not hydrolyzed, it is not recognized as a nutrient in the duodenum; thus, it is not associated with the release of CCK. Consequently, olestra does not cause stomach acid reflux, is not associated with delays in gastric emptying, and does not stimulate gallbladder contraction and bile release. Concern has been raised that olestra may increase the risk of gallstone formation by causing gallbladder hypomotility and by increasing the saturation of bile, particularly with respect to cholesterol. However, the current weight of evidence is not supportive of such an effect, as i) There have been no reports of gallstones in any of the pre-clinical, clinical, and post-marketing surveillance studies; ii) The consumption of even small amounts of protein or digestible fat with olestra results in gallbladder contraction and bile release; and iii) Olestra reduces cholesterol absorption, and tends to decrease, rather than increase, the saturation of bile.

Olestra is not fermented by bacteria residing in the colon. The effects of olestra on several MACs were examined. Although olestra reduces the metabolism of cholesterol to coprostanol and the conversion of bilirubin to urobilinogen, these effects are most likely due to the sequestration, by olestra, of cholesterol and bilirubin, and not to an alteration in microbial metabolism. Olestra has no effects on the inactivation of tryptic activity and the metabolism of β-aspartylglycine. Although olestra was associated with an increase in fecal SCFAs, this was most likely due to a reduced absorption of SCFAs, rather than to an increase in their production. Observations that olestra reduces whole-gut transit times and reduces breath hydrogen excretion are consistent with a reduced absorption, and not in increased production, in SCFAs. SCFAs may reduce the risk of various GI disorders, cancers, and heart disease (Wong *et al.,* 2006). Although there is currently no data available regarding the long-term effects of olestra on SCFA metabolism and absorption, fecal levels of SCFAs remained within the range detected at baseline or in the placebo groups following the daily consumption of relatively large amounts of olestra (24 g) for up to 4 weeks (Siigur *et al.,* 1994, 1996b).

The effects of olestra on the degradation of mucin are similar to those described for various fibers, and may be related to some sort of mechanical stimulatory effect of olestra. Fecal composition with respect to bile acids is not affected by the consumption of olestra; however, there appears to be a trend for reduced levels of secondary bile acids and increased levels of primary bile acids with consumption of olestra. Olestra may sequester bile acids, resulting in a reduced interaction of the primary bile acids with bacteria capable of deconjugation and hydroxylation. This may be beneficial, given that secondary bile acids have irritant, detergent-like effects in the colon. Overall, olestra has minimal effects on several MACs, an indication that olestra does not alter microbial metabolism.

Like bran, olestra reduces the viscosity of stool, resulting in a softer stool. While bran is associated with an increase in the percent water content of stool, olestra is associated with a decrease in the percent water content of stool. The absolute water content of stool is not

altered with the administration of olestra, and the relative water content and viscosity appear reduced due to the physical presence of olestra, a semi-solid, in the stool. The effects of exaggerated intake levels of olestra on stool form and water content were compared with those elicited by the administration of sorbitol. Although sorbital caused very large increases in stool water content and dramatic alterations in stool form (runny, liquid-rice stools), the effects of olestra were far less substantial and akin to those elicited by similar amounts of bran. Unlike sorbitol, olestra is inert and has no osmotic properties; hence, its consumption, even in excessive amounts, is not associated with water and electrolyte losses.

7.3 GI Symptoms

In January 1996, the U.S. FDA approved the use of olestra in savory snacks. As part of the approval process, Procter and Gamble was required to provide safety updates on market experience with olestra to the U.S. FDA, in order to confirm safety under more typical patterns of consumption and in a broader population than what was assessed in the human experimental studies. Market introduction of olestra began in April 1996 and carried through national expansion beginning in February 1998. A multifaceted post-market surveillance program was established to monitor, assess, and investigate consumer-reported adverse events associated with the consumption of olestra (Slough *et al.,* 2001). The first component of the post-market surveillance program was the referral of consumers to a toll-free number (appearing directly on the product label) staffed by the Frito-Lay Co. or by Procter and Gamble, the manufacturers of snack products made with olestra. The second component of the post-market surveillance program ensured that adverse event reports were examined by both internal and external expert medical review. The third component was a continuation of human experimental studies designed to evaluate the scientific basis of adverse events reported by individuals consuming olestra under real-world consumption conditions.

7.3.1 Passive Post-Marketing Surveillance Studies

The olestra post-market surveillance program spanned 49 months and included the introduction of chips made with olestra into test-markets (approximately 22 months) as well as the national market expansion of potato chips made with olestra all over the U.S. (approximately 27 months) (Allgood *et al.,* 2001). It is estimated that, during the olestra surveillance program, 40 million people consumed approximately 3 billion servings of potato chips made with olestra (Allgood *et al.,* 2001). During the national marketing of olestra, 15,081 calls were made to the toll-free line to report adverse events associated with the consumption of olestra, with the majority of adverse events related to GI disturbances (Allgood *et al.,* 2001). Diarrhea (including loose, watery, or soft stools and increased frequency of bowel movements and bowel movement urgency) was reported 10,707 times by 64.4% of callers and abdominal pain (including abdominal cramping, abdominal discomfort, stomach ache, and gas pain) was reported 10,108 times by 60.0% of callers (Allgood *et al.,* 2001). The next most commonly reported GI symptom was flatulence, which was reported 2,101 times by 12.4% of callers (Allgood *et al.,* 2001).

Other, though less commonly reported GI effects included nausea (1,008 complaints reported by 6.6% of callers), vomiting (997 complaints reported by 6.5% of callers), dyspepsia (562 complaints reported by 3.6% of callers), and abnormal stools (376 complaints reported by 2.3% of callers) (Allgood *et al.,* 2001). Fifty-four percent of callers rated the impact of their symptoms as mild, while 20% and 11% rated their symptoms as moderate or severe, respectively (11% of callers did not provide information on severity of symptoms) (Allgood *et al.,* 2001). Approximately 4% (592/15,081) of callers sought medical attention for their symptoms, and 37% of these callers reported an onset of symptoms approximately 6 hours following consumption of olestra chips. There were no reports of deaths associated with the consumption of olestra; however, 0.4% (60/15,081) of callers reporting adverse events claimed to be hospitalized (Allgood *et al.,* 2001).

Internal and external medical panels reviewed adverse event reports made in 800 line calls to the national olestra post-market surveillance program (Allgood *et al.,* 2001). Several inconsistencies between the surveillance data and previous human experimental studies were noted. The primary discrepancy was that the majority of callers reported adverse events following the consumption of a *small amount of olestra* on a *single* eating occasion. Previous controlled studies demonstrated that adverse GI effects were associated with large intakes of olestra over several days. Of callers reporting alleged health effects of olestra during the national post-market surveillance program, 77% reported such effects following a single exposure to olestra, and 11%, following consumption of olestra for 2 days. Of 15,081 callers reporting symptoms associated with the consumption of olestra, 2,137 (14%) consumed 0 to 0.5 oz of chips, 3,947 (26%) consumed 0.5 to 1.0 oz of chips, 3,908 (26%) consumed 1.0 to 2.0 oz of chips, and 2,887 (19%) consumed 2.0 to 4.0 oz of chips. Each ounce of chips contains 8 g of olestra; thus, the majority of callers (66%) reporting adverse events consumed less than 2 oz of olestra chips and less than 16 g of olestra. The types of symptoms reported were very similar across a broad range of olestra intakes, and there was no dose-associated increase in the severity of symptoms reported, as would be expected if a true association existed (Allgood *et al.,* 2001). Thus, the panels found no evidence of clinically significant events associated with olestra consumption.

7.3.2 Post-Marketing Human Experimental Studies

Several controlled human experimental studies were conducted following the post-market introduction of olestra in order to further assess the GI effects of olestra. In 1 study, subjects reporting GI symptoms to the toll-free line following the consumption of olestra chips were contacted and invited to participate in a rechallenge test of chips made with olestra [(the Rechallenge Study) (Zorich et al., 1997b, 1998)]. Cheskin *et al.* (1998) assessed the incidence and severity of GI effects following the acute consumption of up to 369 g (13 oz) of olestra chips, consumed during a 2-hour movie – a scenario that mimicked real-life conditions; from this point forward, this study will be referred to as the Movie Theatre Study. McRorie *et al.*

(2000a,b) compared the GI effects of olestra with those elicited by either wheat bran or sorbitol, 2 compounds that, like olestra, are resistant to digestion and absorption. The Household Chip Consumption Study was designed to assess the GI effects of chronic (6-week) olestra chip consumption by free-living individuals residing in households in which chip consumption was frequent (Sandler *et al.,* 1999). These studies are reviewed in detail in the following sections.

During the 9 months following the test-market introduction of olestra chips (*i.e.,* between 22 April 1996 and 26 January 1997) 508 calls were made to the Frito-Lay Co. or Proctor and Gamble to report effects (mostly related to GI complaints) associated with consumption of olestra (Zorich *et al.,* 1997b). Upon contact, 57 of these 508 callers (15 males and 42 females, most complaining of diarrhea/loose stools or abdominal cramping after a single eating occasion of olestra chips) agreed to participate in a randomized, double-blind, placebo-controlled, crossover rechallenge study assessing the effects of regular triglyceride chips *vs.* olestra potato chips on GI symptoms (Zorich *et al.,* 1997b). Subjects consumed 1 of 4 test products, in a randomized order, with each eating occasion separated by ≥1 week. The test products included 2 brands of potato chips made with conventional triglyceride (Frito-Lay Regular Ruffles and Husman's Regular Potato Chips) and 2 brands of potato chips made with olestra (Frito-Lay MAX Ruffles and Frito-Lay MAX Lay's), each containing 8 g of olestra per ounce of potato chips. Two different brands of olestra-containing chips and 2 different brands of triglyceride-containig chips were used to minimize the potential for unblinding due to product sensory attributes. Potato chips were packaged in 2-ounce portions in identical bags, which were labeled with ingredient listings for both the olestra and triglyceride chips, as well as the olestra product information statement (*i.e.,* "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"). Subjects were instructed to consume as much of the 2-ounce potato chip serving as they could and to consume at least 1 ounce. In addition, they were asked to consume approximately the same amount of potato chips at each visit and to choose the same beverage at each visit. Consumption was monitored by direct observation and by weighing the test product before and after the consumption period. Participants were called 3 to 5 days after each visit and questioned about any GI symptoms, including the time of symptom onset, duration, and date of cessation, as well as the severity of symptoms.

Fifty-three of the 57 subjects completed the study (the 4 withdrawals were unrelated to adverse effects associated with consumption of the regular or olestra chips). All participants consumed at least 1 ounce of chips at each visit, and there was no difference between the 2 test products with respect to compliance. There were no significant differences between the conventional triglyceride and olestra potato chip test groups with respect to the incidence or severity of GI symptoms [any GI symptom, abdominal cramping, diarrhea, loose stools, diarrhea or loose stools, and gas (eructation, flatulence, bloating)]. Although the percentage of subjects reporting diarrhea was higher after consumption of triglyceride chips (8%) than after consumption of olestra chips (4%), the difference was not significant. While the percentage of subjects

reporting gas was higher following consumption of olestra chips (8%) than after consumption of triglyceride chips (4%), again, the difference was not significant. Forty-one additional subjects who had called the toll-free number to report adverse GI effects following the consumption of olestra chips were subsequently enrolled into the Rechallenge Study (Zorich *et al.,* 1998), and the results for these 41 subjects were pooled with those of the 57 subjects initially enrolled in the study. Again, there were no significant differences in the incidence and severity of GI symptoms following consumption of the olestra chips *versus* following consumption of the triglyceride chips. While, during the initial phone call, 48% of the subjects rated their symptoms as severe, during the Rechallenge Study, only 4% of subjects reported GI symptoms as severe, and all 4 reported these symptoms following consumption of the triglyceride chips. Thus, although 66% of symptoms reported to the toll-free post-market surveillance line were associated with the consumption of up to 2 oz of olestra chips (*i.e.,* up to 16 g of olestra) (Allgood *et al.,* 2001), intake of 1 to 2 oz of olestra chips (*i.e.,* 8 to 16 g olestra) under blinded conditions during a rechallenge test did not result in increased GI symptoms as compared with the consumption of similar amounts of regular triglyceride chips.

In response to the publicity of anecdotal reports of adverse GI effects with the consumption of olestra, Cheskin *et al.* (1998) conducted a randomized, double-blind, placebo-controlled study to assess GI symptoms experienced following consumption of olestra-containing potato chips (Frito Lay MAX Ruffles) *versus* triglyceride-containing potato chips (Regular Frito-Lay Ruffles). Subjects were randomized according to age (13 to 17 years; 18 to 34 years; >34 years) and gender into the olestra group or regular triglyceride group, and were offered a plain, white-coded, 369-gram (13 oz) bag of their respective chips. Subjects were also permitted to choose a 960-mL (32-oz) soft drink. Subjects were instructed to consume as many or as few chips as they desired during a 2-hour movie (hence referral to this study as the Movie Theatre Study). Immediately following the movie, bags of chips were weighed to determine the amount of chips consumed, and subjects completed a questionnaire regarding product acceptance, subjective satiety, and sensory attributes. Beginning 40 hours after the movie, subjects were contacted by telephone and questioned about adverse events experienced since the movie, with specific questions regarding digestive symptoms presented. Information regarding the type of symptoms, timing, duration, and severity (mild, moderate, or severe based on partial or complete impairment of daily activities) was captured. Attempts were made to contact all subjects within 4 days of the movie. Attempts to contact subjects continued for another week for those subjects who could not be contacted within the 4-day period.

Of the 1,123 subjects enrolled and randomized in the Movie Theatre Study, 31 individuals could not be recontacted, leaving a total of 1,092 (552 in the control group and 571 in the olestra group) evaluable subjects for data analysis. Follow-up was complete by day 4 for 89% of subjects, and by day ten for 99% of subjects. Subjects in the 2 groups had similar demographics, with 56% and 58% of subjects in the olestra and control groups, respectively, being female, and with a mean age of 35.4 *vs.* 34.7 years, respectively. There was a broad

range of chip consumption in both groups, with the median consumption of triglyceride chips higher than that of olestra chips (77 g/2.7 oz *vs.* 60 g/2.1 oz; p<0.001). The corresponding median triglyceride and olestra intakes were 16.8 g. Chip consumption was similar across age groups, but males tended to eat significantly more chips than females (median, 80 g/2.8 oz. *vs.* 60 g/2.1 oz; p<0.001). The overall palatability of the triglyceride chips was rated higher than that of the olestra chips (6.4 *vs.* 5.6 on a 9-point scale; p<0.001); however, significant differences between the 2 groups in the time since last meal before the movie, the choice of beverage, beverage consumption, or in satiety were not observed. The distribution of chip consumption by percentile in the olestra group is summarized in Table 7-1.

Table 7-1 Distribution of Chip Consumption by Percentile for Subjects in the Olestra Arm of the Movie Theatre Study

Ounces of Olestra Chips Consumed	Grams of Olestra Consumed	Number of Subjects	Percentile
≤1	(≤8)	141	24.5%
1.1 – 2.0	**8.8 – 16.0**	**141**	**49.4%**
2.1 – 3.0	16.8 – 24.0	123	70.9%
3.1 – 4.0	24.8 – 32.0	73	83.7%
4.1 – 5.0	**32.8 – 40.0**	**37**	**90.2%**
5.1 – 6.0	40.8 – 48.0	26	94.7%
6.1 – 7.0	48.8 – 56.0	16	97.5%
7.1 – 8.0	56.8 – 64.0	3	98.1%
8.1 – 9.0	64.8 – 72.0	4	98.8%
9.1 – 10.0	72.8 – 80.0	2	99.1%
10.1 – 11.0	80.8 – 88.0	4	99.8%
11.1 – 12.0	88.8 – 96.0	0	99.8%
12.1 – 13.0	96.8 – 104.0	1	100%

Three adverse events were reported prior to the scheduled contact call. One subject, who reported feeling ill prior to the movie, reported nausea and vomiting during the movie after eating 14 g (0.5 oz) of olestra chips (corresponding to approximately 4 g of olestra); 1 subject had nausea and vomiting after eating 51 g (1.8 oz) of triglyceride chips (the only subject to seek the care of a physician); and 1 subject reported diarrhea, abdominal cramping, and fecal incontinence the morning after the study after consuming 289 g (10.2 oz) of triglyceride chips. The remaining adverse events were collected during the scheduled call-backs.

There was no significant difference between the 2 groups in the percentage of subjects reporting gas, diarrhea, abdominal pain, upset stomach, abdominal cramping, loose stools, any of these GI effects or other GI effects (nausea, bloating, indigestion, aftertaste, belching, constipation, vomiting, or bloody stool). Just over 15% of participants in each group reported at least 1 GI effect. In individuals consuming more than 113 g (4 oz) of chips, there were no

significant differences between the control and olestra groups in the severity of any GI symptom reported. When subjects were grouped according to the amount of chips consumed (0 to 57 g/0 to 2 oz; 57 to 113 g/2 to 4 oz; 113 to 170 g/4 to 6 oz; 170 to 369 g/6 to 13 oz), there was no indication of increasing symptom incidence with greater chip consumption in either group for any GI symptom or for either of the 7 symptoms outlined above, except for an increased incidence of any GI symptom for the triglyceride group consuming 57 to 113 g/2 to 4 oz of chips (20.6% *vs.* 11.3%; $p<0.001$) and a borderline significant increase in the incidence of stomach upset for the olestra group in the 0 to 57 g/0 to 2 oz group (2.6% *vs.* 0%; $p=0.05$). The categories of chip consumption corresponded to a triglyceride or olestra intake of 0 to 16 g, 16 to 32 g, 32 to 48 g, and 48 to 104 g.

Because, in the olestra group, there were only 30 subjects in the highest category of chip consumption, there may have been insufficient statistical power to detect a significant difference in GI symptoms. Thus, a review of the original experimental records was conducted to determine the nature of the GI effects reported by the 30 subjects in the highest category of olestra chip consumption. Twenty-five of the 30 subjects (83.3%) in the highest category of olestra chip consumption did not report adverse events. One subject who consumed 6.4 oz of olestra chips (51.2 g of olestra) reported an upset stomach of moderate severity; 2 subjects who consumed 10.7 and 6.5 oz of olestra chips (85.6 and 52 g of olestra, respectively) reported loose stools/bowels of mild severity; 1 subject who consumed 10.2 oz of olestra chips (81.6 g of olestra) reported moderate diarrhea and severe gas; and 1 subject who consumed 9.3 oz of olestra chips (74.4 g of olestra) reported moderate loose stools and mild stomach discomfort. The one subject consuming nearly the entire 13-oz bag (*i.e.,* 12.7 oz of olestra chips and 101.6 g of olestra) did not report any GI symptoms. For comparison, of the 64 subjects in the highest category of TG chip consumption, 52 (81.3%) did not report adverse events. Six subjects consuming 6.1 – 8.5 oz of TG chips reported mild upset stomach/stomach ache; 1 subject consuming 6.1 oz of TG chips reported moderate upset stomach; 2 subjects consuming 6.7 and 8.5 oz of TG chips reported mild gas; 1 subject consuming 6.6 oz of TG chips reported burping; 1 subject consuming 10.1 oz of TG chips reported moderate diarrhea, moderate cramping, and moderate anal leakage; and 1 subject consuming 10.1 oz of TG chips reported mild gas and moderate loose stools. Thus, the percentages of subjects reporting adverse GI symptoms in the highest categories of chip consumption were essentially identical in the olestra and TG groups.

The post-market human experimental studies described thus far have compared the GI effects of olestra with those of triglycerides. On the one hand, these comparisons are valid, as triglycerides and olestra share many structural similarities. Triglycerides are composed of a glycerol backbone to which 3 fatty acids are esterified. Likewise, olestra is composed of sucrose molecules, each of which is esterified to 6, 7, or 8 fatty acids. The primary difference between triglycerides and olestra is that the former is hydrolyzed by mammalian and bacterial lipases while the latter is not. Because of this difference, olestra traverses through the colon

undigested and unabsorbed, and is eventually excreted in the feces. In contrast, triglycerides are fully metabolized by gastric and pancreatic lipases, and the resulting lipolytic products, namely monoacylglycerols and free fatty acids, are absorbed.

Many GI symptoms (such as flatulence, fecal urgency, loose stools, diarrhea, abdominal cramping, *etc.*) have their origins in the colon; thus, a meaningful comparator in assessing the effects of olestra on the incidence and severity of GI symptoms is a compound that, like olestra, is largely indigestible. In 2 separate randomized, double-blind, placebo-controlled, parallel feeding studies, McRorie *et al.* (2000a,b) evaluated subjective reports of GI symptoms following the consumption, for 6 days, of olestra, wheat bran, or sorbitol.

In the olestra *vs.* wheat bran study (McRorie *et al.,* 2000a), 60 subjects (mean age, 48.7 years) were randomized to 1 of 5 groups and administered either a placebo (5 oz triglyceride potato chips/day) 20 g/day olestra (2.5 oz triglyceride potato chips/day and 2.5 oz olestra potato chips/day), 40 g/day olestra (5.0 oz olestra potato chips/day), 20 g/day wheat bran (0.55 cups Bran Buds and 0.55 cups Puffed Wheat) or 40 g/day wheat bran (1.1 cups Bran Buds). The study, which spanned a total of 9 days, was conducted in a metabolic ward. During the baseline period (days 1 to 3), all subjects consumed an American Heart Association (AHA) Step I Diet (≤30% of calories from fat) as well as placebo snacks. During the subsequent 6 days (days 4 to 9), subjects continued to consume the AHA Step I Diet as well as their respective test snacks. Subjects rated each bowel movement on a 7-point scale (1=watery, difficult-to-control diarrhea; 4=normal; 7=hard, difficult-to-pass constipation). Mean bowel movement rating for the baseline period was 3.96 ± 0.008. During the treatment phase, mean bowel movement rating was 3.7 ± 0.2 for the placebo group, 3.5 ± 0.2 for the olestra 20 g/day group, 3.0 ± 0.2 for the olestra 40 g/day group, 3.3 ± 0.2 for the bran 20 g/day group, and 3.7 ± 0.1 for the bran 40 g/day group. Mean bowel movement rating for the olestra 40 g/day group was significantly ($p<0.05$) less compared to the placebo and bran 40 g/day groups, but not significantly different from the 20 g/day bran and olestra groups. Thus, although consumption of 40 g/day olestra resulted in slightly less formed stools, the effect was no different from that observed with the consumption of 20 g/day bran. Olestra is an inert substance and has no osmotic properties, and it has been shown that while the percent water content of fecal matter is reduced with the consumption of olestra, the absolute water content is unchanged (McRorie *et al.,* 2000a). Thus, the formation of slightly less formed stools with the consumption of 40 g/day olestra is due to the presence of olestra, a semisolid, in fecal matter, and not due to an increase in water content. GI symptoms (bloating, cramping, passing gas, heartburn, nausea, urgency) were self-reported by subjects, rated on a scale of 0 (none) to 5 (severe), and recorded in a daily diary. Compared with the placebo, there were no significant differences in the severity of GI symptoms in any of the treatment groups. With the exception of passing gas, all mean GI severity scores were <1 (mildest rating). The mean severity rating for passing gas was ≤2 for all treatment groups, both at baseline and following the 6-day feeding intervention. Thus, consumption of either 20 or 40 g/day olestra was not associated with GI side effects that were rated any differently from

those reported by subjects consuming the placebo (20 g/day triglyceride) or 20 or 40 g/day wheat bran.

In a subsequent study, McRorie *et al.* (2000b) compared the GI effects elicited by olestra with those elicited by a placebo or sorbitol. The 12-day study was conducted in a metabolic ward. Sixty-six subjects (mean age, 39.8 years) were randomized to 1 of 4 treatment groups and administered a placebo (5 oz triglyceride potato chips and 1.7 oz sucrose candy/day), 20 g/day olestra (2.5 oz olestra potato chips, 2.5 oz triglyceride potato chips, and 1.7 oz sucrose candy/day), 40 g/day olestra (5 oz olestra potato chips and 1.7 oz sucrose candy/day), or 40 g/day sorbitol (5 oz triglyceride potato chips and 1.7 oz sorbitol candy/day). The dose of sorbitol administered was 80% of that requiring a warning label stating "Excess consumption may have a laxative effect" [21 CFR §184.1835(e)] (U.S. FDA, 2006e). Throughout the 12-day study, subjects consumed the AHA Step I diet. The first 2 days were a lead-in period during which subjects consumed placebo snacks and were acclimated to the living conditions. The next 4 days comprised the baseline period, during which subjects rated bowel movements and documented GI side effects as previously discussed (McRorie *et al.,* 2000a). The final 6 days comprised the treatment period. Daily bowel movement frequency was 1.5 ± 0.1 and 1.1 ± 0.2 during the baseline period and in the placebo group, respectively, 1.6 ± 0.2 in the olestra 20 g/day group, 2.0 ± 0.2 in the olestra 40 g/day group, and 2.9 ± 0.5 in the sorbitol 40 g/day group. Daily bowel movement frequency ranged from 0 to 6 during the baseline period, from 0 to 4 in the placebo group, from 0 to 6 in the olestra 20 g/day group, from 0 to 5 in the olestra 40 g/day group, and from 0 to 10 in the sorbitol group. For the sorbitol group, bowel movement frequency increased markedly in the 3-hour period immediately following dosing (which was at 10 am), with 77.3% of bowel movements occurring during this time interval. This was not observed in the placebo and olestra groups. Diarrhea was not reported in the placebo or olestra groups; in contrast, the sorbitol group was associated with 17 treatment days of diarrhea. The University of Maryland stool descriptors [firm (normal, formed); soft (less form); liquid (little solid material); rice water (clear with flecks of solid material)] were used to describe stool form. There were no liquid or rice water stools during the baseline period or in the olestra 20 g/day group. There was 1 liquid/rice stool in each of the placebo and olestra 40 g/day groups. In contrast, there were 140 liquid/rice water stools in the sorbitol group. While olestra consumption did not result in a significant increase in the severity of any GI symptom as compared with the placebo group, sorbitol consumption resulted in a significant increase relative to the placebo group in the severity of cramping, nausea, and urgency. Thus, stools were much less formed and various GI symptoms were far more severe with the consumption of sorbitol as compared with the consumption of olestra. The amount of sorbitol consumed in this study is equivalent to a 1.7 oz serving of smarties and world not require a laxative warning label under the current regulations [21 CFR §184.1835(e)] (U.S. FDA, 2006e).

Sandler *et al.* (1999) conducted a 6-week randomized, double-blind, parallel, placebo-controlled trial to evaluate the frequency of GI symptoms and their impact on daily living in free-living

subjects consuming olestra or regular chips in the home environment (the Household Chip Consumption Study). The study was conducted in Phoenix, Arizona and St. Petersburg, Florida from 28 July 1997 to 22 September 1997. Eligible households were those in which at least half of the members had eaten corn or potato chips ≥4 times in the previous month. All persons older than 2 years of age were eligible for participation. The unit of randomization was the household; thus, all members of the same household received the same study treatment. Olestra and regular (full-fat) potato/corn chips were packaged identically, and both displayed the Olean logo (Olean® is the Procter and Gamble brand name for olestra) and the following information 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." Subjects completed daily records (either for themselves or on behalf of children), which detailed: i) the amount of olestra-labeled and regular chips consumed, in increments of one-quarter of a package; ii) whether any of the following digestive symptoms were experienced: heartburn or indigestion, nausea or queasiness, vomiting, gas, bloating, abdominal cramping or pain, more frequent bowel movements, or looser stools or other digestive symptoms; iii) how the symptoms affected their daily activities (1, noticed symptoms but did not affect activities; 2, symptoms slightly affected activities; 3, missed some time at activities; 4, missed all day at activities); and iv) whether medications were used to alleviate symptoms or whether a physician was visited because of the symptoms. Daily records were reviewed for completeness and accuracy at weekly visits (when the adult subject contact returned to the trial site to pick up the household's weekly supply of potato chips). At the completion of the study, participants indicated which snacks they thought they had eaten.

A total of 3,181 subjects (1,620 subjects in the olestra group and 1,561 subjects in the control group) participated in the study. Subjects from all age groups were represented, including 885 children ages 2 to 12 years and 402 elderly ages 65 to 89 years. Subjects in both groups were similar with respect to age, gender, ethnicity, education level, and household income. Consumption patterns were similar in the olestra and control groups, with the median number of eating days and the total amount of olestra-labeled chips eaten highest among the elderly (median number of eating days, 27; median olestra chip intake, 1.38 oz/eating day). Men consumed more olestra-labeled chips per eating occasion than women (1.41 oz/eating day *vs.* 1.24 oz/eating day), but women tended to eat olestra-labeled chips more frequently (21 eating days) than men (18 eating days) and, as a result, consumed a greater median total amount. The median total amount of olestra-labeled chips eaten by children was approximately 25% less than that eaten by the group as a whole (1.13 oz/eating occasion). In both groups, chips were generally consumed on approximately half of the study days during the 42-day study period. The proportions of participants in the olestra and control groups reporting any GI symptom were similar [619/1620 (38.2%) subjects in the olestra group and 576/1561 (36.9%) subjects in the control group]. There were no significant differences between the 2 groups in the proportion of subjects reporting any of the 8 individual GI symptoms, except that a significantly higher percentage of controls (8.4% *vs.* 5.7%) reported nausea (95% CI, -4.9 to –0.4 percentage

points; p=0.02). Amongst subjects reporting 1 of the 8 GI symptoms, the number of symptom days for each of the 8 GI symptoms was comparable, except for more frequent bowel movements, which was reported as 2.8 symptom days in the control group and 3.7 symptom days in the olestra group (95% CI, 0.1 to 1.8 symptom days; p=0.004). There were no significant differences between the groups in the effect of symptoms on daily activities, with 98.2% of the ratings in the olestra group and 97.2% of ratings in the placebo group indicating that symptoms either did not affect or only slightly affected daily activities.

The study groups were stratified by age (children, 2 to 12 years; teenagers, 13 to 17 years; adults, 18 to 64 years; elderly, 65 to 89 years), by gender, and by deciles of total olestra-labeled chips consumed, and a series of statistical analyses were subsequently conducted. When stratified by age, a significantly higher proportion of children in the control group (2.3% *vs.* 0.2%) reported other GI effects (95% CI, -4.0 to –0.1 percentage points; p=0.04), mostly related to constipation. More adults in the olestra group (30.6% *vs.* 24.8%) reported gas (CI, 0.6 to 11.0 percentage points), and, in the olestra group, the number of symptom days for any GI symptom and for more frequent bowel movements was significantly higher (any GI event: 5.7 *vs.* 4.6 symptom days; 95% CI, 0.1 to 2.1 symptom days; p=0.02; more frequent bowel movements: 4.1 *vs.* 2.9 symptom days; 95% CI, 0.1 to 2.2 symptom days; p=0.02). When the groups were stratified by gender, the percentage of men reporting nausea (3.9% *vs.* 7.4%; p=0.01) and the mean number of symptom days for cramping in men (1.8 *vs.* 2.5; p=0.04) were significantly higher in the control group than in the olestra group. Among women, the number of symptom days for any GI event (5.4 *vs.* 4.2; p=0.004), for gas (4.9 *vs.* 3.7; p=0.009), and for more frequent bowel movements (3.9 *vs.* 2.9; p=0.03) were significantly higher in the olestra group. Although the olestra group was associated with a significant increase in the number of symptom days for these parameters, the increase in the number of symptom days (approximately 1 day out of a possible of 42 days) was small and clinically insignificant. When subjects were stratified by deciles of total olestra-labeled chips consumed, the percentage of participants in the highest decile (consuming approximately 2.5 oz of chips and 20 g of olestra or triglyceride) who reported symptoms was greater in the olestra group than in the control group for more frequent bowel movements (27.9% *vs.* 11.7%; 95% CI, 5.0 to 27.4 percentage points; p=0.005) and looser stools (30.3% *vs.* 16.8%; 95% CI, 2.1 to 25.1 percentage points; p=0.02). The number of symptom days did not differ significantly between the 2 groups for any of the 8 GI symptoms, and symptoms were rated as having no effect or slight effect on 97.8% and 98.4% of symptom days in the olestra and control groups, respectively. Use of medications to treat symptoms was similar in the olestra (132 participants) and control (129 participants) groups. As well, 9 subjects in the control group and 7 in the olestra group reported visiting a physician for GI symptoms. It is noteworthy that no subject reported anal leakage or fecal incontinence.

More than half of the participants (58%) were not sure what kind of chips they were eating. Of the 1,283 subjects who guessed at the type of chips they had eaten, 39% in the olestra group and 12% in the control group correctly guessed which potato chips they had been randomized

to, even though 79% of subjects believed they were eating olestra chips, while 21% believed they were eating regular chips. Reporting of GI symptoms was highest among participants who believed they were eating olestra chips (45.3% in the olestra group and 44.4% in the control group) than among participants who thought they were eating regular chips (31.0% in the olestra group and 29.1% in the control group) (p=0.01). GI symptom reporting in participants who said they were unsure as to the type of chips they were eating did not differ between the olestra (35.0%) and control (35.8%) groups.

7.3.3 Interpretation of Findings from Post-Market Human Experimental Studies

Although, in the Household Chip Consumption Study, the chronic consumption of olestra chips was associated with a statistically significant increase in more frequent bowel movements and in the number of symptom days for more frequent bowel movements (Sandler *et al.,* 1999), these findings are expected given that, unlike digestible fat, i) olestra increases fecal weight gram for gram (McRorie *et al.,* 2000a,b,c), ii) olestra does not delay gastric emptying (Cortot *et al.,* 1982; Kelly and Hunter, 1996; Meyer *et al.,* 1999), and iii) olestra is associated with a slight decrease in whole gut transit time (Kelly and Hunter, 1996; Kelly *et al.,* 1998). The observation that olestra is associated with significant increases in the incidence of and symptom days for more frequent bowel movements is not clinically meaningful, as subjects in the olestra and control groups were comparable with respect to medication use, physician visits, and severity ratings of symptoms. In addition, the number of symptom days for more frequent bowel movements increased only by 1 out of a possible of 42 days in the olestra group.

Thus, controlled human experimental studies conducted following the introduction of olestra into the U.S. market collectively demonstrate that consumption of olestra potato chips is not associated with clinically significant increases in the incidence or severity of GI symptoms as compared with the consumption of triglyceride potato chips (Zorich *et al.,* 1997b*,* 1998; Cheskin *et al.,* 1998; Sandler *et al.,* 1999). These findings are in contrast to those observed in the olestra national post-market surveillance program, where approximately 15,081 callers reported adverse health effects following the consumption of olestra, with the majority of callers (60 to 65%) reporting diarrhea and/or abdominal pain (Allgood *et al.,* 2001). A fair evaluation of the findings published in the post-market human experimental studies necessitates that several variables that may have affected outcome (*i.e.,* reporting of incidence and severity of adverse events) be critically appraised. Such variables include the appropriateness of the blinding procedures, the olestra intake level, the duration of exposure, the time of follow-up, and the methods used to collect information pertaining to the incidence and severity of GI effects.

During the test-market introduction and national expansion of potato chips made with olestra, chips were labeled with a cautionary statement that warned consumers that olestra might cause abdominal cramping and loose stools. Previous studies have demonstrated that subject awareness of potential side effects of a product increases reporting of those side effects. For example, in a multicenter pharmaceutical trial, the inclusion, in the consent forms used at 2 of

the 3 sites, of a statement outlining possible GI effects resulted in a 6-fold increase ($p<0.001$) in the number of subjects withdrawing from the study because of the subjective, minor, GI complaints (Myers *et al.,* 1987). Thus, controlled studies comparing the effects of olestra chips and triglyceride chips on subjective reports of GI effects should label both products identically. In the 6-week Household Chip Consumption Study, olestra and triglyceride chips were packaged in identical bags and were labeled with the olestra warning statement (Sandler *et al.,* 1999). In the Rechallenge Study (Zorich *et al.,* 1997b*,* 1998), olestra and triglyceride chips were packaged in identical bags and were labeled with the ingredient listings for both types of chips as well as the olestra warning statement. In the Movie Theatre Study, chips were packaged in plain white bags labeled only with a randomization number; however, possible GI effects were mentioned in the consent form (Cheskin *et al.,* 1998). The triglyceride and olestra potato chips tested in the studies by McRorie *et al.* (2000a,b) were packaged in plain, food-grade bags made of white foil laminate. Thus, in all these studies, potential for subject bias was balanced in both the olestra and control groups. Furthermore, the chance for investigative staff to introduce bias was minimized, given that investigative staff were unaware of treatment allocations.

The amounts of olestra consumed as well as the duration of exposure to olestra are 2 additional variables that may influence the incidence and severity of GI effects. Earlier human experimental studies suggested that large amounts of olestra consumed over a long period of time were associated with increases in the incidence/severity of GI effects; however, in the olestra post-market surveillance program, GI effects were reported following the consumption of smaller amounts of olestra and predominantly after 1 eating occasion. Of the 15,081 callers reporting adverse events to the olestra national post-market surveillance program, 77% reported such events following a single exposure to olestra (Allgood *et al.,* 2001). Based on this finding, the assessment of GI effects following a single, acute intake of olestra chips (Zorich *et al.,* 1997b*,* 1998; Cheskin *et al.,* 1998) is justified, despite criticisms that acute, “one-time” exposures are inadequate in assessing GI effects of olestra (Jacobson *et al.,* 1998). The average mean amount of chips consumed by healthy male and female volunteers given free access to regular chips as a snack was 2 oz (Miller *et al.,* 1995). Data collected from the national olestra post-marketing surveillance program indicated that more than two-thirds of callers reporting adverse events consumed a relatively small amount of olestra potato chips (less than 2 oz of chips and less than 16 g of olestra). Of the 15,081 callers reporting symptoms associated with the consumption of olestra, 2,137 (14%) consumed 0 to 0.5 oz of chips, 3,947 (26%) consumed 0.5 to 1.0 oz of chips, 3,908 (26%) consumed 1.0 to 2.0 oz of chips, 2,887 (19%) consumed 2.0 to 4.0 oz of chips, while the remainder (14%) consumed more than 4 oz of chips (Allgood *et al.,* 2001). The 20 or 40 g/day olestra intakes administered in the 6-day studies conducted by McRorie *et al.* (2000a,b) were relatively higher than those reported to cause GI effects; however, these levels were appropriate in comparing the GI effects of olestra with those of wheat bran and sorbitol. The amounts of olestra chips consumed by subjects participating in the post-marketing human experimental studies were comparable to the intakes reported by subjects who called in to the post-market surveillance program. In the 6-week

Household Chip Consumption Study, the overall median amount of olestra chips consumed was 1.30 oz/day (corresponding to an olestra intake of 10.4 g). In the Rechallenge Study (Zorich et al., 1997b, 1998), subjects were administered 2 ounces of chips per eating challenge and instructed to consume as much as they wanted, but at least 1 ounce. All participants consumed at least 1 oz of chips and most subjects (just under two-thirds) consumed more than 90% of the 2-oz serving of chips (corresponding to olestra intakes of 8 to 16 g). In the Movie Theatre Study (Cheskin *et al.,* 1998) subjects were given a 369-g (13-oz) bag of chips and instructed to consume as much as they wanted. Although there was a broad range of chip consumption in both the olestra and control groups, the overall median consumption of olestra chips (2.1 oz of chips, equivalent to an olestra intake of 16.8 g) was within the range of intakes reported by consumers in the olestra post-market surveillance program. Thus, olestra intakes and consumption patterns in the human experimental studies were representative of those observed in the olestra post-market surveillance program.

Additional variables that may have affected the reporting of adverse events by subjects participating in the post-market human experimental studies include the time of follow-up and the methods used to collect information regarding the incidence/severity of adverse events. McRorie *et al.* (2000a,b) had subjects self-assess GI symptoms (bloating, cramping, passing gas, heartburn, nausea, urgency) and rate the severity (0, none to 5, severe). Sandler *et al.* (1999) requested that participants complete daily diary records detailing: i) the amount of olestra-labeled and regular chips consumed, in increments of one-quarter of a package; ii) the incidence of heartburn or indigestion, nausea or queasiness, vomiting, gas, bloating, abdominal cramping or pain, more frequent bowel movements, or looser stools or other digestive symptoms; iii) the severity of the symptoms (1, noticed symptoms but did not affect activities; 2, symptoms slightly affected activities; 3, missed some time at activities; 4, missed all day at activities); and iv) whether medications were used to alleviate symptoms or whether a physician was visited because of the symptoms. Investigative staff reviewed diary records weekly to ensure accuracy and completeness. In the other post-market human experimental studies, follow-up was approximately 2 days (Cheskin *et al.,* 1998) or 3 to 5 days or longer (Zorich *et al.,* 1997b, 1998) following the single olestra eating occasion, and, although subjects were asked if they had any digestive symptoms since consuming the chips, they were not prompted or presented with a list of typical GI effects. Because a list of symptoms was not provided to the subjects, it is possible that subjects might have underreported GI symptoms that were experienced following the consumption of olestra chips. Indeed, while, in the “prompted” study, 38.2% of subjects reported 1 or more GI effects with the consumption of olestra chips (Sandler *et al.,* 1999), in the “unprompted” studies, only 15.8% (Cheskin *et al.,* 1998) and 29% (Zorich *et al.,* 1998) of subjects reported 1 or more GI effects with the consumption of olestra chips. In addition, since, in the acute studies, several days may have elapsed before the subjects were recontacted, the subjects’ recollection of events may not have been entirely accurate. Despite these limitations, it is noteworthy that subjects were able to self-report symptoms prior to contact by investigative staff using dedicated toll-free numbers. In addition, that subjects were not

prompted with a list of digestive symptoms during follow-up more closely resembles the situation where consumers call-in their adverse event reports and use their own terminology to describe adverse events. Regardless of whether follow-up was daily or prolonged or whether subjects were prompted about GI effects or unprompted, clinically significant differences between olestra and triglyceride chip groups in GI effects were absent.

7.3.4 Discussion

Findings from controlled human experimental studies regarding the GI effects of olestra are in disaccord with those reported in the olestra post-marketing surveillance program. Despite the lack of agreement, it is not surprising that during the early years of olestra's market introduction, adverse events allegedly related to olestra were reported. History has shown that the introduction of a high-profile food additive into the food industry is commonly associated with consumer misattribution of symptoms to food-product consumption. The classical example of this phenomenon is the introduction of the high-profile, high intensity artificial sweetener, aspartame, into the marketplace. Despite numerous consumer allegations of neurological/ behavioral effects (mostly headaches) associated with consumption of aspartame, a well-controlled, double-blind rechallenge study involving 40 subjects failed to demonstrate any effects of aspartame *vs.* a placebo on the incidence of headaches (Schiffman *et al.,* 1987). Like olestra, aspartame endured considerable negative publicity regarding its safety and neurological effects, and this level of publicity may have prompted increased reporting of adverse events (Butchko *et al.,* 1994). Certainly, during times of heightened awareness of olestra's alleged GI effects (*i.e.,* during local media coverage, press conferences, or protests of olestra), the number of complaints reported to the post-market surveillance program increased (Allgood *et al.,* 2001). This finding indicates that consumers were influenced by media propaganda and that the media's negative publicity of olestra introduced consumer bias in the reporting of olestra-related adverse events.

Another factor that may have influenced consumer reporting of adverse events to the toll-free line was the warning statement that was required to be printed on all packages of savory snacks made with olestra. During the 1996 U.S. FDA ruling on the use of olestra as a food additive in savory snacks, the U.S. FDA decided that because there was insufficient data from human experimental studies regarding the GI effects of olestra when consumed under usual or real-life conditions (as opposed to exaggerated uses of olestra), a label advising consumers of the potential side effects of olestra was required on all snacks made with olestra. Part of the label read, "This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools". Interestingly (or coincidentally), the 2 most commonly reported GI effects associated with olestra (*i.e.,* abdominal pain and diarrhea/loose stools) were identical to those contained in the cautionary statement on the package label. Consumer bias in adverse event reporting was demonstrated by Sandler *et al.* (1999), when subjects who either correctly or incorrectly believed they were consuming olestra chips reported a significantly greater incidence of GI

symptoms as compared with subjects who believed they were eating control chips. Clearly, these findings demonstrate the power of suggestion in influencing consumer perceptions.

GI symptoms are a class of ailments that are largely subjective. A recent cross-sectional telephone survey assessing the prevalence and impact of various digestive symptoms amongst 2,510 subjects residing in the U.S. demonstrated that, under ordinary conditions, 40.5% of subjects reported experiencing 1 or more digestive symptoms within the month prior to the interview, including abdominal pain/discomfort (21.8%), bloating/distension (15.9%) and diarrhea/loose stools (26.9%) (Sandler *et al.,* 2000). In addition, more than 65% of respondents rated their symptoms as moderate or severe in intensity. Interestingly, the 2 most common complaints made to the olestra post-market surveillance program (abdominal pain and diarrhea/loose stools) were also the most common symptoms reported in the cross-sectional telephone survey. In addition, consumption of savory snacks is widespread, with approximately 96% of the U.S. population consuming savory snacks in any given month (Kristal *et al.,* 1998).

Given the high consumption level of savory snacks and the large background prevalence of digestive complaints in the U.S., it is not surprising that chips made with olestra, which carried a cautionary statement regarding potential GI effects, were associated with such effects by consumers who were periodically bombarded with negative, often unfounded information regarding olestra from the media. Well-controlled human experimental studies evaluating the GI effects of chips made with olestra or triglyceride under similar consumption conditions as those reported in the post-market surveillance program failed to demonstrate an increase in GI symptoms with the consumption of potato chips made with olestra.

As part of the 1996 final rule, the FDA committed to review and evaluate any new data and information regarding the safety of olestra and to present such information to the Agency's Food Advisory Committee within 30 months of the approval of olestra for use in savory snacks. Consequently, FDA convened an open public meeting within 30 months of the approval of olestra for use in savory snacks (on June 15 – 17, 1998), and new data collected since the 1996 approval were collected and presented to the Food Advisory Committee. Procter and Gamble subsequently submitted a food additive petition, dated December 1, 1999, to amend the food additive regulations in § 172.867 *Olestra* by removing the requirement for the label statement prescribed in § 172.867(e) [*i.e.,* This product contains olestra (U.S. FDA, 2006a). 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]. The petition incorporated data collected from the OPMSS (the Sentinel Site) and from several human experimental studies, including the Rechallenge Study (Zorich *et al.,* 1997b, 1998), the Movie Theatre Study (Cheskin *et al.,* 1998), the 6-Week Household Chip Consumption Study (Sandler *et al.,* 1999), and the Sorbitol *vs.* Olestra Study (McRorie *et al.,* 2000b). Based on its analysis of the data and information submitted in the petition, the FDA concluded that: i) There is no evidence of an increased frequency of abdominal cramps due to the ingestion of olestra in savory snacks under

usual and customary conditions of use for savory snacks; ii) There is only a minor increase in loose stools and bowels movements, and that the severity and impact of these effects on daily activity are not different from other foods that may cause similar effects; and iii) The label statement is not an effective means of communicating accurate information to olestra consumers (U.S. FDA, 2003a). Thus, the FDA ruled that olestra-containing foods are not required to bear a label statement informing consumers of possible GI symptoms from consumption of olestra (U.S. FDA, 2003a).

7.4 Fat-Soluble Vitamins and Carotenoids

7.4.1 Introduction

Because olestra is highly lipophilic and resistant to digestion, it interferes with the absorption of fat-soluble vitamins and carotenoids by sequestering them. Fat soluble vitamins A, D, E, and K must be added to products containing olestra at concentrations that meet the conditions specified in 21 CFR §172.867(d) (U.S. FDA, 2006a). Studies conducted following the U.S. market introduction of olestra as well as the olestra post-marketing surveillance studies (OPMSS) were critically reviewed to determine if restoration levels for these vitamins are sufficient to offset nutritional imbalances in these vitamins (Section 7.4.2). Effects on carotenoids were determined by critically reviewing studies conducted prior to and after the market introduction of olestra (Section 7.4.3).

7.4.2 Effects of Olestra on Serum Levels of Vitamins A, D, E, and K

To compensate for any interference of olestra with the absorption of fat-soluble vitamins, vitamins A, D, E, and K are required to be added to foods containing olestra [21 CFR §172.867(d)] (U.S. FDA, 2006a). Results from the OPMSS and human experimental studies conducted following the marketing of olestra indicate that olestra, when enriched with the fat-soluble vitamins as per 21 CFR §172.867(d), does not affect serum levels of vitamins A, D, and K (Thornquist *et al.,* 2000; Broekmans *et al.,* 2003; Neuhouser *et al.,* 2006; U.S. FDA, 2006a). At the sentinel site, a significant increase in serum α-tocopherol was reported in the highest olestra intake group (*i.e.,* $\geq$2 g/day) as compared with all other groups (Thornquist *et al.,* 2000); however, at the three other research sites involved in the OPMSS (*i.e.,* the Baltimore, Minneapolis, and San Diego sites), a significant 3.2% reduction in serum α-tocopherol in the olestra intake group (*i.e.,* $\geq$2 g/day) relative to no olestra consumption was reported (Neuhouser *et al.,* 2006). Despite the associations of olestra with either a significant increase or decrease in serum α-tocopherol, the magnitude of change in each case, though statistically significant, is clinically meaningless. For instance, at the sentinel site, subjects in the highest olestra intake group had a serum α-tocopherol level of 29.6 µmol/L, a value approximately 13% greater than that measured in non-olestra consumers (26.1 µmol/L). Both of these levels are well within the normal range for serum α-tocopherol, which is 11 to 37 µmol/L (Farrell, 1980). Likewise, at the

other OPMSS sites, while, in the highest olestra intake group, a significantly lower serum α-tocopherol level was reported as compared with the control group (30.1 µmol/L *vs.* 31.1 µmol/L; P<0.05), the level was well within the normal range for serum α-tocopherol. The OPMSS is described in detail in Appendix B.

That vitamin E status is not altered with the consumption of olestra is supported by the human experimental studies conducted following the marketing of olestra. While Kelly *et al.* (1998) reported a significant decrease in serum α-tocopherol following the 3-month consumption of approximately 26.8 g/day SPE [*i.e.,* from 13.51 mg/dL (31.4 µmol/L) to 11.66 mg/dL (27.0 µmol/L); P≤0.001], this was an expected finding given that the SPE (made by Unilever) used in the formulations of the various foods was not enriched with any of the fat-soluble vitamins. It is worth noting that many of the foods containing SPE (such as sausage rolls, meat pies, margarine, processed cheese, beefburger, and salad cream) would most likely have been consumed with main meals, thus maximizing the potential for SPE to interact with vitamins. Despite the high mean intake of SPE (26.8 g/day, which is approximately 3.5 times the projected total population users-only 90th percentile chronic intake of olestra from savory snacks and cookies), the 15% difference in serum α-tocopherol was clinically insignificant, as levels remained within the normal range for *all* subjects. This observation is remarkable, given the high, chronic (3-month) intake of foods containing unenriched SPE, and given the great potential for SPE to interact with vitamin-rich foods that would have been co-consumed with the SPE foods.

In another Unilever-sponsored study, significant reductions in α-tocopherol were noted in groups consuming, for one year, 7 g/day olestra, 10 g/day SPE, or 17 g/day olestra+SPE in the form of olestra chips, an SPE spread, or olestra chips+SPE spread, respectively, relative to the control group (Broekmans *et al.,* 2003). Although the SPE spreads were prepared by Unilever (Netherlands), the olestra chips were purchased in the U.S. and repackaged in neutral bags. The SPE spreads were enriched with vitamins A, D, E, and K at levels required by the U.S. FDA for the use of olestra in chips [21 CFR §172.867(d)] (U.S. FDA, 2006a). Serum α-tocopherol levels were standardized to levels of total cholesterol and total triacyglycerols, and expressed as µmol of α-tocopherol per mmol total lipids. To permit comparisons of the serum α-tocopherol levels reported in this study with what is considered normal, the lipid standardized values and the total cholesterol and triacyglycerol values were used to calculate absolute levels of serum α-tocopherol. This resulted in serum α-tocopherol values of 26.7, 28.5, 26.8, and 24.1 µmol/L for the 0, 7, 10, and 17 g/day olestra/SPE groups. Looking at the absolute levels of serum α-tocopherol (rather than the lipid standardized values), two important observations are apparent: i) All serum α-tocopherol levels are within the normal range [11 to 37 µmol/L; Ferrell *et al.,* 1980); and ii) Relative to the control serum α-tocopherol level, that observed in the 7 g/ay olestra group is 6.3% higher, while that in the 10 g/day SPE group is essentially identical.

By standardizing serum α-tocopherol levels with respect to total cholesterol and triacyglycerols, serum α-tocopherol levels in the SPE groups were diluted. This was an artifact of the unexpected increases in serum lipids in the SPE groups following the one-year intervention study. The population studied was Dutch, and it is well documented that food consumption patterns in the general Dutch population are independently associated with cholesterol levels (van Dam *et al.,* 2003). Moreover, the cut-offs for serum cholesterol (>7.5 mmol/L) and triacylglycerol (>2.3 mmol/L) in the exclusion criteria were not conservative enough to ensure that subjects had normal lipid metabolism (notably, the study included both normolipidemic and hyperlipidemic subjects on stable hyperlipidemia treatment). According to the American Heart Association, a normal total cholesterol is defined as a total blood cholesterol <5.17 mmol/L (<200 mg/dL), and a normal triglyceride level <1.69 mmol/L (<150 mg/dL) (Youngerman-Cole, 2005). Because the exclusion criteria for total cholesterol and triglycerides were set so high, it is not clear that the subjects included in the study had normal lipid metabolism, and so standardization of serum α-tocopherol to total lipids may not have been appropriate. Clearly, the unstandardized serum α-tocopherol values are normal, and measures of LDL oxidation, protein oxidation, lipid peroxidation, and DNA damage were no different in the SPE groups than in the control group, further indicating that antioxidant status was not compromised.

Given that serum α-tocopherol levels remain well within the normal range following the long-term consumption of olestra, the restoration level for vitamin E is considered sufficient, as are the restoration levels for vitamins A, D, and K.

7.4.3 Effects of Olestra on Serum Carotenoid Levels

7.4.3.1 Overview

Octanol-water partition coefficients (expressed in log units as $\log_{10}P_c$) are directly proportional to the lipophilicity of a compound. $\text{Log}_{10}P_c$ values for the carotenoids were either compiled from the scientific literature or calculated from the molecular structure of the compound (Cooper *et al.,* 1997a). The $\text{Log}_{10}P_c$ values for several carotenoids and other compounds are summarized in Table 7-2. Several studies have demonstrated that olestra reduces serum cholesterol levels (Fallat *et al.,* 1976; Mattson *et al*., 1976; Crouse and Grundy, 1979; Jandacek *et al.*, 1980, 1990; Adams *et al.,* 1981; Aust *et al.,* 1981; Mattson and Jandacek, 1985; Hager and Schneeman, 1986); thus, the absorption of compounds with $\log_{10}P_c$ values higher than that for cholesterol is expected to be reduced with the administration of olestra. It is clear from Table 7-2 that α-carotene, β-carotene, and lycopene are 398 times more lipophilic than zeaxanthin and 631 times more lipophilic than lutein. Based on these data, olestra is expected to affect the absorption of α-carotene, β-carotene, and lycopene moreso than that of lutein and zeaxanthin. Indeed, several human experimental studies, as well as the Olestra Post-Marketing Surveillance Study (OPMSS) have demonstrated that olestra reduces serum levels of the carotenoids (Table 7-3), with serum levels of the hydroxylated carotenoids (lutein, zeaxanthin, and β-cryptoxanthin)

less affected (Table 7-4). Randomized controlled trials and observational studies assessing the effects of olestra or SPE on serum carotenoid levels are reviewed in detail in Section 7.4.3.2.

Table 7-2 Octanol-Water Partition Coefficients ($log_{10}P_c$) for Various Compounds

Compound	$Log_{10}P_c$
α-carotene	17.6
β-carotene	17.6
Lycopene	17.6
Zeaxanthin	15.0
Lutein	14.8
α-tocopherol	12.2
Phylloquinone	11.7
Ergocalciferol	10.4
Cholesterol	8.7

Table 7-3 Effects of Olestra on Serum Carotenoid Levels

Reference	Intervention	Length	Significant Effects on Carotenoids
Weststrate and van het Hof, 1995	12.4 g/day SPE in margarine consumed with main meal	4 weeks	↓ in all carotenoids; β-carotene and lycopene ↓ to 66% and 48% of control levels.
	3 g/day SPE in margarine consumed with main meal	4 weeks	β-carotene and lycopene ↓ to 63% and 66% of control levels.
Koonsvitsky *et al.,* 1997	18 g/day olestra in 1 frozen dessert and 3 cookies	16 weeks	Total carotenoids ↓ to 68% of control levels.
Kelly *et al.,* 1998	27 g/day SPE in various foods	12 weeks	All carotenoids ↓ 58 – 75% of control levels.
Schlagheck *et al.,* 1997	0, 8, 20, or 32 g/day olestra in cookies, chips, muffins, biscuits consumed with main meals	8 weeks	Dose-dependent ↓; total carotenoids were 49%, 39%, and 32% of control levels.
Broekmans *et al.,* 2003	0, 7, 10, or 17 g/day olestra (in chips) and/or SPE (in margarine)	1 year	13 – 33% ↓ in all carotenoids; carotenes and lycopene most affected.
Tulley *et al.,* 2005	20 – 45 g/day olestra plus multivitamin containing β-carotene (2.24 µmol) and lutein (0.44 µmol).	36 weeks	↓ from baseline in β-carotene (by 54%), lycopene (by 47%), and lutein+zeaxanthin (by 29%).
Thornquist *et al.,* 2000	Observational (OPMSS)	1 year	14.5% ↓ in total carotenoids in the highest olestra intake group.
Neuhouser *et al.,* 2006	Observational (OPMSS)	1 year	Dose-dependent ↓ in all carotenoids except lutein+zeaxanthin.

Abbreviations: OPMSS, Olestra Post-Marketing Surveillance Study; SPE, sucrose polyeste

Table 7-4 Effects of Olestra on Individual Serum Carotenoid Levels

Reference	Intervention	Length	Serum Carotenoid Level (as a Percentage of Baseline or Control Levels)				
			α-Carotene	β-Carotene	Lycopene	B-cryptoxanthin	Lutein+zeaxanthin
Weststrate and van het Hof, 1995 (% control)	12.4 g/day SPE in margarine consumed with main meal	4 weeks	Not measured	66%	48%	75%	Lutein: 80% Zeaxanthin: 80%
Koonsvitsky *et al.,* 1997 (% baseline)	18 g/day olestra in 1 frozen dessert and 3 cookies	16 weeks	64%	59%	71%	Not measured	82%
Kelly *et al.,* 1998 (% control)	27 g/day SPE in various foods	12 weeks	75%	60%	58%	61%	Lutein: 71%
Schlagheck *et al.,* 1997 (% control)	32 g/day olestra in cookies, chips, muffins, biscuits consumed with main meals	8 weeks	28%	31%	23%	Not measured	52%
Broekmans *et al.,* 2003 (% baseline)	17 g/day olestra (in chips) and/or SPE (in margarine)	1 year	67%	69%	76%	82%	Lutein: 82% Zeaxanthin: 87%
Tulley *et al.,* 2005 (% baseline)	20 – 45 g/day olestra plus multivitamin containing β-carotene (2.24 μmol) and lutein (0.44 μmol).	36 weeks	Not measured	53%	46%	Not measured	71%
Neuhouser *et al.,* 2006 (% control)	OPMSS	1 year	86%	90%	88%	94%	96% (not significant)

Abbreviations: OPMSS, Olestra Post-Marketing Surveillance Study; SPE, sucrose polyeste

7.4.3.2 *Effects of Olestra on Serum Carotenoid Levels: Data Collected from Randomized Controlled Trials and the OPMSS*

Several clinical studies have assessed the effects of olestra on serum carotenoid levels. Schlagheck *et al.* (1997) conducted an 8-week double-blind, parallel, placebo-controlled study to assess the effects of graded intakes of olestra on the status of the fat-soluble vitamins and carotenoids; from this point forward, this study will be referred to as the 8-week Olestra Dose-Response Study. Ninety healthy male and female subjects aged 18 to 44 years were randomly assigned to 1 of 4 groups balanced with respect to age, gender, body mass index, and serum total carotenoid and alpha-tocopherol concentrations. Subjects were administered, for 8 weeks, 0, 8, 20, or 32 g/day olestra in potato chips, muffins, biscuits, and cookies. To maximize the opportunity for olestra to affect the availability of the nutrients, foods containing olestra were eaten at every meal everyday for 56 consecutive days (*i.e.,* 168 consecutive meals), and subjects were asked not to eat between meals so that olestra and nutrients were always present simultaneously in the gut. In this study, consumption of 8, 20, or 32 g/day olestra resulted in significant, dose-dependent reductions in serum levels of α-carotene, β-carotene, lycopene, lutein+zeaxanthin, and total carotenoids (Schlagheck *et al.,* 1997; Table 7-5). All serum carotenoids were reduced similarly by olestra, except lutein+zexanthin, which were less affected by olestra.

Table 7-5 Serum Carotenoid Levels in the 8-Week Olestra Dose-Response Study**

Olestra Intake (g/day)	α-carotene (μmol/L)	β-carotene (μmol/L)	Lycopene (μmol/L)	Lutein+Zeaxanthin (μmol/L)	Total carotenoids (μmol/L)
0	0.18 ± 0.02	0.26 ± 0.02	0.52 ± 0.03	0.21 ± 0.01	628 ± 31
8	0.07 ± 0.02*	0.10 ± 0.02*	0.22 ± 0.03*	0.18 ± 0.01	306 ± 30*
20	0.07 ± 0.02*	0.10 ± 0.02*	0.15 ± 0.03*	0.12 ± 0.01*	243 ± 29*
32	0.05 ± 0.02*	0.08 ± 0.02*	0.12 ± 0.03*	0.11 ± 0.01*	201 ± 30*

*Significantly different from control (P<0.05).
**Values shown are those measured at the end of the study (8th week).

In another study (Koonsvitsky *et al.,* 1997), 194 healthy subjects were administered 18 g/day olestra or triglycerides, either with or without 1.1 mg tocopherol acetate, for 16 weeks. Olestra or triglycerides were consumed daily in the form of 1 frozen dessert (9 g olestra or triglyceride) and 3 cookies (3 g olestra or triglyceride per cookie). Subjects were asked to consume the test foods with meals at their discretion. All other foods were self-selected and freely consumed. At the end of the 16-week study, β-carotene decreased by approximately 35% (P<0.05 relative to the triglyceride control group). When adjustments were made for the 8% decrease in serum carotenoid levels in the placebo group, the net effect of olestra on serum β-carotene concentrations was a 26 to 28% reduction (P<0.05 relative to the control group). The serum concentrations of α-carotene, lycopene, lutein+zeaxanthin, and total carotenoids, when adjusted for the small reductions in total carotenoids in the placebo group, were reduced by 21 to 29%.

The results were not affected by normalization of the serum carotenoid concentrations with respect to total serum lipids (which were not significantly altered with the administration of olestra).

In a 4-week crossover study sponsored by Unilever (Weststrate and van het Hof, 1995), the administration of 12.4 g/day SPE in the form of a margarine-like spread resulted in significantly lower plasma carotenoid concentrations relative to the administration of 12 g/day triglycerides. β-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin were 66%, 48%, 75%, 80%, and 80% of control values ($P<0.001$ for all relative to control). As predicted by Cooper *et al.* (1997a), β-carotene and lycopene were most affected by olestra; thus, a second 4-week study was carried out, using an SPE dose of 3 g/day. At this SPE intake, plasma β-carotene and lycopene levels were significantly reduced to 63% and 66%, respectively, of control levels ($P<0.005$ relative to control values). Thus, the consumption of 3 g/day SPE, which is equivalent to the total population all-user 50th percentile intake of olestra from cookies and savory snacks, resulted in significant reductions in plasma β-carotene and lycopene levels. The magnitude of effect of 3 g/day SPE on plasma levels of β-carotene and lycopene was comparable to that observed with the higher SPE intake of 12 g/day. In this study, subjects were required to consume the SPE spread with the main meal, which is presumably the most important source of carotenoids. While the intake of 3 *vs.* 12 g/day SPE with the main meal had similar effects on serum levels of β-carotene and lycopene, the effects may have been less pronounced if the same amounts of SPE were consumed between meals as opposed to with meals.

The effects of olestra on the absorption of the individual carotenoids vary, depending on the lipophophilicities of the carotenoids. In general, the hydroxylated carotenoids (β-cryptoxanthin, lutein, and zeaxanthin) are less lipophilic than the unhydroxylated, more lipophilic carotenoids (β-carotene, α-carotene, and lycopene), and so are less affected by olestra (Table 8.4-3). Also, the effects of olestra on the absorption of the carotenoids are influenced by the patterns of olestra consumption. In the study by Schlagheck *et al.* (1997), total serum carotenoids were only 39% of control values following the 8-week administration of 20 g/day olestra. Weststrate and van het Hof (1995) demonstrated that the consumption of 3 or 12 g/day SPE, consumed with the main meal, reduced serum levels of β-carotene and lycopene to approximately 65% of control levels. Similarly, in the study by Koonsvitsky *et al.* (1997) total serum carotenoids were 68% of control values with the 16-week administration of 18 g/day olestra. These differences support the findings of Daher *et al.* (1997a) that for a given amount of olestra, the patterns of olestra consumption (*i.e.,* with meals or between meals) have a tremendous impact on the bioavailability of nutrients. In the 8-week Olestra Dose-Response Study, olestra was consumed with each meal, and individuals were not permitted to snack between meals. In contrast, in the study by Koonsvitsky *et al.* (1997), subjects were required to consume 1 frozen dessert and 3 cookies each day with meals, but were not required to divide the daily allocation among the meals, and there was no restriction on what other foods could be eaten with meals or between

meals. Similarly, in the study by Weststrate and van het Hof (1995), SPE was required to be consumed with the main meal, as opposed to with all 3 meals, and free-living subjects were free to consume whatever foods and snacks they wanted. Under these "real-world" consumption patterns, the effects of olestra on the absorption of the carotenoids were attenuated.

Three additional human experimental studies were published since the 1996 U.S. FDA approval of olestra for use as a fat substitute in savory snacks. Two of these studies were sponsored by Unilever (Kelly *et al.,* 1998; Broekmans *et al.,* 2003), and 1 study was sponsored by P&G (Tulley *et al.,* 2005). Although, in the Unilever-sponsored studies, the SPE formulations studied had properties slightly different from those specified in the olestra specifications, the caloric value of the SPE formulations was declared as zero in the studies (Kelly *et al.,* 1998; Broekmans *et al.,* 2002); thus, the formulations must have contained predominantly hexa-, hepta-, and octa-esters and, like olestra, must have been resistant to digestion and absorption in the GI tract. For these reasons, the studies were included in the current safety review.

The effects of SPE on serum carotenoid levels were investigated by Kelly *et al.* (1998). The 6-month trial was a randomized, double-blind, placebo-controlled crossover study consisting of two, 3-month periods. Seventy-six, healthy, free-living male and female subjects were randomized to receive either foods containing SPE or identically packaged control foods (made of triglycerides) for a period of 3 months, followed by a further 3 months on the alternative foods. SPE was added to a variety of products, including bakery products, dairy products, fats, and other foods. Subjects were required to consume 20 to 40 g/day SPE, and the mean consumption was 26.8 g/day (equivalent to approximately 3 ounces of potato chips made with olestra). All carotenoids decreased significantly during SPE consumption as compared with during consumption of triglycerides (Table 7-6).

Table 7-6 Serum Carotenoid Concentrations (µmol/L) Following the 3-Month Intake of Foods Containing SPE or Triglyceride

	Lutein	β-Cryptoxanthin	Lycopene	α-Carotene	β-Carotene	Cis-β-carotene
SPE	0.24 ± 0.10	0.14 ± 0.11	0.28 ± 0.18	0.06 ± 0.03	0.26 ± 0.16	0.03 ± 0.023
Triglyceride	0.34 ± 0.14	0.23 ± 0.14	0.48 ± 0.25	0.08 ± 0.05	0.43 ± 0.26	0.05 ± 0.04
% Difference	29.4%	39.1%	41.7%	25.0%	39.5%	40.0%
P-value	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.02

Tulley *et al.* (2005) assessed the effects of chronic consumption of olestra on the status of the carotenoids in subjects who were taking a multivitamin. This was a randomized, double-blind, parallel arms 36-week trial involving 37 healthy male subjects (ages, 21 to 60 years; BMI, 27 to 35 kg/m^2). Subjects were randomized, within the strata of age, BMI, and screening cholesterol, to a control group, a fat-reduced group, and an olestra group. The control diet contained approximately 33% of energy as fat, while the olestra and fat-reduced diets contained 25% of

energy as fat. Diets were tailored to maintain body weight; thus, olestra intakes ranged from approximately 20 to 45 g/day. The olestra contained RRR-α-tocopherol acetate at 4.44 µmol/g (2.1 mg/g). The multivitamin contained retinyl acetate [3.14 µmol (1.0 mg)], β-carotene [2.24 µmol (1.2 mg)], ergocalciferol [0.02 µmol (7.9 µg)], all racemic α-tocopheryl acetate [63.5 µmol (30.0 mg)], phytonadione [0.06 µmol (27.0 µg)], and lutein [0.44 µmol (250.3 µg)], as well as other vitamins and minerals. Blood samples for serum carotenoid measures were collected at 12, 24, and 36 weeks.

Compared with the control group, serum levels of β-carotene, lycopene, and lutein+zeaxanthin were significantly lower in the olestra group, but not in the fat-reduced group. Normalization of values for changes in cholesterol or BMI did not alter the significance of these changes. Although supplementation with β-carotene and lutein was ineffective at preventing reductions in serum levels of β-carotene and lutein, it should be noted that the amounts of lutein and β-carotene present in the multivitamin were very low; the amount of β-carotene in the multivitamin is equivalent to the amount present in 1/2 of a small (51/2 inch long) carrot and the amount of lutein in the multivitamin is equivalent to the amount present in 1/10th of a cup of raw spinach (USDA, Release 17). That serum carotenoid levels were not reduced in the fat-reduced group suggests that the reduction in serum carotenoid levels in the fat-reduced olestra group is due to their sequestration by olestra, and not due to a reduction in fat intake.

Broekmans *et al.* (2003) conducted a one-year human intervention trial to investigate the effects of SPE consumption on serum concentrations of carotenoids and fat-soluble vitamins, on markers of oxidative damage, and on functional markers of eye health, cardiovascular health, and immune status. The randomized, double-blind, placebo-controlled parallel design trial included 341 subjects (164 males and 177 females) aged 18 to 75 years (mean age was approximately 42 years). Subjects were selected from a total of 2,734 individuals who expressed interest in participating in the study; selection was based on subjects being either in the highest or lowest quintiles for fruit and vegetable consumption. Subjects were randomized to 1 of 4 treatment groups, balanced for high/low fruit and vegetable consumption, age, gender, and smoking status. The subjects consumed TG chips+TG spread, olestra chips+TG spread, SPE spread+TG chips, or olestra chips+SPE spread to permit olestra and/or SPE intakes of 0, 7, 10, or 17 g/day, respectively. Although the SPE spreads were prepared by Unilever (Netherlands), the olestra chips were purchased in the U.S. and repackaged in neutral bags. The SPE spreads were enriched with vitamins A, D, E, and K at levels required by the U.S. FDA for the use of olestra in chips [21 CFR §172.867(d)] (U.S. FDA, 2006a). Although the stiffness and the degree of esterification of the SPE used in the production of the spread were slightly different from the olestra specifications, all other parameters were within specification. Body weight was assessed at monthly intervals. Morning blood samples were collected from fasted subjects at baseline and after 13, 26, and 52 weeks for analysis of fat-soluble vitamins and carotenoids. Other measurements included LDL oxidation (as a marker of oxidative stress), 8-epi-prostaglandin $F_{2\alpha}$ (as a marker of lipid oxidation), protein carbonyls (as measures of

protein oxidation), measures of immune function, macular pigment optical density (as a marker of lutein and zeaxanthin in the eye), and flow-mediated vasodilation of the brachial artery (as a measure of endothelial function).

Compliance was >98.8% in all the groups. Compared with the control group, lipid standardized concentrations of carotenoids decreased by 33% (P<0.0001) for α-carotene, followed by β-carotene (31%; P<0.0001), lycopene (24%; P<0.001), β-cryptoxanthin (18%; P<0.0001), lutein (18%; P<0.0001) and zeaxanthin (13%; P<0.001) in the 17 g/day group. In the lowest olestra intake group (*i.e.,* 7 g/day) significant reductions were observed only in zeaxanthin, α-carotene, and β-carotene. Reductions in serum carotenoid levels were generally greatest in SPE groups, a finding consistent with the observation that approximately 1/3 of subjects consumed the SPE spread on bread or on vegetables (indicative of consumption with main meals). No differences were found among the 4 treatment groups in LDL oxidation, protein carbonyls (protein oxidation), lipid peroxidation products (8-epi-prostaglandins $F_{2\alpha}$), and DNA damage, as measured by the comet assay. Changes in macular pigment optical density did not differ among the groups, nor did changes in mean calculated endothelial function and immune function. The authors concluded that although the long-term consumption of SPE resulted in significant reductions in the carotenoids, these carotenoid reductions did not affect possible markers of disease risk.

The OPMSS provides valuable insight regarding the long-term effects of olestra intakes on nutritional status. At the sentinel site (Thornquiest *et al.,* 2000), total carotenoids were significantly lower in the highest olestra intake group (≥2 g/day) as compared with the group that did not consume olestra (-14.5% *vs.* –4.5%; P<0.05). The other OPMSS sites reported significant dose-dependent reductions in serum levels of α-carotene, β-carotene, β-cryptoxanthin, lycopene, and total carotenoids, with serum concentrations of α-carotene, lycopene, and total carotenoids significantly lower with olestra consumption as compared with no olestra consumption (Neuhouser *et al.,* 2006). At the highest quartile of olestra intake (>4.4 g/week or 0.63 g/day), serum carotenoid levels were generally ≥85% of control levels (Neuhouser *et al.,* 2006). The OPMSS is described in detail in Appendix B.

7.4.3.3 Conclusions

The effects of olestra on serum carotenoid levels appear to be dependent on at least three factors: i) The amount of olestra consumed; ii) Whether olestra is consumed as a snack or as a component of a mixed meal; and iii) The octanol-water partition coefficient of the carotenoid. The modest effects of olestra on serum carotenoid levels in the OPMSS are most likely due to the low amounts of olestra that are consumed under real-world conditions, as well as the patterns of olestra chip consumption, which are mostly as snacks and not as components of mixed meals. This latter point is supported by the United States Department of Agriculture's (USDA) 1994 – 1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996) and

the 1998 Supplemental Children's Survey (CSFII 1998) (USDA, 2000), which indicate that approximately two-thirds of consumption occasions for fat-modified cookies and savory snacks are as snacks and the remaining one-third are as components of mixed meals. Thus, under real-world consumption patterns, consumption of savory snacks and cookies made with olestra is expected to have minimal effects on serum carotenoid levels.

In the OPMSS, olestra dose-dependently reduced levels of all serum carotenoids evaluated except lutein+zeaxanthin [(Appendix B) (Neuhouser *et al.,* 2006)]. Lutein, zeaxanthin, and β-cryptoxanthin are hydroxylated carotenoids and consequently have lower octanol-water partition coefficients than the unhydroxylated carotenes and lycopene; specifically, lutein and zeaxanthin are 630 and 398 times, respectively, less lipophilic than the carotenes and lycopene (Cooper *et al.,* 1997a). Several studies have demonstrated that olestra/SPE reduces serum levels of lutein and zeaxanthin to a lesser degree as compared with the other carotenoids (Table 8.4-3). The 9-month administration of 20 – 45 g/day olestra resulted in significant reductions in all of the carotenoids evaluated; however, while β-carotene and lycopene were 53% and 46%, respectively, of baseline values, lutein+zeaxanthin were 71% of baseline values (Tulley *et al.,* 2005). In the 8-week dose-response study (Schlagheck *et al.,* 1997), the administration of 32 g/day olestra resulted in significant reductions in all the carotenoids measured; however, while α-carotene, β-carotene, and lycopene were reduced to 28%, 31%, and 23%, respectively, of control levels, serum lutein+zeaxanthin was reduced to 52% of control levels. The 4-week administration of 12.4 g/day SPE resulted in significantly lower serum carotenoid concentrations as compared with the administration of 12 g/day triglycerides; however, while β-carotene and lycopene were reduced to 66% and 48%, respectively, of control levels, β-cryptoxanthin, lutein and zeaxanthin were less affected, being reduced to 75%, 80%, and 80%, respectively, of control levels (Weststrate and van het Hof, 1995). Lipid standardized concentrations of carotenoids decreased significantly by 33% for α-carotene, by 31% for β-carotene, by 24% for lycopene, by 18% for β-cryptoxanthin, and by 18% and 13% for lutein and zeaxanthin, respectively, following the 1-year administration of 17 g/day SPE+olestra (Broekmans *et al.,* 2003). Following the 4-week administration of 18 g/day olestra, serum α-carotene, β-carotene, and lycopene were 64%, 59% and 71%, respectively, of baseline values, while serum lutein+zeaxanthin was less affected, being 82% of baseline measures (Koonsvitsky *et al.,* 1997).

The finding, by Broekmans *et al.* (2003), that reductions in serum carotenoids following the 1-year feeding of up to 17 g/day SPE are not associated with alterations in markers of oxidation, eye health, cardiovascular health, or immune status further supports the long-term safety of olestra, particularly with respect to alterations in serum carotenoids. In addition, the National Academies' Institute of Medicine has concluded, from its review of the literature on carontenoids, that if adequate retinol (vitamin A) is provided in the diet, there are no known clinical effects of consuming diets low in carotenes (IOM, 2006). Olestra is enriched with sufficient retinyl ester to offset effects on vitman A. Observations that olestra does not

sequester lutein and zeaxanthin to the same extent as the other, more lipophilic carotenoids (*i.e.,* the carotenes and lycopene) are important, particularly since lutein and zeaxanthin may play a role in reducing the risks of age-related macular degeneration and cataract formation. That macular pigment optical density between olestra consumers and non-consumers in the OPMSS at the sentinel site were similar (Cooper *et al.,* 2000) is consistent with the finding by Broekmans *et al.* (2003) that consumption of up to 17 g/day SPE+olestra for one year had no effect on macular pigment optical density. Macular pigment optical density responds in a sensitive manner to alterations in the dietary intake of lutein and zeaxanthin. In a 12-week study, Berendschot *et al.* (2000) demonstrated that after only 4 weeks of lutein supplementation, increases in macular pigment optical density were apparent. Thus, it is reasonable to assume that a one year intervention with either olestra (Cooper *et al.,* 2000) and/or SPE (Broekmans *et al.,* 2003) would have been sufficient to detect alterations in macular pigment optical density.

Procter and Gamble submitted a food additive petition dated December 1, 1999, to amend the food additive regulations in § 172.867 *Olestra* by removing the requirement for the label statement prescribed in § 172.867(e) [*i.e.,* This Product Contains Olestra (U.S. FDA, 2006a). 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]. The U.S. FDA ruled that this statement was no longer required to appear on the labeling of olestra containing foods, based on 3 findings (U.S. FDA, 2003a): i) Early results from the OPMSS (at the Sentinel Site) showed no clear effects of olestra on serum carotenoid levels; ii) Other than the provitamin A activity of some of the carotenoids, there were no clear health effects attributable to the carotenoids; and iii) Consumer studies indicated that the statement was not an effective means of communicating olestra's nutritional effects to consumers. To not mislead consumers into thinking that olestra-containing products are fortified with vitamins A, D, E, and K, the U.S. FDA ruled that, in the ingredient list, each vitamin be followed by an asterisk, which would refer to a statement "dietarily insignificant" (U.S. FDA, 2003a).

7.4.3.4 Discussion

Olestra reduces the bioavailability of carotenoids, particularly when consumed with main meals. Similar effects on the absorption of carotenoids have been observed with other dietary constituents, such as various dietary fibers and sterols and stanols, the latter of which are added to products like margarine for the purpose of inhibiting dietary cholesterol absorption. Plasma β-carotene was reduced by more than 50% in healthy males and females administered 12 g of citrus pectin in a controlled 500 kcal meal (Rock and Swendseid, 1992). In another study, the effects of various fibers on carotenoid bioavailability were assessed in healthy young females (Riedl *et al.,* 1999). The subjects were administered an antioxidant mixture (consisting of β-carotene, lycopene, lutein, canthaxanthin, and α-tocopherol) together with a standard meal containing no added fiber or pectin, guar (from the group of gums), alginate (from the group of mucialges), cellulose, or wheat bran (0.15 g/kg body weight). Although the 24-hour area under

the curve concentrations (AUC_{24h}) for plasma α-tocopherol were not affected by the administration of the fibers, plasma lutein and lycopene AUC_{24h} were reduced by all tested fibers by 40 to 74% ($P<0.05$), whereas the AUC_{24h} for β-carotene was significantly reduced by the water-soluble fibers, pectin, guar, and alginate, by 33 to 43% ($P<0.05$). For canthaxanthin, the 14 to 18% reductions in the AUC_{24h} caused by the water-soluble fibers were nearly significant ($P=0.059$). Thus, when consumed in reasonable amounts [*i.e.,* 7.8 to 10.4 g/meal, generally representing about one-third of the DRIs for dietary fibers (30 g/day)], dietary fiber interferes with the absorption of carotenoids to a similar extent as that observed with the consumption of olestra.

Similarly, consumption of sterols and stanols has been associated with a reduction in serum carotenoid levels. Plat and Mensink (2001) demonstrated a significant reduction in total carotenoids (α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin) following the administration, for 4 weeks, of 3.8 g vegetable oil-based stanols to normocholesterolemic subjects, with serum carotenoid levels approximately 85% of control levels. The more hydrophobic caronetoids (*i.e.,* α-carotene, β-carotene, and lycopene) were slightly more affected than the less hydrophic carotenoids (*i.e.,* β-cryptoxanthin, lutein, and zeaxanthin). In another study (Hallikainen *et al.,* 1999), the administration of 2.3 g of a wood stanol ester margarine or 2.1 g of a plant stanol ester margarine to hypercholesterolemic subjects resulted in significant reductions, from baseline, in β-carotene (by 27%; $P=0.002$) and in β- plus α-carotene (by 24%; $P=0.010$), but not in lycopene. Similar reductions in serum carotenoids have been observed following the administration of plant sterols (Weststrate and Meijer, 1998; Hendriks *et al.,* 1999; Sierksma *et al.,* 1999).

The effects of dietary fiber on the bioavailability of carotenoids are difficult to avoid, given that high-fiber foods are usually rich in carotenoids. Likewise, sterols and stanols, which are marketed largely in margarine-like spreads, are presumably consumed as components of mixed meals, and so they are likely to reduce the bioavailability of the carotenoids by interfering with intestinal micelle formation. In contrast, current intake data suggest that most (two-thirds of) savory snacks and cookies are consumed as snacks and not as components of mixed meals, and so the effects of olestra, when consumed under typical eating patterns, on the absorption of carotenoids are expected to be insignificant. This is particularly true in light of post-market surveillance and human experimental studies demonstrating that, despite statistically significant reductions in serum carotenoid levels, the long-term consumption of olestra has no effect on markers of oxidation, eye health, cardiovascular health, or immune status (Cooper *et al.,* 2000; Broekmans *et al.,* 2003).

Several epidemiological and intervention studies demonstrate that serum levels of carotenoids or dietary intakes of carotenoids are inversely associated with a reduced risk of chronic diseases such as various forms of cancer and heart disease (Joshipura *et al.,* 1999; De Waart *et al.,* 2001; Liu *et al.,* 2001; Sato *et al.,* 2002; Taylor *et al.,* 2002; Osganian *et al.,* 2003; Hak *et*

al., 2004; Anderson and Appel, 2006; Howard *et al*., 2006a; Sesso, 2006). Despite these associations, it is impossible to conclude that carotenoids, as a class, or any individual carotenoid is responsible for the observed effects. High intakes or serum levels of carotenoids are indicative of diets that are likely low in fat and saturated fat, and rich in other vitamins, minerals, and non-nutritive phytochemicals such as flavonoids, indoles, polyphenols, saponins, *etc.* In addition, individuals who consume a healthy diet are more likely to have healthier lifestyles. They may exercise regularly, drink in moderation, and avoid substances known to negatively affect health, such as tobacco. Thus, high dietary intakes or serum levels of carotenoids may simply be surrogate measures of a healthy diet and lifestyle.

Several epidemiological and intervention studies have shown no association between the intake of carotenoids and the risk of various chronic diseases (Hennekens *et al.,* 1996; Kushi *et al.,* 1996; Ascherio *et al.,* 1999; Michels *et al.,* 2000; Yochum *et al.,* 2000; Joshipura *et al.,* 2001; Smith-Warner *et al.,* 2001; Heart Protection Study Collaborative Group, 2002; Hak *et al.,* 2003a; Chirsten *et al.,* 2004; Kris-Etherton *et al.,* 2004; Beresford *et al.,* 2006; Buzdar, 2006; Sesso *et al.,* 2005; Howard *et al.,* 2006b; Prentice *et al.,* 2006). Moreover, some intervention studies suggest possible harm from large intakes of individual carotenoids in population subgroups, such as smokers, former smokers, and subjects previously exposed to asbestos (Albanes *et al.,* 1996; Omenn *et al*., 1996; Duffield-Lillico and Begg, 2004; Goodman *et al*., 2004; Bairati *et al*., 2005; Kim and Hong, 2005).

There are national recommendations for increased consumption of fruits and vegetables, as well as authorized health claims pertaining to reduced risk of cancer and heart disease with diets rich in fruits and vegetables and low in fat; however, recommendations for specific carotenoids do not currently exist as there is insufficient evidence in support of such recommendations. While the U.S. FDA approved a qualified health claim for tomatoes/tomato sauce and a reduced risk of various cancers, the same claim relating to lycopene was not approved due to the lack of scientific evidence (U.S. FDA, 2005a). Likewise, in December 2005, a qualified health claim for lutein esters, lutein, or zeaxanthin and age-related macular degeneration or cataract formation was denied by the U.S. FDA due to the lack of credible evidence (U.S. FDA, 2005b). While the roles of lutein and zeaxanthin in the maintenance of eye health continue to be studied and the the science continues to evolve, it should be noted that olestra-induced alterations in serum levels of lutein and zeaxanthin are expected to be minimal, given that: i) Most olestra consumption occasions from the existing and proposed uses occur as snacks and not as meals; and ii) Of the carotenoids evaluated, serum levels of lutein and zeaxanthin appear to be least affected by olestra.

Several lutein and zeaxanthin formulations have been self-affirmed as GRAS, and upon notification, U.S. FDA raised no questions or concernes regarding the GRAS status of these formulations (U.S. FDA, 2003b; 2004). Lutein ester formulations (Cognis Corporation), which contain 10 – 15%, by weight, lutein esters, are GRAS for use as ingredients in a variety of food

categories (*i.e.,* baked goods and baking mixes, soy milk, beverages and beverage powders, frozen dairy desserts and mixes, processed fruit and vegetable products, egg products and egg substitutes, breakfast cereals, fats and oils, hard candy, fruit snacks, dairy products) in amounts ranging from 2 to 6 mg per serving and in medical foods intended as the sole item of the diet, at a dosage of up to 40 mg per day (U.S. FDA, 2003b). These uses and use levels translate to mean and 90th percentile intakes of lutein of 12 and 22 mg/person/day, respectively (U.S. FDA, 2003b). Crystalline lutein (Kemin Foods, L.C.), an ingredient containing, by weight, 76% lutein and 7% zeaxanthin, is GRAS for use as an ingredient in several food categories (*i.e.,* baked goods and baking mixes, beverages and beverage bases, breakfast cereals, chewing gum, dairy product analogs, egg products, fats and oils, frozen dairy desserts and mixes) in amounts ranging from 0.3 to 3.0 mg per eating occasion, and in medical foods intended as the sole item of the diet, at a dosage of up to 20 mg per day (U.S. FDA, 2004). These uses and use levels translate to mean intakes of lutein and zeaxanthin of 7 and 0.7 mg/person/day, respectively and 90th percentile intakes of 13 and 1.2 mg/person/day, respectively (U.S. FDA, 2004). Several other lutein and zeaxanthin formulations are GRAS for use as ingredients in various food categories and in medical foods (*ex.,* DSM Nutritional Products OPTISHARP™ zeaxanthin; Industrial Organica Hi-Fil Lutein, *etc.)*. Background intakes of lutein and zeaxanthin range from 2 to 4 mg/person/day (U.S. FDA, 2004). Thus, intakes of lutein and zeaxanthin are expected to increase substantially should lutein and zeaxanthin be added as ingredients to various food categories.

Other than the role of provitamin A carotenoids in contributing to the RDA for vitamin A, the physiological importance of carotenoids in the maintenance of human health is not well established. There currently are no DRIs for the carotenoids (not even adequate intakes could be established from the available literature). Although the provitamin A carotenoids can be converted to retinol, their conversion is generally inefficient (Tang *et al.,* 2000; 2003; 2005), and there is currently no requirement that a certain fraction of the RDA for vitamin A be met from carotenoids. Moreover, olestra is enriched with sufficient retinyl ester to offset effects on vitamin A.

Olestra affects the absorption of the carotenoids, particularly the more hydrophobic carotenoids (α-carotene, β-carotene, and lycopene). Despite these findings, measures associated with carotenoid intake, such as macular optical pigment density, are not adversely affected following the long-term (1 year) daily consumption of olestra in free-living (Cooper *et al.,* 2000) and in experimental (Broekmans *et al.,* 2003) subjects. Reductions in carotenoids are not unique to olestra, as other dietary constituents, such as various fibers and the plant sterols and stanols, have also been shown to reduce serum carotenoid levels. The precise role of carotenoids in the maintenance of health and in the prevention of disease is currently unclear. While the science in support of a role for lutein and zeaxanthin in reducing the risks of age-related macular degeneration and cataract formation is still evolving, clinical studies conducted on olestra demonstrate that serum levels of these carotenoids are affected less as compared with serum

levels of the carotenes and lycopene. These observations are consistent with the octanol-water partition coefficients, which are substantially lower for lutein and zeaxanthin than for lycopene and the carotenes. Thus, the consumption of olestra from permitted and proposed food uses is not expected to cause nutritional imbalances or to be associated with adverse nutrition-related issues. Moreover, the OPMSS provides assurance that the long-term consumption of olestra by free-living individuals is safe (*i.e.,* serious adverse events associated with consumption of olestra chips were not reported).

7.5 Assessment of Olestra and Potential Drug Interactions

Most drug preparations are administered *via* the oral route, and the vast majority of drugs are readily absorbed through the extensive network of the portal circulation draining the intestinal compartment. In contrast, the absorption of fat-soluble vitamins, cholesterol, and many other lipophilic compounds with high molecular weights is generally a slower process, as they must enter the circulation *via* passive diffusion (DDT, PCB's) or are incorporated into intestinal micelles and shuttled through the lymphatics (many fat soluble vitamins and cholesterol). Most drugs are developed with a goal to achieve high absorption efficiencies, and to display rapid absorption profiles, properties that in general are not conductive to the sequestration effects of olestra. Nevertheless, the issue of potential drug interactions is an important consideration and the available clinical evidence is reviewed and discussed below.

To date, a number of clinical studies have investigated potential interactions of olestra with various drugs. Studies were conducted with the oral contraceptives norgestrel and ethinyl estradiol (Miller *et al.*, 1990), the immunosuppressant cyclosporine (Terrill *et al.*, 2003), and the anti-coagulant warfarin (Beckey *et al.*, 1999). The drugs studied cover a range of lipophilicities, have wide-spread and long-term use, and are utilized for the prevention of life-threatening illnesses.

Of the studies listed above, the only compound for which significant olestra-drug interaction effects were noted occurred with cyclosporine, where the consumption of olestra (0.35 g/kg/day; up to 16 g/person/day) was associated with reduced area under the curve (AUC) values and a reduction in the maximum plasma concentrations (C_{max}) by 18 ($p<0.001$) and 27% ($p<0.015$), respectively. This cross-over study was associated with several limiting factors, including small study size (n=7) and lack of appropriate placebo treatment; thus, it cannot be definitively determined whether the reported effects were attributable to olestra or to the consumption of 2 servings of potato chips following cyclosporine administration. The lack of appropriate placebo treatment is important as food within the GI tract impacts significantly on drug bioavailability through effects on transit profiles, pH, and drug solubility (Charman *et al.*, 1997). For example, the consumption of food following cyclosporine administration is reported to decrease the AUC by 13% and C_{max} by 33% (PDR, 2006 online). The mechanistic basis for the observed effect is also unclear as cyclosporine is several thousand-fold less lipophilic than oleic acid, and Daher

et al. (1997c) have shown that the consumption of 32 g of olestra in conjunction with radiolabeled triolean only marginally (-1.2%; P<0.05) reduced oleic acid absorption. Finally, it should also be noted that the effect observed in the cyclosporine study occurred in association with the consumption of olestra at quantities that are 2-fold above the estimated 90th percentile estimated chronic intakes for permitted and proposed uses, combined; thus, it is unlikely that observations made during the study would be relevant to the use of olestra at its expected use levels.

Concerns over the potential interaction between warfarin and regular olestra use have been suggested by the Center for Science in the Public Interest (CSPI), and in the literature (Harrell and Kline, 1999). These concerns regard the potential for impaired anticoagulation management by the use of olestra or by the use of olestra-containing foods supplemented with vitamin K. Bleeding may occur if the effect of olestra is to decrease vitamin K bioavailability by sequestering vitamin K in the GI tract; in contrast warfarin-mediated anticoagulation could be reduced if vitamin K bioavailability is increased from consuming olestra containing products that are supplemented with vitamin K. The results of a randomized double-blind placebo controlled prospective clinical study contudted by Beckey *et al.* (1999) do not support the contentions made by CSPI and others that olestra may be associated with safety concerns in patients receiving warfarin therapy. Over a two week period, the daily consumption of olestra containing potato chips (12 g olestra/day) did not result in any significant changes in the anticoagulation status of the patients (as determined by INR values) relative to baseline or control patients receiving regular potato chips. The authors concluded that olestra does not affect the anticoagulation status of patients receiving long-term warfarin therapy. This view is also supported in a systematic review by Holbrook *et al.* (2005) of warfarin and its drug and food interactions, where olestra was listed as “no effect”.

Insights into the potential for olestra to affect drug absorption can be inferred from drug interaction studies investigating the use of olrlistat. Orlistat is a pancreatic lipase inhibitor that is prescribed for the management of weight loss. Use of the drug results in the presence of significant amounts of undigested fat in the intestinal lumen. The pharmacologic activity of orlistat as a weight loss drug results from a 30% inhibition in fat digestion efficiency, and approximately 26 g per day of undigested fats would be expected for adults consuming 67-89g of fat from a regular diet consisting of 30% energy from fat; the presence of this amount of unabsorbed fat is similar to olestra used in clinical studies, where daily quantities of 8, 20 and 32 g of olestra were consumed during meals; in addition, this quantity of undigested fat would correspond to roughly 3.5 times the estimated 90th percentile estimated intakes of olestra from permitted and proposed uses, combined, and is therefore a conservative model to evaluate the effects of olestra on drug interactions at the new proposed intakes. Evidence to support the relevance of extrapolating the use of orlistat drug interaction studies in the evaluation of potential olestra drug interaction effects is supported by clinical studies, which show that similar

to olestra, the presence of large amounts of undigested fat in the intestinal lumen following the regular use of orlistat, also results in the sequestering and reduced absorption of dietary lipid soluble vitamins, an effect that, similar to olestra, can be offset by supplementation of the affected nutrients (Hill *et al.*, 1999; McDuffie *et al.*, 2002; Davidson *et al.*, 1999) A large number of drugs over a wide lipophilic range have been investigated for orlistat-drug interactions, and the majority of studies are of high quality that utilize bioequivalence methodology in healthy patients (Weber *et al.*, 1996; Zhi *et al.,*1996a,b, 2002; Zhi *et al.*, 2003; Hilger *et al.*, 2002). Of these studies only 2 drugs, cyclosporine and amiodarone, displayed significant drug interactions, where the bioavailability of each was decreased relative to non-orlistat controls (Approx 18 to 34% decreases in AUC values were reported). Orlistat-cyclosporine drug interactions have also been reported in a number of small observational case studies (Nagele *et al.*, 1999; Colman *et al.*, 2000; Schnetzler *et al.*, 2000; Errasti *et al.*, 2002; Evans *et al.*, 2003).

Although orlistat was shown to decrease cyclosporine bioavailability, it is unclear if the effect is entirely mediated by a partitioning mechanism. Cyclosporine is usually formulated as a microemulsion containing corn oil, mono-, di-, and triglycerides, and castor oil to improve absorption. Therefore it is likely that orlistat affects cyclosporine bioavailability by inhibiting the function of digestive lipases, rather than through a sequestering mechanism. Unfortunately, the results of the orlistat-cyclosporine study do not provide additional information regarding the potential for olestra-cyclosporine interactions. In the case of amiodarone an important consideration is that there is no established relationship between serum concentrations of amiodarone and its efficacy, and absorption of the drug is erratic and unpredictable under normal circumstances (PDR, 2006 online). The observed changes in the absorption of amiodarone by orlistat are insignificant relative to changes in pharmacokinetics that are observed with food consumption, where high-fat meals have been shown to alter amiodarone AUC values by as much as 200% (PDR, 2006 online). Due to the high variability in its pharmacokinetic-pharmacodynamic profiles, regular therapeutic monitoring is recommended for amiodarone use (Takada *et al.*, 2005; Raebel *et al.*, 2006; PDR, 2006 online), and it is unlikely that olestra would have clinically significant, undetected drug interactions in patients that require such extensive drug monitoring. More importantly, in both cases, the observed reduction in drug absorption occurred with levels of undigested dietary fat that are 3.5 times the 90th percentile estimated chronic intakes of olestra from permitted and proposed uses, combined.

The results of the available clinical studies investigating potential drug interaction effects of olestra reviewed above, and observations that large quantities of undigested fat (as a result of orlistat use) do not affect drug absorption, remain consistent with the original FDA opinion that olestra will not affect drug absorption in a manner that is clinically meaningful (U.S. FDA, 1996). Therefore, in general, the routine consumption of olestra at the estimated 50th and 90th percentile all-user chronic intakes of approximately 3.1 and 7.7 g/day, respectively, are not expected to present safety issues with drug therapy in the general population.

7.6 Subpopulations of Concern

In healthy individuals, dietary fats are digested and absorbed predominantly in the small intestine, and large amounts of undigested fats generally do not reach the lower GI tract. Some food additives like sorbitol have been shown to provoke symptoms in patients with irritable bowel syndrome (Symons *et al.*, 1992; Evans *et al.,* 1998); thus, the potential irritable effects of undigestible fats in the lower bowel as a result of olestra consumption were considered. Therefore, a number of studies were performed in animals and in clinical settings to address the possibility that olestra may adversely affect special populations with compromised GI tracts. Long-term studies in mice, rats (Wood *et al.*, 1991a), and dogs (Miller *et al.*, 1991) consistently show that olestra does not alter the morphology of the GI tract in healthy animals and also does not potentate ulcer formation in a rat cysteamine-induced ulcer model. In addition, Daher *et al.* (1997b) have shown that guinea pigs with polygeenan induced inflammatory bowel conditions do not absorb radiolabeled olestra to any greater extent than in normal healthy animals. Consistent with observations in animals, Zorich *et al.* (1997a) have also reported that olestra does not augment the disease state or symptoms of subjects with IBD who consumed 20 g of olestra (2.5-fold greater than the estimated chronic 90th percentile all-user consumption from permitted and proposed uses, combined) for a period of 30 days. Overall, the Zorich *et al.* (1997a) study was of high quality, used a randomized double-blind prospective methodology, a large number of observational endpoints, and extensive safety monitoring; based primarily on this study, and in conjunction with corroborating animal evidence showing that olestra is not absorbed in animals with polygeenan induced inflammatory bowel lesions, olestra would not be expected to present a safety issue in people with compromised GI tracts.

8.0 SUMMARY OF NUTRITION

Olestra is approved for use as a noncaloric fat substitute in savory snacks (U.S. FDA, 1996). In this dossier, approval for use of olestra as a fat substitute in cookies is being sought. The estimated all-user 50th and 90th percentile daily chronic intakes of olestra from savory snacks and cookies are approximately 3.1 and 7.7 grams, respectively. Because olestra is intended to replace up to 100% of digestible fat in cookies and savory snacks, its effects on various nutrition-related outcomes have been critically reviewed.

Olestra is resistant to digestion by gastric and pancreatic lipases. Several studies have demonstrated that olestra has no effect on the release of hormones, such as CCK and peptide YY. These observations demonstrate that the duodenum responds to olestra as a non-nutritive ingredient rather than as a digestible fat. CCK, which is secreted by the duodenum in response to products of lipolysis, causes transient relaxations of the lower esophageal sphincter, thereby increasing the tendency for acid contents of the stomach to reflux into the esophagus. Because olestra is resistant to hydrolysis, it does not stimulate the duodenal release of CCK, and therefore is not associated with gastric acid reflux. In fact, the administration of chips made with

olestra has been associated with a significant reduction in gastric acid reflux as compared with the administration of chips made with triglyceride. The release of CCK in response to digestible fat also causes delays in gastric emptying; thus, because olestra has no effect on the release of CCK, it has no effect on gastric emptying. Although, relative to digestible fat, olestra appears to accelerate gastric emptying, its effects on gastric emptying are essentially the same as those of water, and interpretation of results from studies showing that olestra accelerates gastric emptying are confounded by the fact that control groups were administered digestible fat, which delays gastric emptying.

In addition to its effects on the lower esophageal sphincter and on gastric emptying, CCK is a potent stimulator of gallbladder contraction and bile release. Because olestra does not stimulate the duodenal release of CCK, it has no effect on gallbladder contraction and bile release. Gallstone formation may result from gallbladder hypomotility, as bile stasis facilitates cholesterol crystallization. Especially at risk are obese subjects attempting rapid weight loss with very low-fat diets. Post-market surveillance studies indicate that most users of olestra, particularly those in the in the 90th percentile intake for olestra, are either overweight or obese females. Although there is justification for concern that consumption of olestra, particularly by overweight and obese subjects, will increase the risk of gallstone formation, increased gallstone formation has not been observed in any of the clinical or post-market surveillance studies of olestra. Furthermore, while the intraduodenal infusion of olestra has no effects on gallbladder contractility, consumption of olestra with minimal amounts of protein and/or fat is associated with CCK release, gallbladder contraction, and bile acid secretion. The estimated total-population all-user 50th and 90th percentile intakes of olestra from savory snacks and cookies (approximately 3.1 and 7.7 g/day, respectively) are much lower than those administered in experimental studies demonstrating no effects of olestra on CCK release and gallbladder contraction (50 or 60 g); thus, when one considers that a typical 2,000 kcal/day diet consists of approximately 65 g of fat (*i.e.,* 30% of energy), the amount of fat displaced by olestra is expected to be nominal. Studies demonstrate that olestra is not associated with saturation of gallbladder bile, particularly with respect to cholesterol content (which can precipitate out of bile and crystallize, leading to stone formation). In contrast, there is evidence that olestra interferes with the enterohepatic circulation of cholesterol, thereby reducing cholesterol levels in bile. Gallstones have not been reported in any of the pre-clinical or clinical studies consucted with SPE or olestra. Thus, the current scientific literature does not support a role for olestra in the pathogenesis of gallstones.

Because olestra traverses the small and large intestine, it has the potential to act as a substrate for microbial metabolism or to affect microbial metabolism by altering the intestinal microflora. However, when radiolabeled olestra was inoculated with fecal samples from subjects who were administered olestra for up to 4 weeks, no degradation products of olestra (such as $^{14}CO_2$, $^{14}CH_4$, ^{14}C-SCFAs and ^{14}C-long chain fatty acids) were detected. The effects of olestra on several MACs were assessed. Olestra had no effect on tryptic activity or fecal levels of β-

aspartylglycine. While olestra reduced the conversion of cholesterol to coprastanol and the conversion of bilirubin to urobilingen, these effects were most likely due to the partitioning of cholesterol and bilirubin into the olestra phase, thereby reducing their interaction with intestinal microbes. Fecal levels of SCFAs were increased with the administration of olestra; however, olestra is resistant to metabolism by fecal bacteria, and the increased levels are most likely due to increased fecal excretion of SCFAs, and not to an increase in their production. A reduction in the absorption of SCFAs is consistent with findings that olestra reduces whole-gut transit time and is associated with reduced breath hydrogen levels. While olestra was associated with increases in fecal mucin secretion, similar effects have been observed with various fibers, and may be related to mechanical stimulation effects, or interactions with SCFAs. The fecal composition of bile acids is not affected by the consumption of olestra; however, there appears to be a trend for reduced levels of secondary bile acids and increased levels of primary bile acids with consumption of olestra. Olestra may sequester bile acids, resulting in a reduced interaction of the primary bile acids with bacteria capable of deconjugation and hydroxylation. This may be beneficial, given that secondary bile acids have irritant, detergent-like effects in the colon.

The effects of olestra on the absorption of water-soluble and fat-soluble nutrients and various drugs have been assessed. Olestra does not affect the absorption of water-soluble vitamins and minerals. The vast majority of drugs are water soluble, and clinical studies show that olestra does not affect the absorption of even moderately lipophilic drugs. To compensate for any interference of olestra with the absorption of fat-soluble vitamins, vitamins A, D, E, and K are required to be added to foods containing olestra [21 CFR §172.867(d)] (U.S. FDA, 2006a). Results from the OPMSS and human experimental studies conducted following the marketing of olestra indicate that olestra, when enriched with the fat-soluble vitamins as per 21 CFR §172.867(d), does not affect serum levels of vitamins A, D, E, and K (Thornquist *et al.,* 2000; Broekmans *et al.,* 2003; Neuhouser *et al.,* 2006; U.S. FDA, 2006a). Procter and Gamble submitted a food additive petition dated December 1, 1999, to amend the food additive regulations in §172.867 *Olestra* by removing the requirement for the label statement prescribed in § 172.867(e) [… Olestra inhibits the absorption of some vitamins and other nutrients (U.S. FDA, 2006a). Vitamins A, D, E, and K have been added]. The U.S. FDA ruled that this statement was no longer required to appear on the labeling of olestra containing foods.

Pre-market and post-market studies demonstrate that consumption of olestra is associated with reduced serum carotenoid levels. The bioavailability of carotenoids is similarly reduced by the concomitant consumption of various dietary fibers, plant sterols, and plant stanols. While epidemiological studies demonstrate that a diet rich in fruits and vegetables is associated with a reduced risk of various chronic diseases, the role of individual carotenoids in health and disease (outside of the provitamin A activity of α-carotene, β-carotene, and β-cryptoxanthin) is presently unclear, and there is no scientific justification for restoration of serum carotenoid levels by addition of carotenoids to cookies and snacks containing olestra. That addition of carotenoids

to current olestra formulations is not warranted is supported by post-market human experimental studies demonstrating that, despite statistically significant reductions in serum carotenoid levels, the long-term consumption of olestra has no effect on markers of oxidation, eye health, cardiovascular health, or immune status.

Olestra passes through the digestive tract and is excreted, unchanged, in the feces. Olestra, like wheat bran, causes reductions in stool viscosity and a slight softening in stool form; however, while wheat bran increases the percent fecal water content, olestra decreases the percent fecal water content. The absolute amount of water in the feces is unaffected by olestra; thus, olestra has no effect on water and electrolyte excretion, and it is the presence of olestra, a semi-solid in the feces, that leads to a reduction in stool viscosity and in the relative amount of water in the feces. Alterations in stool viscosity, fecal water (and electrolyte) output, and stool form are far more substantial with the consumption of sorbitol in amounts that currently do not require the labeling of a product with a warning statement that excess consumption may have a laxative effect.

SPE formulations developed early in the development of olestra were liquid at room and body temperature; hence, they had a tendency to separate out from the fecal matrix and leak passively past the anal sphincter, resulting in anal leakage. Subsequent formulations that were semi-solid at body (*i.e.,* had a thixotropic area ≥50 kPa/s) were associated with significant reductions in the incidence of anal leakage. Thixotropic area is currently one of the specifications for olestra.

Many of the clinical studies assessing the effects of olestra on GI symptoms administered exaggerated levels of olestra under atypical consumption patterns. Because there were insufficient data from human experimental studies regarding the GI effects of olestra when consumed under usual or real-life conditions, the U.S. FDA, during its 1996 ruling on the use of olestra as a food additive in savory snacks, decided that olestra-containing foods were required to bear a label statement to inform consumers about the possible effects of olestra on the GI system. Although it was determined that olestra-related GI effects were not adverse health effects, based on the available evidence at the time, the label was required to include the statement “Olestra may cause abdominal cramping and loose stools”. In 2003, based on its review of data generated since the 1996 approval of olestra as a food additive in savory snacks, the U.S. FDA removed the requirement for the label statement. This regulatory decision was based on the finding that when consumed under usual and customary (rather than exaggerated) conditions, olestra, like other indigestible compounds, has nominal and clinically insignificant effects on the incidence of abdominal cramping and loose stools. Studies demonstrating the safety of olestra in particularly vulnerable subpopulations, including children, the elderly, and individuals with compromised GI tracts, further attest to the safety of olestra.

In conclusion, olestra consumption, at the new estimated intakes from savory snacks and cookies, is not expected to be associated with adverse nutrition-related outcomes. Rather, with recommendations from authoritative bodies for reductions in total fat, saturated fat and energy intakes, the replacement of digestible fat with olestra in foods such as chips and cookies may offer individuals a way to alter their dietary risk factors for obesity and other chronic diseases without altering their food selections.

9.0 OVERALL CONCLUSIONS PERTAINING TO SAFETY

The data and information summarized in this dossier demonstrate that olestra, meeting appropriate food grade specifications and manufactured in accordance with current Good Manufacturing Practice (GMP), would be Generally Recognized as Safe (GRAS) for use as a food ingredient under the conditions of intended use. This decision is supported by the following important details.

- The chemistry of olestra is well established and stability studies have demonstrated that it is as stable as triglycerides under storage, frying and baking conditions.

- Specifications have not changed and have been established to ensure the octa-ester structure, stiffness parameters, and limit potential impurities.

- The additional proposed use of olestra in all reduced-fat, low-fat, and fat-free cookies would result in intakes only marginally greater than for current U.S. FDA approved food uses (pre-packaged ready-to-eat savory snacks and pre-packaged ready-to-heat popcorn), as follows:

    - 3.11 g/day for permitted and proposed uses *vs*. 2.58 g/day for permitted uses only (mean total population, users-only);

    - 7.74 g/day for permitted and proposed uses *vs*. 7.01 g/day for permitted uses only (90th percentile total population, users-only).

- There is no appreciable absorption of olestra;

    - Greater than 99% of olestra is excreted in the feces unchanged;

    - Intravenous studies indicate that the nominal amount of sucrose esters absorbed would be rapidly removed from the circulation, and distributed primarily to the liver and secondarily to the spleen followed by excretion in the bile and feces.

- A multitude of studies in several species (rats, mice, pigs, dogs) covering all toxicological endpoints have been conducted. The results of these studies support the following:

    - Olestra is non-genotoxic; negative results were obtained in standard *in vitro* and *in vivo* assays even when conducted in the presence of a detergent to increase olestra solubility and cellular uptake.

    - No developmental or teratogenic effects are associated with Olestra.

    - Olestra is not carcinogenic.

- Mortality attributable to vitamin K deficiency in mice administered high doses of olestra is not observed following supplementation with vitamins A, D, E, K.

- Contact with olestra does not cause GI tract tissue abnormalities.

- No treatment related toxicologically significant findings were observed in 2-year carcinogenicity studies.

- While olestra may sequester fat-soluble vitamins (A, D, E, K), studies have been conducted to determine proper vitamin restorative levels. Any cookies made with olestra will be formulated to include these vitamins at the levels specified by the U.S. FDA.

  - Stability studies on fortified cookies and crackers confirm that the restoration levels of vitamins would be present at the time of consumption.

- Nutrition studies conducted using the pig and humans, at dose levels considerably higher than the expected chronic and acute olestra intakes from proposed and permitted uses, demonstrated the following:

  - Olestra is not recognized as a lipid by the GI tract. Thus, unlike digestible fat, olestra does not stimulate the release of hormones associated with gastroesophageal reflux, delays in gastric emptying, or gallbladder contractility.

  - Olestra is resistant to metabolism by intestinal bacteria and does not directly alter microbiota-associated characteristics. Olestra sequesters cholesterol, bilirubin, and primary bile acids, therefore indirectly reducing the bacterial conversion of cholesterol to coprostanol, bilirubin to urobilinogen, and primary bile acids to secondary bile acids, respectively. These indirect effects may be desirable from a health perspective.

  - Anal leakage observed with early SPE formulations, which were liquid at body temperature, in not associated with current stiffer formulations of olestra.

  - Although olestra can sequester fat soluble vitamins, restoration levels of vitamins A, D, E, and K in olestra containing foods, as mandated by the U.S. FDA, will offset any potential for olestra induced vitamin deficiency. The requirement for a label on olestra containing snacks that olestra interferes with the absorption of some vitamins and other nutrients was removed by the U.S. FDA.

  - Despite olestra's effects on serum carotenoid levels, markers of lipid peroxidation, protein oxidation, LDL oxidation, DNA damage, and macular optical pigment density are not affected with the chronic consumption of up to 17 g/day olestra. These findings are consistent with the position by the National

Academies' Institute of Medicine, that there is currently insufficient data for recommendations regarding the intake of carotenoids.

- The consumption of olestra by individuals with compromised GI tracts, such as inflammatory bowel disease, is safe.

- The requirement for a label on olestra containing snacks to warn of potential GI effects such as abdominal cramping and loose stools was removed by the U.S. FDA upon evaluation of data showing that olestra when consumed under normal (rather than exaggerated) conditions, has nominal and clinically insignificant effects on the GI tract.

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APPENDIX A

ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM PERMITTED AND PROPOSED FOOD-USES

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ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM PERMITTED AND PROPOSED FOOD-USES

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ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM PERMITTED AND PROPOSED FOOD-USES

1.0 INTRODUCTION

An assessment of the consumption of olestra from permitted and proposed uses as a replacement for conventional fats. Olestra is currently permitted for use in prepackaged ready-to-eat savory snacks (*i.e.*, salty or piquant, but not sweet) and prepackaged ready-to-heat, unpopped popcorn kernels in place of fats and oils (21 CFR §172.867) (CFR, 2006a). Olestra is currently proposed for use in all reduced fat, low fat, and fat free cookies.

Estimates for the intake of olestra were based on permitted and proposed food-uses and use-levels for olestra in the United States in conjunction with food consumption data included in the United States Department of Agriculture's (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996) and the 1998 Supplemental Children's Survey (CSFII 1998) (USDA, 2000). Calculations for the mean and 90th percentile all-person and all-user intakes, and percent consuming were performed for each of the individual identified food-uses of olestra. Similar calculations were used to determine the estimated total intake of olestra from all identified food-uses combined. In both cases, the per person and per kilogram body weight intakes were reported for the following population groups:

- infants, ages 0 to 2;
- children, ages 3 to 11;
- female teenagers, ages 12 to 19;
- male teenagers, ages 12 to 19;
- female adults, ages 20 and up;
- male adults, ages 20 and up; and,
- total population (all population and gender groups combined).

2.0 FOOD CONSUMPTION SURVEY DATA

2.1 Survey Description

Nationwide dietary intake data for the years 2003-2004 are now available for public use; however, only two years of interview data are included in the present release. It is well

established that the length of a dietary survey affects the estimated consumption of individual users and that short-term surveys, such as the typical 1-day dietary survey, overestimate consumption over longer time periods (Anderson, 1988). Because two 24-hour dietary recalls administered on 2 non-consecutive days (day 1 and day 2) are available from the CSFII 1994-1996, 1998 surveys that involve 4 years of intake data that double the number of individuals surveyed and includes a significant increase in the number of children surveyed, these data were used to generate estimates for the current intake analysis.

USDA, CSFII 1994-1996 provides food consumption data on persons of all ages; whereas, CSFII 1998 is limited to children birth through 9 years of age. Combined, these surveys provide the most appropriate data for evaluating food-use and food-consumption patterns in the United States, containing 4 years of data on individuals selected *via* stratified, multistage area probability sampling of American households within all 50 states.

CSFII 1994-1996, 1998 survey data were collected from individuals and households *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Data were collected in-person, a minimum of 3 days apart, on different days of the week, to achieve the desired degree of statistical independence. CSFII 1994-1996 contains 2-day dietary food consumption data for more than 15,000 individuals of all ages, and 1-day data for 16,103 individuals. CSFII 1998 contributes data from an additional 5,559 children, birth through 9 years of age, to data reported for 4,253 children of the same ages within CSFII 1994-1996. The overall CSFII 1994-1996, 1998 response rate for individuals selected for participation in the survey was 81.5 and 77.5% for Day 1 and Day 2, respectively.

In addition to collecting information on the types and quantities of foods being consumed, CSFII 1994-1996, 1998 collected physiological and demographic information from individual participants in the survey, such as sex, age, self-reported height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population. USDA sample weights were developed and incorporated with CSFII 1994-1996, 1998 to compensate for the potential under-representation of intakes from specific population groups as a result of sample variability due to survey design, differential non-response rates, or other factors, such as deficiencies in the sampling frame (USDA, 2000).

2.2 Statistical Methods

Consumption data from individual dietary records, detailing food items ingested by each survey participant on each of the two survey days, were collated by computer and used to generate estimates for the intake of olestra by the U.S. population. Estimates for the daily intake of olestra represent projected 2-day averages for each individual from Day 1 and Day 2 of CSFII 1994-96, 1998 data; these average amounts comprised the distribution from which mean and percentile intake estimates were produced. Mean and percentile estimates were generated

incorporating USDA survey weights in order to provide representative intakes for the entire U.S. population. All-person intake refers to the estimated intake of olestra averaged over all individuals surveyed, regardless of whether they consumed food products containing olestra, and therefore includes "zero" consumers (those who reported no intake of food products containing olestra during the two survey days). All-user intake refers to the estimated intake of olestra by those individuals consuming food products containing olestra, hence the "all-user" designation. Individuals were considered users if they consumed 1 or more food products containing olestra on either Day 1 or Day 2 of the survey.

2.3 Statistical Reliability

Mean or percentile intake estimates based on small sample sizes or with high variability relative to the mean [assessed using the coefficient of variation (CV)] may be less statistically reliable than estimates based on adequate sample sizes or low variability relative to the mean (LSRO, 1995). Data presented herein for the estimated daily intake of olestra follow the guidelines proposed by the Human Nutrition Information Service/National Center for Health Statistics Analytic Working Group for evaluating the reliability of statistical estimates adopted in the "Third Report on Nutrition Monitoring in the United States", whereby an estimated mean may be unreliable if the CV is equal to or greater than 30% (LSRO, 1995). The CV is the ratio of the estimated standard error of the mean to the estimated mean, expressed as a percentage (LSRO, 1995). Therefore, for the estimated intakes of olestra presented herein, values were considered statistically unreliable if the CV was equal to or greater than 30%. These values were not considered when assessing the relative contribution of specific food-uses to total olestra consumption and are marked with an asterisk.

3.0 FOOD USAGE DATA

The individual permitted and proposed food-uses and use-levels for olestra employed in the current intake analysis are summarized in Tables 3.1-1 and 3.1-2, respectively. Food codes representative of each of the permitted and proposed food-uses that were specified as "reduced fat", "low-fat", "fat-free", "low calorie", "light" or "diet" were chosen from the CSFII 1994-1996, 1998 (USDA, 2000). All olestra-containing products meet the specific requirements for fat content claims in the US (21 CFR §101.62) and are labeled with the appropriate claim (CFR, 2006b).

Food codes were grouped in food-use categories according to Title 21, Section §170.3 of the Code of Federal Regulations (CFR, 2006c). Product-specific adjustment factors were developed based on data provided in the standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000). All food codes included in the current intake assessment are listed in Attachment A-III.

Table 3.1-1 Summary of the Permitted Food Uses and Use-Levels for Olestra in the U.S.		
Food Category	**Permitted Food-Use**	**Use-Levels for Olestra**
Snack Foods	Prepackaged Ready-to-Heat, Unpopped Popcorn	100% replacement of fat of a regular product
	Prepackaged Ready-to-Eat Savory Snacks	100% replacement of fat of a regular product

Table 3.1-2 Summary of the Individual Proposed Food Use and Use-Level for Olestra in the U.S.		
Food Category	**Proposed Food-Use**	**Use-Level for Olestra**
Baked Goods and Baking Mixes	Reduced Fat, Low Fat, and Fat Free Cookies	100% replacement of fat of a regular product

The use-level, 100% replacement of fat, is based on the fat content of an equivalent regular product (*i.e.*, fat content has not been modified). This is consistent with the methodology used by Webb *et al.* (1997) for a study on predicted olestra intake from savory snacks, whereby the fat content of reduced fat products was also assumed to be the same as their full-fat counterparts. The fat content of the regular products used for this assessment was determined from the USDA National Nutrient Database for Standard Reference, Release 17. The fat content of regular cookies and snacks is variable; thus, for illustrative purposes, the fat content of the more popular cookies and snacks are presented. For cookies, the reference amount customarily consumed (RACC) per eating occasion is 30 g (21 CFR 101.12). Thus, a typical serving of chocolate chip cookies has 7.3 g of fat, while a typical serving of chocolate sandwich cookies with cream filling has 5.7 g of fat. For chips, the RACC per eating occasion is also 30 g (21 CFR 101.12). Thus a typical serving of plain potato chips has 10.4 g of fat, while a typical serving of tortilla chips (nacho flavor) has 7.7 g of fat.

Although olestra is permitted for use in all prepackaged ready-to-eat savory snacks and in prepackaged, ready-to-heat unpopped popcorn, the only olestra-containing products currently available on the U.S. market include potato chips and corn/cornmeal-based chips. Food codes for these specific olestra-containing products were identified. However, estimates of intake for this assessment were based on all identified food codes for all prepackaged ready-to-eat savory snacks (*e.g.*, crackers, puffs, pretzels) and prepackaged ready-to-heat popcorn that were "reduced fat", "low-fat", "fat-free", "low calorie", "light" or "diet" in order to derive the most conservative estimate of olestra intake from permitted uses (Attachment A-III). Food codes were not identified that were representative of prepackaged ready-to-heat popcorn; thus, codes for air-popped popcorn and popcorn popped in oil were used.

4.0 DAILY OLESTRA INTAKE FROM ALL PERMITTED FOOD-USES

Estimates for the total daily intake of olestra from permitted uses (prepackaged ready-to-eat savory snacks and prepackaged ready-to-heat popcorn) are provided in Tables 4.1-1 and 4.1-2 on a per person and per kilogram body weight basis, respectively. Estimates for daily intake on an absolute basis (g/day) basis and on a per kilogram body weight basis (mg/kg body weight/day) from individual permitted food-uses in the U.S. are summarized in Tables I-1 to I-7 of Attachment A-I and Tables II-1 to II-7 of Attachment A-II, respectively.

4.1 Estimated Daily Olestra Intake from All Permitted Food-Uses

Approximately 10% of the total U.S. population was identified as consumers of prepackaged ready-to-eat savory snacks and prepackaged ready-to-heat popcorn (2,055 actual users). Consumption of permitted uses of olestra by the total U.S. population resulted in estimated mean all-person intakes of 0.28 g/person/day (4.92 mg/kg body weight/day), and mean and 90th percentile all-user intakes of 2.58 g/person/day (45.53 mg/kg body weight/day) and 7.01 g/person/day (114.63 mg/kg body weight/day), respectively (Tables 4.1-1 and 4.1-2).

Table 4.1-1 Summary of the Estimated Daily Intake of Olestra from Permitted Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Infant	0-2	7.7	277	0.09	na	0.98	1.99
Child	3-11	11.9	753	0.20	na	1.73	4.13
Female Teenager	12-19	10.1	71	0.29	na	2.73	7.01
Male Teenager	12-19	8.5	59	0.27	na	2.99	7.37
Female Adult	20 and Up	11.0	501	0.31	na	2.58	6.71
Male Adult	20 and Up	8.3	394	0.29	na	3.12	9.30
Total Population	All Ages	10.0	2,055	0.28	na	2.58	7.01

On an individual population basis, female adults were determined to have the greatest absolute mean all-person intakes, with values of 0.31 g/person/day (4.82 mg/kg body weight/day). Male adults were determined to have the greatest absolute mean and 90th percentile intakes on an all-user basis, with values of 3.12 g/person/day (37.01 mg/kg body weight/day) and 9.30 g/person/day (94.39 mg/kg body weight/day), respectively. Children reported the greatest percentage of users of any population group at 11.9%. Infants had the lowest all-person intakes on an absolute basis, with a mean intake of 0.09 g/person/day (7 mg/kg body weight/day). Infants also had the lowest all-user intakes of olestra from permitted food uses with mean and 90th percentile values of 0.98 g/person/day and 1.99 g/person/day, respectively. However, on a

body weight basis, mean and 90th percentile all-user intakes of olestra were highest in infants (75.75 mg/kg body weight/day) and children (154 mg/kg body weight/day), respectively.

Table 4.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Olestra from Permitted Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infant	0-2	7.7	277	7.00	na	75.75	151.08
Child	3-11	11.9	753	8.46	na	69.78	154.00
Female Teenager	12-19	10.1	71	5.00	na	47.03	126.65
Male Teenager	12-19	8.5	59	4.44	na	48.59	105.40
Female Adult	20 and Up	11.0	501	4.82	na	39.57	108.73
Male Adult	20 and Up	8.3	394	3.47	na	37.01	94.39
Total Population	All Ages	10.0	2,055	4.92	na	45.53	114.63

5.0 DAILY INTAKE OF OLESTRA AND PATTERNS OF CONSUMPTION FROM ALL PERMITTED AND PROPOSED FOOD-USES

Estimates for the total daily intake of olestra from permitted plus proposed uses (reduced fat, low fat and fat free cookies) in the U.S. by population group are provided in Tables 5.1.1-1 and 5.1.1-2 on an absolute (g/day) and a per kilogram body weight (mg/kg body weight/day) basis, respectively. Corresponding estimates of intake of difatty ketones and vitamins A, E, D, and K from the intake of olestra are presented in Sections 5.1.2 and 5.1.3, respectively. Estimates for daily intake on an absolute (g/day) and a per kilogram body weight (mg/kg body weight/day) basis from individual permitted and proposed food-uses in the U.S. are summarized in Tables I-1 to I-7 of Attachment A-I and Tables II-1 to II-7 of Attachment A-II, respectively. An examination of acute and chronic intake of olestra is discussed in Section 5.4, while patterns of intake at meals *versus* snacking occasions are presented in Section 5.5.

5.1 Estimated Daily Intake of Olestra, Difatty Ketones, and Vitamins A, E, D, and K from All Permitted and Proposed Food-Uses

5.1.1 Estimated Daily Intake of Olestra from All Permitted and Proposed Food-Uses

Approximately 11.7% of the total U.S. population was identified as consumers of prepackaged ready-to-eat savory snacks, prepackaged ready-to-heat popcorn, and/or reduced fat, low fat and

fat free cookies (2,419 actual users). Consumption of permitted and proposed uses for olestra by the total U.S. population resulted in estimated mean all-person intakes of 0.40 g/person/day (7.08 mg/kg body weight/day), and mean and 90th percentile all-user intakes of 3.11 g/person/day (54.98 mg/kg body weight/day) and 7.74 g/person/day (132.72 mg/kg body weight/day), respectively (Tables 5.1-1 and 5.1-2).

Table 5.1.1-1 Summary of the Estimated Daily Intake of Olestra from All Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Infant	0-2	8.9	318	0.12	na	1.24	2.75
Child	3-11	13.5	849	0.28	na	2.10	4.78
Female Teenager	12-19	12.3	86	0.45	na	3.42	7.38
Male Teenager	12-19	9.8	68	0.38	na	3.67	8.46
Female Adult	20 and Up	13.6	622	0.47	na	3.14	8.03
Male Adult	20 and Up	10.0	476	0.40	na	3.65	9.30
Total Population	All Ages	11.7	2,419	0.40	na	3.11	7.74

In contrast to the results of analyses on olestra intake from only permitted uses that showed that children had the greatest percentage of users, with the inclusion of proposed uses to the analyses, female adults report the greatest percentage of users of permitted and proposed food uses of olestra, 13.6%. On an individual population basis, female adults were determined to have the greatest absolute mean all-person intakes, with values of 0.47 g/person/day (7.25 mg/kg body weight/day). Male teenagers were determined to have the greatest mean all-user intake, 3.67 g/person/day (62.40 mg/kg body weight/day) while male adults had the greatest 90th percentile all-user intake, with a value of 9.30 g/person/day (98.81 mg/kg body weight/day). Infants had the lowest all-person intakes on an absolute basis, with mean values of 0.12 g/person/day. Infants also had the lowest all-user intakes, with mean and 90th percentile values of 1.24 g/person/day and 2.75 g/person/day, respectively. However, on a per kilogram body weight basis, infants had the highest all-user mean and 90th percentile intakes, with values of 97.74 and 215.67 mg/kg body weight/day, respectively.

In comparison to the results presented in Section 4.1 that show the estimated olestra intake from permitted uses only, the addition of reduced fat, low fat and fat free cookies to the assessment had a small impact on total olestra intake. The users-only 90th percentile total population olestra intake increased from 7.01 g/person/day (114.63 mg/kg body weight/day) for permitted uses (Tables 4.1-1 and 4.1-2), to only 7.74 g/person/day (132.72 mg/kg body weight/day) (Tables 5.1.1-1 and 5.1.1-2) with the addition of proposed uses.

Table 5.1.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Olestra from All Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infant	0-2	8.9	318	10.21	na	97.74	215.67
Child	3-11	13.5	849	11.31	na	81.81	192.68
Female Teenager	12-19	12.3	86	7.87	na	59.35	144.10
Male Teenager	12-19	9.8	68	6.62	na	62.40	133.56
Female Adult	20 and Up	13.6	622	7.25	na	48.75	131.81
Male Adult	20 and Up	10.0	476	4.82	na	43.60	98.81
Total Population	All Ages	11.7	2,419	7.08	na	54.98	132.72

5.1.2 Estimated Daily Intake of Difatty Ketones Corresponding to Intake of Olestra from All Permitted and Proposed Food-Uses

The production of olestra results in the formation of trace amounts of unsaponifiables including difatty ketones (Section 3.6.1). Tables 5.1.2-1 and 5.1.2-2 present the estimated intake of difatty ketones on a mg/person/day basis corresponding to olestra intake from all permitted and proposed food uses using the mean (108 ppm) and highest levels (217 ppm) of difatty ketones (Table 3.6.1-2), respectively, that were present in 15 lots of olestra, while these data are presented on a µg/kg body weight/day basis in Tables 5.1.2-3 and 5.1.2-4, respectively. The total population 90th percentile intake of difatty ketones for users only is 0.84 mg/person/day (14.3 µg/kg body weight/day) assuming an average level formed from the manufacture of olestra, and in the worst case is 1.68 mg/person/day (28.8 µg/kg body weight/day) assuming the highest level formed.

Table 5.1.2-1 Summary of the Estimated Daily Intake of Difatty Ketones, Assuming an Average Level of Formation (108 ppm), Corresponding to the Intake of Olestra from All Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Infant	0-2	8.9	318	0.01	na	0.13	0.30
Child	3-11	13.5	849	0.03	na	0.23	0.52
Female Teenager	12-19	12.3	86	0.05	na	0.37	0.80
Male Teenager	12-19	9.8	68	0.04	na	0.40	0.91
Female Adult	20 and Up	13.6	622	0.05	na	0.34	0.87
Male Adult	20 and Up	10.0	476	0.04	na	0.39	1.00
Total Population	All Ages	11.7	2,419	0.04	na	0.34	0.84

Table 5.1.2-2 Summary of the Estimated Daily Intake of Difatty Ketones, Assuming the Highest Level of Formation (217 ppm), Corresponding to the Intake of Olestra from All Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Infant	0-2	8.9	318	0.03	na	0.27	0.60
Child	3-11	13.5	849	0.06	na	0.46	1.04
Female Teenager	12-19	12.3	86	0.10	na	0.74	1.60
Male Teenager	12-19	9.8	68	0.08	na	0.80	1.84
Female Adult	20 and Up	13.6	622	0.10	na	0.68	1.74
Male Adult	20 and Up	10.0	476	0.09	na	0.79	2.02
Total Population	All Ages	11.7	2,419	0.09	na	0.68	1.68

Table 5.1.2-3 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Difatty Ketones, Assuming an Average Level of Formation (108 ppm), Corresponding to the Intake of Olestra from All Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (µg/kg)	90th Percentile (µg/kg)	Mean (µg/kg)	90th Percentile (µg/kg)
Infant	0-2	8.9	318	1.1	na	10.6	23.3
Child	3-11	13.5	849	1.2	na	8.8	20.8
Female Teenager	12-19	12.3	86	0.9	na	6.4	15.6
Male Teenager	12-19	9.8	68	0.7	na	6.7	14.4
Female Adult	20 and Up	13.6	622	0.8	na	5.3	14.2
Male Adult	20 and Up	10.0	476	0.5	na	4.7	10.7
Total Population	All Ages	11.7	2,419	0.8	na	5.9	14.3

Table 5.1.2-4 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Difatty Ketones, Assuming the Highest Level of Formation (217 ppm), Corresponding to the Intake of Olestra from All Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (µg/kg)	90th Percentile (µg/kg)	Mean (µg/kg)	90th Percentile (µg/kg)
Infant	0-2	8.9	318	2.2	na	21.2	46.8
Child	3-11	13.5	849	2.5	na	17.8	41.8
Female Teenager	12-19	12.3	86	1.7	na	12.9	31.3
Male Teenager	12-19	9.8	68	1.4	na	13.5	29.0
Female Adult	20 and Up	13.6	622	1.6	na	10.6	28.6
Male Adult	20 and Up	10.0	476	1.0	na	9.5	21.4
Total Population	All Ages	11.7	2,419	1.5	na	11.9	28.8

5.1.3 Estimated Daily Intake of Vitamins A, E, D, and K Corresponding to the Addition of These Vitamins to All Permitted and Proposed Food-Uses of Olestra

Consistent with the regulations that require the addition of vitamins A, E, D, and K at specified levels to foods that are currently permitted to contain olestra (21 CFR §172.867), proposed food uses for olestra will also contain these vitamins at the same levels. Tables 5.1.3-1, 5.1.3-2, 5.1.3-3, and 5.1.3-4 show the estimated intake of vitamins A, E, D, and K, respectively, that correspond to the addition of these vitamins to all permitted and proposed food uses of olestra at levels consistent with the current regulations.

Table 5.1.3-1 Summary of the Estimated Daily Intake of Vitamin A Corresponding to Its Addition to All Permitted and Proposed Uses of Olestra in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (RAE[1])	90th Percentile (RAE)	Mean (RAE)	90th Percentile (RAE)
Infant	0-2	8.9	318	6.4	na	63.4	140.3
Child	3-11	13.5	849	14.5	na	107.3	243.6
Female Teenager	12-19	12.3	86	22.9	na	174.2	376.2
Male Teenager	12-19	9.8	68	19.6	na	187.2	431.6
Female Adult	20 and Up	13.6	622	23.9	na	160.1	409.3
Male Adult	20 and Up	10.0	476	20.6	na	186.3	474.4
Total Population	All Ages	11.7	2,419	20.4	na	158.8	394.9

[1]RAE=Retinol Activity Equivalents

Table 5.1.3-2 Summary of the Estimated Daily Intake of Vitamin E Corresponding to Its Addition to All Permitted and Proposed Uses of Olestra in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg α-tocopherol)	90th Percentile (mg α-tocopherol)	Mean (mg α-tocopherol)	90th Percentile (mg α-tocopherol)
Infant	0-2	8.9	318	0.2	na	2.4	5.2
Child	3-11	13.5	849	0.5	na	4.0	9.1
Female Teenager	12-19	12.3	86	0.9	na	6.5	14.0
Male Teenager	12-19	9.8	68	0.7	na	7.0	16.1
Female Adult	20 and Up	13.6	622	0.9	na	6.0	15.2
Male Adult	20 and Up	10.0	476	0.8	na	6.9	17.7
Total Population	All Ages	11.7	2,419	0.8	na	5.9	14.7

Table 5.1.3-3 Summary of the Estimated Daily Intake of Vitamin D Corresponding to Its Addition to All Permitted and Proposed Uses of Olestra in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (µg)	90th Percentile (µg)	Mean (µg)	90th Percentile (µg)
Infant	0-2	8.9	318	< 0.1	na	0.4	0.8
Child	3-11	13.5	849	0.1	na	0.6	1.4
Female Teenager	12-19	12.3	86	0.1	na	1.0	2.2
Male Teenager	12-19	9.8	68	0.1	na	1.1	2.5
Female Adult	20 and Up	13.6	622	0.1	na	0.9	2.4
Male Adult	20 and Up	10.0	476	0.1	na	1.1	2.8
Total Population	All Ages	11.7	2,419	0.1	na	0.9	2.3

Table 5.1.3-4 Summary of the Estimated Daily Intake of Vitamin K Corresponding to Its Addition to All Permitted and Proposed Uses of Olestra in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (µg)	90th Percentile (µg)	Mean (µg)	90th Percentile (µg)
Infant	0-2	8.9	318	1.0	na	9.9	22.0
Child	3-11	13.5	849	2.3	na	16.8	38.2
Female Teenager	12-19	12.3	86	3.6	na	27.3	59.0
Male Teenager	12-19	9.8	68	3.1	na	29.4	67.7
Female Adult	20 and Up	13.6	622	3.7	na	25.1	64.2
Male Adult	20 and Up	10.0	476	3.2	na	29.2	74.4
Total Population	All Ages	11.7	2,419	3.2	na	24.9	61.9

Total population users-only mean and 90th percentile intakes of vitamin A corresponding to the addition of this vitamin to permitted and proposed uses of olestra are 158.8 and 394.9 RAE/day, respectively. By comparison, previously published total population mean and 90th percentile background intakes of total vitamin A from food sources are 924 and 1,405 µg RAE/day, respectively (IOM, 2001).

Vitamin E mean and 90th percentile intakes by the total population for users-only of permitted and proposed uses of olestra are 5.9 and 14.7 mg α-tocopherol/day. In terms of background intakes, total population mean and 90th percentile values for vitamin E are 9.2 and 11.5 mg α-tocopherol/day, respectively (IOM, 2000).

The mean and 90th percentile total population vitamin D users-only intakes corresponding to its addition to permitted and proposed food uses are 0.9 and 2.3 µg/day. For background intakes, accurate estimates of vitamin D intakes from dietary sources in the United States are not available because the U.S. intake surveys do not include estimates of vitamin D intake, due, in part, to the high variability of vitamin D composition of fortified foods (IOM, 2006c). However, Adequate Intake (AI) values for vitamin D have been derived, with the AI of most population groups being 5 µg/day, with the exception of adults 51 through 70 years (10 µg/day) and adults >70 years (15 µg/day) (IOM, 2006c).

Vitamin K total population users-only mean and 90th percentile intakes corresponding to the addition of vitamin K to permitted and proposed food uses are 24.9 and 61.9 µg/day, respectively. The mean and 90th percentile background intakes of vitamin K from food sources for the total population are 93.7 and 155 µg/day, respectively (IOM, 2001).

Relative to background intakes, intakes of vitamins A and K from their addition to permitted and proposed food uses of olestra are substantially lower, while intakes of vitamin E are similar. Though background intakes of vitamin D are unavailable, comparisons with the AI show that intakes of vitamin D from its addition to permitted and proposed food uses are also substantially lower.

5.2 All-Person Intakes of Individual Permitted and Proposed Uses of Olestra

Estimates for the mean daily intakes of olestra from each of the individual permitted and proposed food categories are summarized in Tables I-1 to I-7 on a g/day basis and Tables II-1 to II-7 on a mg/kg body weight/day basis. Table I-7 summarizes the estimates for the mean all-person intakes of olestra by the total population (all ages) from each of the individual proposed food-uses on a g/person/day basis, while this information is presented on a mg/kg body weight/day basis in Table II-7.

The total U.S. population was identified as being substantial consumers of prepackaged ready-to-eat savory snacks with 8.8% users, followed by reduced fat, low fat, and fat free cookies with 2.4% users, and prepackaged ready-to-heat popcorn with 1.6% users. Consumption of prepackaged ready-to-eat savory snacks made the most significant contribution to the mean all-person intakes of olestra at 0.20 g/person/day (3.7 mg/kg body weight/day). A significant impact on the mean all-person intakes of olestra was also made from the consumption of reduced fat, low fat and fat free cookies at 0.12 g/person/day (2.16 mg/kg body weight/day), and prepackaged ready-to-heat popcorn at 0.08 g/person/day (1.23 mg/kg body weight/day).

Of the individual population groups, the consumption of prepackaged ready-to-eat savory snacks made the most significant contribution to the mean all-person intakes of olestra (Tables I-1 to I-6). The highest mean all-person intakes of olestra, on an absolute basis, were reported

in female adults consuming prepackaged ready-to eat savory snacks, at 0.23 g/person/day (3.59 mg/kg body weight/day). On a body weight basis, children had the highest mean all-person intakes of olestra, which corresponded to the intake of prepackaged ready-to-eat savory snacks, with values of 6.82 mg/kg body weight/day.

5.3 All-User Intakes of Individual Permitted and Proposed Uses of Olestra

Tables I-7 and II-7 also summarize the estimates for the mean all-user intakes of olestra by the total population (all ages) from each of the individual food-uses on a g/person/day basis and mg/kg body weight/day basis, respectively. In contrast to the results observed for the all-person intakes, consumers of prepackaged ready-to-heat popcorn were identified as having the greatest mean and 90th percentile all-user intakes of olestra at 4.37 g/person/day (69.75 mg/kg body weight/day) and 10.87 g/person/day (136.90 mg/kg body weight/day), respectively, on a total population basis. Reduced fat, low fat and fat free cookies also made a substantial contribution to the estimates for the mean and 90th percentile all-user intakes of olestra by the total population, with values of 4.22 g/person/day (74.76 mg/kg body weight/day) and 8.03 g/person/day (153.71 mg/kg body weight/day), respectively. The lowest all-user mean and 90th percentile intakes of olestra were observed for prepackaged ready-to-eat savory snacks, at 2.15 g/person/day (39.37 mg/kg body weight/day) and 5.27 g/person/day (98.82 mg/kg body weight/day), respectively.

On an individual population group basis, the consumption of prepackaged ready-to-heat popcorn tended to make the most significant contribution to the mean and 90th percentile all-user intakes of olestra (Tables I-1 to I-6, and II-1 to II-6), though this varied by population group. Male adults consuming prepackaged ready-to-heat popcorn were determined to have the highest statistically reliable mean all-user intake of olestra of 5.87 g/person/day (66.96 mg/kg body weight/day), while male adults and female teenagers consuming prepackaged ready-to-heat popcorn were determined to have the highest 90th percentile all-user intake of olestra from this source, with a value of 11.46 g/person/day (132.72 and 219.28 mg/kg body weight/day, respectively). Of the statistically reliable estimates, on a body weight basis infants consuming reduced fat, low fat, and fat free cookies had the highest mean and 90th percentile all-user intakes with values of 165.44 and 322.57 mg/kg body weight/day, respectively.

5.4 Acute and Chronic Olestra Intake from Permitted and Proposed Uses

Values for olestra intake presented in Sections 5.1 to 5.3 represent estimated chronic intake from permitted and proposed uses. For an individual, this is equal to the cumulative intake over the 2 days of the survey divided by 2, yielding a mean olestra intake over the course of 2 days. Although these values are meant to represent chronic intake of olestra, short-term surveys, such as the typical 2-day dietary survey utilized by USDA CSFII 1994-1996, 1998, are well established to overestimate consumption over longer time periods (greater than 3 months) that

are more appropriate to safety assessments (Anderson, 1988). In fact, the impact of the length of dietary surveys on the consumption of different types of food products was investigated in a study conducted by the Institute of European Food Studies (IEFS, 1998), which showed that mean and 90th percentile users-only intakes of crisps (*i.e.*, chips) and biscuits (*i.e.*, cookies) based on 1 or 3 days of intake records are substantially higher than intakes based on 14 days of dietary records (by a factor of up to 4). This suggests that estimates of olestra intake presented in this report are highly conservative. Nevertheless, USDA CSFII 1994-1996, 1998 are currently the most appropriate data available to base evaluations of intake upon.

While values presented in Sections 5.1 to 5.3 represent chronic intake of olestra, estimated acute daily intakes were also estimated by reserving from the analysis all days whose olestra intake values were zero. Thus, a user of olestra from permitted and/or proposed uses contributes either 1 or 2 acute daily intake values to this set of analyses. Estimated acute daily intakes of olestra by olestra users are presented in Table 5.4-1.

Table 5.4-1 Summary of the Estimated Acute Daily Intake of Olestra from All Permitted and Proposed Uses by Users Only in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	Actual # of User-Days	All-Users Consumption	
			Mean (g)	90th Percentile (g)
Infant	0-2	377	2.09	4.56
Child	3-11	995	3.64	8.59
Female Teenager	12-19	103	5.50	14.01
Male Teenager	12-19	83	6.11	15.33
Female Adult	20 and Up	735	5.27	12.07
Male Adult	20 and Up	563	6.28	15.18
Total Population	All Ages	2856	5.27	12.58

The acute 90th percentile intake of users only for the total population is 12.58 g/person/day (Table 5.4-1), which is higher than the chronic daily 90th percentile intake for the total population of 7.74 g/person/day (Table 5.1.1-1). This would suggest that in general, the intake of permitted and/or proposed uses of olestra did not occur on both days of the survey, which led to a lower chronic intake value in comparison to the acute value. In addition, of the 2,419 users (Table 5.1.1-1) of permitted and/or proposed uses of olestra, 2,856 days (Table 5.4-1) of consumption were recorded. Thus, 437 of 2,419 individuals, or only 18% of olestra users (represents 2.1% of the total population) consumed a minimum of one permitted or proposed food use of olestra on both days of the survey.

With the addition of proposed uses of olestra, there will be some individuals who consume olestra from both permitted and proposed uses within a given day. Analyses were conducted to identify these individuals and estimates of their olestra intake are presented in Table 5.4-2.

Table 5.4-2 Summary of the Estimated Chronic Daily Intake of Olestra by Users of Both Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	Actual # of Users	% Users	All-Users Consumption	
				Mean (g)	90th Percentile (g)
Infant	0-2	18	0.50	2.74	4.24
Child	3-11	27	0.43	5.27	8.82
Female Teenager	12-19	3	0.43	5.40	6.69
Male Teenager	12-19	10	1.44	7.38	11.67
Female Adult	20 and Up	29	0.64	9.40	16.67
Male Adult	20 and Up	50	1.05	7.87	17.92
Total Population	All Ages	137	0.67	7.75	16.67

Results shown in Table 5.4-2 represent estimates of chronic (2-day mean) of olestra intake by individuals who consumed a minimum of one permitted food use plus one proposed food use of olestra within a day on either one or both days of the survey. Only 0.67% of the U.S. population was identified as users of both permitted and proposed food uses of olestra within a day. For the total population, the 90th percentile chronic intake of olestra for these individuals was estimated to be 16.67g/person/day.

Values presented in Table 5.4-2 represent chronic intake of olestra by individuals who consumed both permitted and proposed food uses of olestra within a day on at least one day of the survey. The estimated acute intakes of olestra on a day when both permitted and proposed food uses were consumed were also estimated by reserving from the analysis all days that did not include consumption of at least one permitted plus one proposed food use. Estimated daily intakes that include only days when both permitted and proposed uses were consumed are presented in Table 5.4-3.

Table 5.4-3 Summary of the Estimated Acute Daily Intake of Olestra by Users of Both Permitted and Proposed Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)				
Population Group	**Age Group (Years)**	**Actual # of User-Days**	**All-Users Consumption**	
			Mean (g)	**90th Percentile (g)**
Infant	0-2	26	2.75	4.90
Child	3-11	40	6.79	13.14
Female Teenager	12-19	6	5.40	8.12
Male Teenager	12-19	14	9.75	19.85
Female Adult	20 and Up	36	14.04	28.19
Male Adult	20 and Up	68	10.64	23.61
Total Population	All Ages	190	10.44	22.84

For the total population, the daily intake of heavy consumers (*i.e.*, 90th percentile intake) of both permitted and proposed food uses of olestra within a day is 22.84 g/person/day. This value would represent a worst-case scenario for olestra intake from both permitted and proposed uses by heavy consumers within a single day.

5.5 Intake of Olestra from Permitted and Proposed Uses at Meals *versus* Snacks

The pattern of olestra consumption was examined by investigating the intake of olestra intake from permitted and proposed food uses at meals *versus* snacks. The results of these analyses for prepackaged ready-to-heat popcorn, prepackaged ready-to-eat savory snacks, and reduced fat, low fat, and fat free cookies are presented in Tables 5.5-1, 5.5-2, and 5.5-3, respectively.

Table 5.5-1 Intake of Olestra at Meals *versus* Snacks from Prepackaged Ready-to-Heat Popcorn in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	Eating Occasion	Percentage of Consumption Occasions	Mean (g)	90th Percentile (g)
Infant	0-2	Meals	2.7	0.52	0.52
		Snacks	97.3	1.00	1.99
Child	3-11	Meals	4.2	2.52	3.98
		Snacks	95.8	2.19	4.91
Female Teenager	12-19	Meals	16.7	7.08*	11.46*
		Snacks	83.3	3.05*	10.48*
Male Teenager	12-19	Meals	10.0	4.39	4.39
		Snacks	90.0	4.78*	19.65*
Female Adult	20 and Up	Meals	15.2	4.49	11.14
		Snacks	84.8	3.89	9.83
Male Adult	20 and Up	Meals	17.6	5.25	9.83
		Snacks	82.4	5.79	11.46
Total Population	All Ages	Meals	10.4	4.87	11.14
		Snacks	89.6	4.08	9.83

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

Table 5.5-2 Intake of Olestra at Meals *versus* Snacks from Prepackaged Ready-to-Eat Savory Snacks in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	Eating Occasion	Percentage of Consumption Occasions	Mean (g)	90th Percentile (g)
Infant	0-2	Meals	23.8	1.25	2.06
		Snacks	76.2	0.59	1.16
Child	3-11	Meals	31.2	1.46	4.13
		Snacks	68.8	1.08	2.30
Female Teenager	12-19	Meals	42.9	1.47	4.81
		Snacks	57.1	1.93	6.56
Male Teenager	12-19	Meals	38.8	3.34	8.10
		Snacks	61.2	1.30	4.07
Female Adult	20 and Up	Meals	39.5	2.66	5.44
		Snacks	60.5	1.08	2.51
Male Adult	20 and Up	Meals	40.5	2.88	6.92
		Snacks	59.5	1.33	3.67
Total Population	All Ages	Meals	34.5	2.49	5.38
		Snacks	65.5	1.19	2.98

Table 5.5-3 Intake of Olestra at Meals *versus* Snacks from Reduced Fat, Low Fat, and Fat Free Cookies in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	Eating Occasion	Percentage of Consumption Occasions	Mean (g)	90th Percentile (g)
Infant	0-2	Meals	12.3	1.79	2.71
		Snacks	87.7	1.48	2.75
Child	3-11	Meals	17.6	2.22	4.50
		Snacks	82.4	3.26	7.35
Female Teenager	12-19	Meals	46.4	3.64	9.79
		Snacks	53.6	3.23	4.84
Male Teenager	12-19	Meals	12.5	2.14*	3.66*
		Snacks	87.5	4.62	9.79
Female Adult	20 and Up	Meals	36.2	2.87	4.90
		Snacks	63.8	2.98	5.07
Male Adult	20 and Up	Meals	52.5	3.60	7.35
		Snacks	47.5	3.92	7.35
Total Population	All Ages	Meals	32.6	3.16	5.55
		Snacks	67.4	3.23	6.10

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

Intake of olestra from all permitted uses occurs primarily as a snack, with 89.6 and 65.5% of eating occasions occurring as a snack for prepackaged ready-to-heat popcorn and prepackaged ready-to-eat savory snacks, respectively, for the total population. Consistent with this, 67.4% of reduced fat, low fat and fat free cookie eating occasions occurred as a snack for the total population. The younger age groups tended to consume a high proportion of cookies as snacks, as opposed to consuming them with main meals, with infants and children consuming olestra from reduced fat, low fat and fat free cookies as snacks during 87.7 and 82.4% of eating occasions, respectively.

Though the majority of eating occasions for prepackaged ready-to-heat popcorn and prepackaged ready-to-eat savory snacks occurred as snacks, mean and 90th percentile intakes of olestra from these food-uses tended to be similar at meal and snack occasions, or slightly higher at meals. For reduced fat, low fat and fat-free cookies, intakes of olestra at meals *versus* snacks also tended to be similar, but slightly higher at snack occasions.

6.0 CONCLUSIONS

Consumption data and information pertaining to the individual identified food-uses were used to estimate the all-person and all-user intakes of olestra for specific demographic groups and for the total U.S. population. This type of intake methodology is generally considered to be "worst case" as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently.

In summary, on an all-user basis, the estimated mean and 90th percentile intakes of olestra from the consumption of the proposed food-use of reduced fat, low fat and fat free cookies, in addition to the consumption of the permitted uses of prepackaged ready-to-eat savory snacks and prepackaged ready-to-heat popcorn by the total U.S. population were estimated to be 3.11 g/person/day (54.98 mg/kg body weight/day) and 7.74 g/person/day (132.72 mg/kg body weight/day), respectively. These intake estimates are only slightly higher than the estimated mean and 90th percentile intakes of olestra by the total population from only permitted uses, 2.58 g/person/day (45.53 mg/kg body weight/day) and 7.01 g/person/day (114.63 mg/kg body weight/day), respectively.

On an individual population basis, the greatest mean all-user intake of olestra from permitted and proposed uses occurred in male teenagers, 3.67 g/person/day (62.40 mg/kg body weight/day), while the highest 90th percentile all-user intake occurred in male adults, 9.30 g/person/day (98.81 mg/kg body weight/day).

Corresponding to the formation of difatty ketones from the production of olestra, the total population 90th percentile intake of difatty ketones for users only is 0.84 mg/person/day (14.3 µg/kg body weight/day) assuming an average level formed from the manufacture of olestra, and in the worst case is 1.68 mg/person/day (28.8 µg/kg body weight/day) assuming the highest level formed. The addition of vitamins A, E, D, and K to permitted and proposed food uses of olestra resulted in intakes of vitamins A and K from these sources that are substantially lower in comparison to background intakes, while intakes vitamin E are similar. Though background intakes of vitamin D are unavailable, comparisons with the AI show that intakes of vitamin D from its addition to permitted and proposed food uses are also substantially lower.

Acute 90th percentile intake of olestra by users only for the total population was 12.58 g/person/day. Consumption of a minimum of one permitted and/or proposed food use on both days of the survey occurred for only about 2% of the total population. Chronic olestra intake at the 90th percentile by individuals who consumed both permitted and proposed food uses of olestra within

a day was 16.67 g/person/day, though only 0.67% of the population was identified as consumers of both permitted and proposed food uses within a single day. The estimated daily intake of olestra including only the days when both a permitted plus a proposed food use is consumed is 22.84 g/person/day at the 90th percentile for the total population. This value would represent a worst-case scenario for olestra intake from both permitted and proposed uses by heavy consumers within a single day.

Analyses on the patterns of olestra intake from permitted and proposed uses shows that the majority of eating occasions occur as snacks, particularly for infants and children.

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ATTACHMENT A-I

Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Different Population Groups Within the United States

Table A-I-1 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 2 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.0	36	0.01	na	1.00	1.99
Prepackaged Ready-to-Eat Savory Snacks	6.9	246	0.07	na	0.96	2.06
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	1.6	59	0.04	na	2.01	3.62

Table A-I-2 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 3 to 11 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.7	108	0.04	na	2.55	3.98
Prepackaged Ready-to-Eat Savory Snacks	10.6	671	0.16	na	1.55	3.92
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	2.0	123	0.08	na	3.81	9.50

Table A-I-3 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.6	11	0.07*	na	4.29	11.46
Prepackaged Ready-to-Eat Savory Snacks	8.5	60	0.22	na	2.44	7.01
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	3.6	25	0.16	na	3.85	9.79

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

Table A-I-4 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.4	10	0.07*	na	4.73*	13.00*
Prepackaged Ready-to-Eat Savory Snacks	7.0	49	0.20	na	2.68	7.37
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	1.7	12	0.11*	na	6.35*	20.74*

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

Table A-I-5 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 20 Years and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.9	88	0.08	na	4.09	10.64
Prepackaged Ready-to-Eat Savory Snacks	9.4	429	0.23	na	2.16	5.44
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	3.7	171	0.16	na	3.94	8.00

Table A-I-6 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 20 Years and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.4	66	0.09	na	5.87	11.46
Prepackaged Ready-to-Eat Savory Snacks	7.1	339	0.20	na	2.48	6.92
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	2.3	111	0.11	na	4.99	8.03

Table A-I-7 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population (All Ages) Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.6	319	0.08	na	4.37	10.87
Prepackaged Ready-to-Eat Savory Snacks	8.8	1,794	0.20	na	2.15	5.27
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	2.4	501	0.12	na	4.22	8.03

ATTACHMENT A-II

Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Different Population Groups Within the United States

Table A-II-1 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 2 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.0	36	1.04	na	77.61	156.45
Prepackaged Ready-to-Eat Savory Snacks	6.9	246	5.96	na	73.57	144.33
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	1.6	59	3.21	na	165.44	322.57

Table A-II-2 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 3 to 11 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.7	108	1.63	na	102.36	193.26
Prepackaged Ready-to-Eat Savory Snacks	10.6	671	6.82	na	62.71	135.56
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	2.0	123	2.86	na	137.68	261.25

Table A-II-3 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.6	11	1.39*	na	82.75	219.28
Prepackaged Ready-to-Eat Savory Snacks	8.5	60	3.61	na	40.33	111.70
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	3.6	25	2.87	na	67.37	175.17

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

Table A-II-4 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.4	10	1.31*	na	92.88*	226.97*
Prepackaged Ready-to-Eat Savory Snacks	7.0	49	3.13	na	40.49	105.40
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	1.7	12	2.18*	na	119.40*	434.47*

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

Table A-II-5 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 20 Years and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.9	88	1.23	na	58.12	136.80
Prepackaged Ready-to-Eat Savory Snacks	9.4	429	3.59	na	33.97	85.91
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	3.7	171	2.43	na	62.61	134.44

Table A-II-6 Estimated Daily Intake Per Kilogram Body Weight of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 20 Years and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.4	66	1.05	na	66.96	132.72
Prepackaged Ready-to-Eat Savory Snacks	7.1	339	2.43	na	29.96	72.25
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	2.3	111	1.34	na	60.40	107.00

Table A-II-7 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population (All Ages) Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Permitted Uses						
Snack Foods						
Prepackaged Ready-to-Heat Popcorn	1.6	319	1.23	na	69.75	136.90
Prepackaged Ready-to-Eat Savory Snacks	8.8	1,794	3.70	na	39.37	98.82
Proposed Use						
Baked Goods and Baking Mixes						
Reduced Fat, Low Fat, and Fat Free Cookies	2.4	501	2.16	na	74.76	153.71

ATTACHMENT A-III

Representative CSFII 1994-1996, 1998 Food Codes for All Permitted and Proposed Food-Uses of Olestra in the United States

Representative CSFII 1994-1996, 1998 Food Codes for All Permitted and Proposed Food-Uses of Olestra in the United States

Note: The use-level, 100% replacement of fat, is based on the fat content of an equivalent regular product (*i.e.*, fat content has not been modified).

Snack Foods

Prepackaged Ready-to-Heat Popcorn
[olestra] = 26.2%

54403010	Popcorn, air-popped (no butter or no oil added)
54403060	Popcorn, popped in oil, low fat, low sodium
54403070	Popcorn, popped in oil, low fat

Prepackaged Ready-to-Eat Savory Snacks
[olestra] = 3.5 to 38.4%

54202050	Crackers, saltine, fat free, low sodium
54205100	Cracker, snack, low fat, low sodium
54301100	Cracker, snack, reduced fat
54301200	Cracker, snack, fat free
54304100	Cracker, cheese, reduced fat
54304500	Cracker, high fiber, no added fat
54322000	Crisp bread, rye, no added fat
54337050	Cracker, 100% whole wheat, reduced fat
54338100	Crackers, wheat, reduced fat
54401100	Salty snacks, corn or cornmeal base, tortilla chips, light (baked with less oil)
54401120	Salty snacks, corn or cornmeal base, tortilla chips, fat free, made with Olean
54401150	Salty snacks, corn or cornmeal base, tortilla chips, low fat, baked without fat
54401170	Salty snacks, corn or cornmeal base, tortilla chips, low fat, baked without fat, unsalted
54401210	Salty snacks, corn based puffs and twists, cheese puffs and twists, low fat
54408010	Pretzels, hard
54408030	Pretzel, hard, unsalted
71201050	White potato, chips, reduced fat
71201080	White potato, chips, fat free
71201090	White potato chips, fat free, made with Olean
71201200	White potato, chips, restructured, reduced fat and reduced sodium
71201210	White potato, chips, restructured, fat free, made with Olean
71201300	Potato based snacks, reduced fat, low sodium, and all flavors
71202100	White potato, chips, unsalted, reduced fat

Baked Goods and Baking Mixes

Reduced Fat, Low Fat, and Fat Free Cookies
[olestra] = 7.3 to 30.6%

53200100	Cookie, batter or dough, raw, not chocolate
53204800	Cookie, brownie, diet, NS as to icing
53204830	Cookie, brownie, low fat, with icing
53204840	Cookie, brownie, low fat, without icing
53204850	Cookie, brownie, fat free, cholesterol free, with icing
53204860	Cookie, brownie, fat free, without icing

53206030	Cookie, chocolate chip, reduced fat
53207050	Cookie, chocolate, with chocolate filling or coating, fat free
53209020	Cookie, chocolate sandwich, reduced fat
53220010	Cookie, fruit-filled bar, fat free
53220040	Cookie, fig bar, fat free
53233030	Cookie, oatmeal, fat free, with raisins
53233040	Cookie, oatmeal, reduced fat, with raisins
53239010	Cookie, shortbread, reduced fat
53243050	Cookie, vanilla sandwich, reduced fat
53247050	Cookie, vanilla wafer, reduced fat
53260000	Cookie, dietetic, NFS
53260010	Cookie, dietetic, apple pastry
53260030	Cookie, dietetic, chocolate chip
53260050	Cookie, dietetic, chocolate flavored
53260100	Cookie, dietetic, fruit types
53260150	Cookie, lemon wafer, low fat
53260200	Cookie, dietetic, oatmeal with raisins
53260300	Cookie, dietetic, sandwich type
53260400	Cookie, dietetic, sugar or plain
54102100	Crackers, graham, low fat
54102110	Crackers, graham, fat free

Appendix B

Description and Results from the Olestra Post-Marketing Surveillance Study

Appendix B

Description and Results from the Olestra Post-Marketing Surveillance Study

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1.0 OVERVIEW OF THE OLESTRA POST-MARKETING SURVEILLANCE STUDY

Although, in 1996, the U.S. Food and Drug Administration (U.S. FDA) approved the use of olestra as a fat substitute in savory snacks (U.S. FDA, 1996), as part of the approval process, the U.S. FDA mandated an active post-marketing surveillance study of the consumption patterns of olestra, as well as of the effects of olestra on nutritional status. Thus, several human experimental studies were conducted to investigate the influence of olestra consumption on serum concentrations of 6 carotenoids (α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin) and 4 fat-soluble vitamins (vitamins A, D, E, and K). The effects of olestra consumption on serum levels of these micronutrients were investigated in the Olestra Post-Marketing Surveillance Study (OPMSS). The goals of the OPMSS were 3-fold: i) To monitor adoption and patterns of use of olestra-containing food products in representative samples of the U.S. population; ii) To assess the effects of the introduction of olestra-containing foods on serum concentrations of carotenoids and fat-soluble vitamins in representative cross-sections of the U.S. population; and iii) To assess the long-term effects of consumption of olestra-containing foods on serum concentrations of carotenoids and fat-soluble vitamins among a cohort of olestra consumers (Kristal *et al.,* 1998).

The OPMSS consisted of 4 field sites (Kristal *et al.,* 1998). The Marion County Indiana site, termed the sentinel site, began recruitment in October 1996 immediately prior to the test-market release of olestra snacks in February 1997. The remaining 3 sites [Johns Hopkins University (Baltimore, MD), University of Minnesota (Minneapolis, MN), and University of California (California, SD)] began recruitment in September 1997, immediately prior to the national release of olestra-containing snacks in February 1998 (Kristal *et al.,* 1998). In addition, the OPMSS consisted of an operations support unit at Westat Inc. (Rockville, MD) and a coordinating centre at the Fred Hutchinson Cancer Research Center (Seattle, Washington).

The OPMSS can be regarded as a series of 3 related studies: The population cross-section survey, the clinic cross-section study, and the clinic cohort study (Kristal *et al.,* 1998). The population cross-section survey was a list-assisted random-digit-dial telephone survey conducted by Westat Inc. (Rockville, MD) in which adults $\geq$18 years in 4 U.S. cities (Indianapolis, Baltimore, Minneapolis, and San Diego) and their surrounding suburbs were recruited to complete a telephone survey regarding beliefs and attitudes about diet and health; consumption patterns of fruits, vegetables, and savory snacks; and demographic characteristics. Information on the patterns of consumption of fruits and vegetables (particularly with respect to the consumption of savory snacks) was collected because pre-market studies demonstrated that olestra reduced the absorption of carotenoids. In the clinic cross-section study, a random sample of the telephone survey respondents was invited to join a clinical component of the study in which they completed detailed questionnaires on diet, medical

history, and lifestyle habits; provided blood samples and anthropometric measures; and completed quarterly follow-up telephone surveys over a 1-year period. The initial telephone surveys and clinic visits were conducted prior to the marketing of olestra-based snacks and resumed after the marketing of olestra. Thus, data were obtained before and after the marketing of olestra-based snacks in the marketplace. For the clinic cohort study, a subset of the subjects who participated in the clinic cross-section study were invited to continue in the study for an additional 2 years of data collection, during which all clinic measures were repeated annually. The clinic cross-section and cohort studies tested the hypothesis that olestra-associated changes in serum concentrations of fat-soluble vitamins and carotenoids would be <10%, based on the assumption that changes below this cut-off are consistent with random variation (Kristal *et al.,* 1998). The OPMSS was operated as the National Study of Nutrition and Health so that study participants were not aware that they were in a study examining the effects of olestra-containing snack foods (Neuhouser *et al.,* 2006). Also, although the studies were funded by Procter and Gamble (as per the directive of the U.S. FDA), contractual agreements ensured that the scientists at the coordinating center and the university-based field sites were solely and independently responsible for the study design; data collection, management, and analysis; and publications (Kristal *et al.,* 1998; Neuhouser *et al.,* 2006).

The sentinel site (Marion County, Indianapolis, IN) began recruitment of subjects in October 1996, in anticipation of the February 1997 test-market introduction of olestra snacks; in contrast, the other 3 research sites began recruitment of subjects in September 1997 in anticipation of the February 1998 national market release of olestra. The study instruments used at the sentinel site were slightly different from those used at the other 3 research facilities. Results at the sentinel site were collected earlier than those at the other 3 sites; also, the U.S. FDA reviewed results collected at the sentinel site in its June 1998 review. Thus, although there were 4 research sites involved in the OPMSS, results for the sentinel site (Thornquist *et al.,* 2000) will be discussed separately from those collected at the other 3 research sites (Neuhouser *et al.,* 2006).

2.0 OLESTRA POST-MARKETING SURVEILLANCE STUDY: RESULTS FROM THE SENTINEL SITE

In Marion County, the baseline clinic cross-section study was conducted from September 1996 to January 1997, prior to the February 1997 regional test-market introduction of olestra (Thornquist *et al.,* 2000). The first follow-up survey and follow-up clinic visits were conducted from September 1997 to January 1998. Nutrient intakes (except vitamin K) were measured using a 122-item food-frequency questionnaire (Patterson *et al.,* 1999). A 16-item savory snack questionnaire (Neuhouser *et al.,* 2000) was used to assess intakes of savory snacks [regular, reduced-fat, baked, non-fat, and fat substitute (*i.e.,* olestra) potato chips, tortilla chips, pretzels, extruded snacks, and crackers]. The food frequency and savory snack questionnaires both

queried about usual consumption frequency and portion sizes during the previous month. Because serum vitamin K concentrations are most strongly influenced by recent diet, vitamin K intakes were estimated from a 24-hour diet recall. Data on vitamin supplement use over the past month were captured using a validated inventory procedure (Patterson *et al.,* 2000), which was modified to collect precise dose information on vitamins A, D, E, and K and β-carotene (the only carotenoid available in supplement form at the time). Information on demographic characteristics, health-related behavior, and medical history was collected; as well, anthropometric measures (height, weight, and waist circumference) were collected. Serum concentrations of vitamin A (retinol), vitamin D (25-hydroxyvitamin D), vitamin E (α-tocopherol), vitamin K (phylloquinone), and 6 carotenoids (α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin) were assessed at each clinic visit during the clinic cross-section and cohort studies. The other research sites involved in the OPMSS (*i.e.,* Baltimore, Minneapolis, and San Diego) utilized the same study instruments, except the 24-hour diet recall for the estimation of vitamin K intake. Study parameters measured at the sentinel site and at the other 3 research sites are summarized in Table 2-1.

Table 2-1 Research Instruments and Parameters Measured in the Olestra Post-Marketing Surveillance Study Conducted at the Indiana, Baltimore, Minneapolis, and San Diego Sites

Dietary Assessment	Serum Measures	Anthropometry	Other Measures
16-item savory snack questionnaire[1,2] 122-item food-frequency questionnaire[2] Vitamin supplement use[3] 24-hour diet recall[4]	Vitamin E (α-tocopherol) Vitamin A (*all-trans*-retinol) Vitamin D (25-hydroxyvitamin D) Vitamin K (phylloquinone) Carotenoids[5] Total cholesterol[6] Triacylglycerols[6]	Body mass index	Physical activity Medical history Usual sun exposure Household income Alcohol/tobacco use Demographics[7]

[1] Included questions on use of regular, reduced-fat, baked, non-fat, and fat substitute (*i.e.,* olestra) potato chips, tortilla chips, pretzels, extruded snacks, and crackers.
[2] The food frequency and savory snack questionnaires both queried about usual consumption frequency and portion sizes during the previous month.
[3] A validated inventory procedure that was modified to collect detailed dosage information on vitamin A, D, E, K and β-carotene was used. Total micronutrient intake used in analyses included sources from all supplements plus food.
[4] Used to estimate vitamin K intakes at the sentinel (Indiana) site only.
[5] α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin.
[6] Cholesterol was used as an adjustment factor in the expression of α-tocopherol and carotenoids, while triacylglycerols was used as an adjustment factor in the expression of vitamin K.
[7] Gender, age, race/ethnicity, education.

At baseline, the clinic cross-section study included 1,042 primarily Caucasian adults (631 females and 411 males), with the majority of participants (82.3%) aged 18 to 54 years. At 1 year, the clinic cross-section study included 931 adults, and the clinic cohort study included 398 subjects. Cohort participants, who were selected to represent the highest consumers of olestra-containing foods, were more likely to be Caucasian and overweight than the year-0 clinic cross-section group from which they were selected. The demographic composition of the cohort

indicated that Caucasian race, female gender, higher education, and being overweight were predictors of early adoption of olestra-containing foods. Twenty-four percent of the clinic cross-section participants reported eating any olestra chips in the month prior to the clinic visit, and 3% reported consuming an average intake of ≥2 g/day.

Olestra intakes were categorized on the basis of daily olestra intake in the previous month: None (0 g/day); Low Intake (>0 to <0.4 g/day, approximately the median intake among users in the year-1 clinic cross-section); Moderate Intake (0.4 to <2.0 g/day, from the median intake up to the 90th percentile of intake among users); Heavy Intake (≥2 g/day, the 90th percentile of intake and higher). Data collected from the year-0 clinic cross-section study were used to develop models predictive of serum nutrient concentrations. All models included age, sex, race, total energy intake (except the model for vitamin K), and dietary plus supplemental intake of the nutrient. Additional variables (such as cholesterol) were added if they were significant at the $P<0.05$ level. Serum nutrient concentrations measured at year-1 were then modeled using the control variables identified from the year-0 data, and then olestra was added to the model to assess its significance in predicting serum nutrient concentrations. For the cohort analyses, models to predict changes in serum nutrient concentrations were developed without regard to olestra. All models included age, sex, race, year-0 serum concentration, year-0 and change in total intake of the nutrient, and year 0 and change in total energy intake, with additional variables added if they were significant.

Of the 931 subjects participating in the year-1 clinic cross-section study, 714 (76.7%) reported not eating any snacks made with olestra in the previous month, while 129 (13.9%), 62 (6.7%), and 26 (2.8%) reported eating >0 to <0.4, ≥0.4 to <2.0, and ≥2.0 g of olestra per day, respectively. There were no significant trends detected between olestra intake and serum nutrient concentration, except for serum vitamin K, which increased significantly with increases in olestra intake ($P=0.03$). α-Carotene was significantly higher at baseline (0.049 µmol/L) as compared with the lowest olestra intake category (0.041 µmol/L) but not significantly different from the highest (0.042 µmol/L) and second-highest (0.047 µmol/L) olestra intake categories. α-Tocopherol was significantly higher in the highest olestra intake group as compared with all the other groups. Although serum levels of retinol and vitamin D were significantly lower in the second-highest olestra intake group, all other olestra intake categories had comparable serum retinol and vitamin D levels. For the most part, there were no identifiable trends among olestra intakes and serum nutrient concentrations.

Thirty-six percent of subjects recruited in the olestra cohort reported eating olestra-containing foods in the month prior to their follow-up clinic visit. Of the 398 subjects participating in the cohort study, 262 (65.8%) reported not eating any snacks made with olestra in the previous month, while 71 (17.8%), 45 (11.3%), and 20 (5.0%) reported eating >0 to <0.4, ≥0.4 to <2.0, and ≥2.0 g of olestra per day, respectively. There were no significant trends detected between olestra intakes and serum nutrient concentrations, except for serum vitamin K, which, as

observed in the clinic cross-section, increased with increases in olestra intake (P=0.06). Changes in serum fat-soluble concentrations in the olestra intake groups were comparable to those measured in subjects who did not consume olestra in the previous month; however, in the highest olestra intake group, reductions in total carotenoids were significantly greater as compared with the group that did not consume olestra (-14.5% *vs.* –4.5%; P<0.05). Although lutein increased significantly in the second-highest olestra intake group as compared with the zero-olestra intake group, this was most likely a chance occurrence. It should be noted that, at the sentinel site, macular pigment optical density was measured during a single clinic visit in 280 subjects (81 of whom reported consuming olestra) participating in the cross-sectional survey (Cooper *et al.,* 2000). There were no significant differences noted between olestra consumers and nonconsumers in macular pigment optical density, thus further supporting the observation that olestra had no clinically meaningful effects on serum levels of lutein and zeaxanthin.

3.0 OLESTRA POST-MARKETING SURVEILLANCE STUDY: RESULTS FROM THE BALTIMORE, MINNEAPOLIS, AND SAN DIEGO SITES

The various research instruments and parameters measured in the OPMSS are summarized in Table 2-1 (Neuhouser *et al.,* 2006). Two thousand five hundred and thirty-five adults (1,561 females and 974 males with a mean age of 44.9 ± 15.6 years) and 272 adolescents (124 females and 148 males with a mean age of 14.7 ± 1.6 years) participated in the study. The majority of subjects were white (75.4% of adults and 61.5% of adolescents), and the distribution of subjects with respect to BMI was as follows: [Adults: 34.4% normal (18.5 to 24.9 kg/m^2), 34.3% overweight (25.0 to 29.9 kg/m^2), and 31.2% obese (≥30.0 kg/m^2); Adolescents: 62.9% normal, 19.3% overweight, and 17.8% obese]. Of the adult subjects, 41.3% were highly educated (at least a college degree), while 31.4% had some college and 27.3% had either a high school diploma or did not complete high school. Recruitment of adult subjects was similar across the 3 research sites (Baltimore, 31.7%; Minneapolis, 33.4%; San Diego, 34.9%), while the Baltimore and Minneapolis sites recruited the majority of adolescents (40.8 and 37.3%, respectively). Among the adults, there were 3,728 observations from 2,535 subjects, and among the adolescents, there were 352 observations from 272 individuals. Results from the cross-sectional and cohort studies were combined, as the proportion of olestra consumers in the cohort was small.

The mean daily olestra consumption at the population level averaged 0.78 ± 1.39 g/day for adults (10th, 50th, and 90th percentiles were 0.06, 0.34, and 1.8 g/day, respectively) and 0.74 ± 1.0 g/day for adolescents (10th, 50th, and 90th percentiles were 0.07, 0.34, and 2.1 g/day, respectively). It is noteworthy that a single 1-ounce (28 g) serving of potato chips made with olestra contains approximately 8 g of olestra. Thus, the mean olestra consumption corresponds

to an intake of approximately two-thirds of a serving of olestra snacks per week, while the 90th percentile intake corresponds to an intake of approximately 2 servings of olestra snacks per week. Olestra consumption was categorized for the multivariate models (0 g/week, <1.3 g/week, 1.3 to 4.4 g/week, and >4.4 g/week for the adults and 0 g/week, <1.25 g/week, 1.25 to 4.8 g/week, and >4.8 g/week for the adolescents.

All linear regression models were adjusted for age, sex, race/ethnicity, clinic site, education, participant enrolment status (cross-sectional or cohort), total energy intake, total intake of the nutrient being modeled (food+supplement), fasting status, and year of blood draw. Models for serum α-tocopherol and carotenoids included serum cholesterol, the model for vitamin K included serum triacylglycerol, and the model for vitamin D included sunlight exposure. Additional variables, including percentage of energy from fat, daily servings of fruits and vegetables, BMI, physical activity, smoking, and alcohol use were permitted in the model if the P value for their parameter estimate was <0.10. Olestra was added to each model to assess its association with each serum nutrient concentration.

In adults, there were no significant associations between olestra intake and serum levels of fat-soluble vitamins (Table 3-1), and the only statistically significant finding was a 3.2% reduction in serum vitamin E in the highest quartile of olestra consumption relative to no consumption. However, there were consistent reductions in serum carotenoid concentrations that were associated with increasing olestra intakes (Table 3-2), with statistically significant trends noted for all carotenoids except (serum lutein+zeaxanthin). The largest percent reduction (22%) was noted for α-carotene. Serum concentrations of α-carotene (in the 1.3 to 4.4 g/week olestra intake quartile) and lycopene and total carotenoids (in the >4.4 g/week olestra intake quartile) were significantly lower as compared with no olestra intake. In adolescents, olestra intake was not associated with changes in serum fat-soluble vitamins (Table 3-3), and although there were modest reductions in serum carotenoid concentrations (Table 3-4), significant trends could not be detected. Whether there was sufficient power to detect significant differences is questionable, given that the number of observations was small (35 to 37). Although BMI was strongly, inversely correlated with all serum nutrient outcome measures, there was no differential association of olestra intake with serum nutrient measures between those who were obese and those who were of normal weight.

Table 3-1 Associations of Olestra Intake with Serum Fat-Soluble Vitamin Concentrations in Free-Living Adults[1]

	Retinol (µmol/L)[2]	25-Hydroxyvitamin D (ng/mL)[3]	α-Tocopherol (µmol/L)[4]	Phylooquinone (nmol/L)[5]
Adjusted concentration before consideration of olestra effect	1.74 ± 0.001	20.8 ± 0.09	31.1 ± 0.16	0.94 ± 0.001
% Change in Concentration Attributable to Olestra[6,7]				
No olestra intake (reference) (n=2963)	___	___	___	___
<1.3 g olestra/wk[8] (n=254)	-1.0 ± 1.0	1.4 ± 1.8	-2.4 ± 1.5	1.0 ± 5.8
1.3–4.4 g olestra/wk (n=258)	-1.0 ± 1.0	-1.0 ± 1.9	<1.0 ± 1.0	1.1 ± 5.7
>4.4 g olestra/week (n=253)	1.6 ± 1.5	2.1 ± 1.8	-3.2 ± 1.5[9]	-8.7 ± 5.8

[1] All values are means ± SEM. All models were adjusted for age, sex, race/ethnicity, clinic site, education, participant enrolment status (cross-sectional or cohort), total energy intake, total intake of the nutrient being modeled (food+supplement), fasting status, and year of blood draw.
[2] Additionally adjusted for percentages of energy from fat and alcohol, dietary supplement use, and season.
[3] Additionally adjusted for sunlight exposure, percentage of energy from fat, BMI, smoking, physical activity, and season.
[4] Additionally adjusted for total serum cholesterol, percentage of energy from fat, smoking, dietary supplement use, physical activity, and season.
[5] Additionally adjusted for serum triacylglycerol, BMI, alcohol use, smoking, and season.
[6] No tests for trends were significant.
[7] *n* values are the number of observations, from a total of 2535 subjects, used in general estimating equations.
[8] 1 oz (28 g) of potato chips made with olestra contains approximately 8 g of olestra.
[9] Significantly different from no olestra intake; P<0.05.

Table 3-2 Associations of Olestra Intake with Serum Carotenoid Concentrations in Free-Living Adults[1]

	α-Carotene[2]	β-Carotene[3]	β-Cryptoxanthin[4]	Lycopene[5]	Lutein + Zeaxanthin[6]	Total carotenoids[7]
Adjusted concentration before consideration of olestra effect (µmol/L)	0.07 ± 0.001	0.29 ± 0.002	0.14 ± 0.001	0.55 ± 0.003	0.32 ± 0.001	1.54 ± 0.006
% Change in Concentration Attributable to Olestra (µmol/L)[8]						
No olestra intake (reference) (n=2963)	___	___	___	___	___	___
<1.3 g olestra/wk[9] (n=254)	-10.1 ± 6.3	-3.6 ± 4.3	1.5 ± 3.5	-1.0 ± 2.6	2.5 ± 2.2	-1.1 ± 2.1
1.3–4.4 g olestra/wk (n=258)	-22.4 ± 6.4[10]	-8.0 ± 4.1	-10.1 ± 3.3	-1.1 ± 3.4	-1.1 ± 2.2	-4.3 ± 2.1
>4.4 g olestra/week (n=253)	-14.1 ± 5.9	-10.1 ± 4.2	-6.5 ± 3.6	-11.8 ± 3.1[10]	-3.8 ± 2.3	-9.7 ± 2.3[10]
P for trend	<0.001	<0.01	<0.01	<0.01	0.21	<0.001

[1] All values are means ± SEM. All models were adjusted for age, sex, race/ethnicity, clinic site, education, participant enrolment status (cross-sectional or cohort), total energy intake, total intake of the nutrient being modeled (food+supplement), fasting status, and year of blood draw.
[2] Additionally adjusted for fruit and vegetable intake, BMI, smoking, dietary supplement use, and season.
[3] Additionally adjusted for fruit and vegetable intake, BMI, smoking, alcohol use, physical activity, and season.
[4] Additionally adjusted for fruit and vegetable intake, BMI, and smoking
[5] Additionally adjusted for percentage of energy from fat, BMI, smoking, alcohol use, and season.
[6] Additionally adjusted for fruit and vegetable intake, BMI, smoking, alcohol use, and season.
[7] Additionally adjusted for fruit and vegetable intake, BMI, smoking, physical activity, and season.
[8] *n* values are the number of observations, from a total of 2535 subjects, used in general estimating equations.
[9] 1 oz (28 g) of potato chips made with olestra contains approximately 8 g of olestra.
[10] Significantly different from no olestra intake; P<0.05.

Table 3-3 Associations of Olestra Intake with Serum Fat-Soluble Vitamin Concentrations in Free-Living Adolescents Aged 12 to 17 Years[1]

	Retinol (µmol/L)[2]	25-Hydroxyvitamin D (ng/mL)[3]	α-Tocopherol (µmol/L)[4]	Phylooquinone (nmol/L)[5]
Adjusted concentration before consideration of olestra effect	1.74 ± 0.01	20.2 ± 0.35	8.7 ± 0.21	0.62 ± 0.009
% Change in Concentration Attributable to Olestra[6,7]				
No olestra intake (reference) (n=244)	___	___	___	___
<1.3 g olestra/wk[8] (n=36)	3.4 ± 5.2	2.0 ± 5.6	2.3 ± 3.3	-15.8 ± 18.1
1.3–4.4 g olestra/wk (n=35)	5.0 ± 3.8	-10.4 ± 6.9	1.0 ± 3.0	1.2 ± 13.8
>4.4 g olestra/week (n=37)	2.6 ± 3.8	4.9 ± 5.8	-6.7 ± 4.5	15.7 ± 14.4

[1] All values are means ± SEM. All models were adjusted for age, sex, race/ethnicity, clinic site, education, participant enrolment status (cross-sectional or cohort), total energy intake, total intake of the nutrient being modeled (food+supplement), and year of blood draw.
[2] Additionally adjusted for smoking and season.
[3] Additionally adjusted for sunlight exposure, percentage of energy from fat, BMI, alcohol use, dietary supplement use, and season.
[4] Additionally adjusted for total serum cholesterol and BMI.
[5] Additionally adjusted for serum triacylglycerol, dietary supplement use, and parental household income.
[6] No tests for trends were significant.
[7] *n* values are the number of observations, from a total of 272 subjects, used in general estimating equations.
[8] 1 oz (28 g) of potato chips made with olestra contains approximately 8 g of olestra.

Table 3-4 Associations of Olestra Intake with Serum Carotenoid Concentrations in Free-Living Adolescents Aged 12 to 17 Years[1]

	α-Carotene2	β-Carotene3	β-Cryptoxanthin4	Lycopene[5]	Lutein + Zeaxanthin[6]	Total carotenoids[7]
Adjusted concentration before consideration of olestra effect (µmol/L)	0.07 ± 0.001	0.29 ± 0.002	0.14 ± 0.001	0.55 ± 0.003	0.32 ± 0.001	1.54 ± 0.006
% Change in Concentration Attributable to Olestra (µmol/L)[8]						
No olestra intake (reference) (n=244)	___	___	___	___	___	___
<1.3 g olestra/wk[9] (n=36)	-10.1 ± 6.3	-3.6 ± 4.3	1.5 ± 3.5	-1.0 ± 2.6	2.5 ± 2.2	-1.1 ± 2.1
1.3–4.4 g olestra/wk (n=35)	-22.4 ± 6.4[10]	-8.0 ± 4.1	-10.1 ± 3.3	-1.1 ± 3.4	-1.1 ± 2.2	-4.3 ± 2.1
>4.4 g olestra/week (n=37)	-14.1 ± 5.9	-10.1 ± 4.2	-6.5 ± 3.6	-11.8 ± 3.1[10]	-3.8 ± 2.3	-9.7 ± 2.3[10]

[1] All values are means ± SEM. All models were adjusted for age, sex, race/ethnicity, clinic site, education, participant enrolment status (cross-sectional or cohort), total energy intake, total intake of the nutrient being modeled (food+supplement), and year of blood draw.
[2] Additionally adjusted for fruit and vegetable intake, BMI, and dietary supplement use.
[3] Additionally adjusted for BMI and alcohol use.
[4] Additionally adjusted for BMI and season.
[5] No additional covariates entered the model.
[6] Additionally adjusted for fruit and vegetable intake, BMI, and parental household income.
[7] Additionally adjusted for fruit and vegetable intake, BMI, alcohol use, and parental household income.
[8] *n* values are the number of observations, from a total of 272 subjects, used in general estimating equations; no tests for trend were significant.
[9] 1 oz (28 g) of potato chips made with olestra contains approximately 8 g of olestra.

4.0 DISCUSSION

The proportion of subjects who reported consuming savory snacks made with olestra in the clinic cross-section and cohort studies at the sentinel site was 24 and 36%, respectively. Similarly, at the other sites involved in the OPMSS, 25.6% of total observations indicated that olestra had been consumed in the month prior to the clinic visit. The clinic cohort study was designed to select, from the clinic cross-section study, those subjects appearing to be the heaviest olestra consumers; however, the majority of subjects in the clinic cohort study had not consumed olestra in the month prior to the clinic visit, and therefore served as controls. In the clinic cross-section and cohort studies, 2.5 and 5.0% of subjects, respectively, reported having consumed ≥2 g of olestra per day at the sentinel site. At the other sites, 8.5% of total observations were associated with an olestra intake ≥2 g/day. The consumption of ≥2 g of olestra per day was considered the 90th percentile consumption.

A single 1-ounce serving of potato chips made with olestra contains approximately 8 g of olestra. The consumption of 2 g/day olestra is equivalent to the consumption of 8, one-ounce bags of potato chips in 1 month, or 2, one-ounce bags per week. Olestra pre-marketing studies estimated that the mean *daily* intake of olestra would be approximately 3.7 g for persons aged 18 to 44 years and 2.5 g for persons aged 45 to 64 years (Webb *et al.,* 1997). The median intake of olestra at the sentinel site was approximately 0.4 g/day, and the mean olestra intake at the other OPMSS sites was approximately 0.75 g/day.

The apparent discrepancies between the actual olestra intakes measured in the OPMSS and the projected olestra intakes estimated prior to the marketing of olestra are expected, given that projected intakes are calculated using highly conservative assumptions. Projections of olestra intake were calculated using the Market Research Corporation of America (MRCA) menu census data, which was conducted annually and captured the 14-day dietary intakes of approximately 5,000 individuals and 2,000 households (Webb *et al.,* 1997). In calculating the estimated daily intakes of olestra, two assumptions were made: i) All savory snacks consumed (*i.e.,* curls, puffs, and extruded snacks; corn chips; tortilla, nacho, and taco chips; potato chips; backed crackers and chips; saltine and oyster crackers; butter- and other flavored snack crackers; and filled and sandwich-type crackers) were made of olestra; and ii) Olestra replaced 100% of the digestible fat in the savory snack. In addition, only subjects who reported eating savory snacks at least once during the 14-day survey were included in the derivation of the estimated daily intake of olestra (so as to not dilute the intake estimates by inclusion of the non-users); and, to be conservative, intake estimates were increased by an additional 10%. During the OPMSS, the only products made with olestra were potato chips (and these were limited to specific brands). Thus, it is not surprising that actual olestra intakes were far lower than projected intakes.

That actual intakes observed during post-marketing surveillance studies are often several-fold lower than pre-marketing projected estimates is a common phenomenon, and has been demonstrated with other ingredients. For example, prior to the U.S. market introduction of aspartame, projections for aspartame intakes for a 60 kg adult ranged from 8.3 mg/kg body weight/day, if aspartame replaced all sucrose in the diet, to 25 mg/kg body weight/day, if aspartame replaced all carbohydrate in the diet (Butchko and Kotsonis, 1991). Actual intakes, which were measured yearly from 1984 to 1989 by the MRCA during the post-marketing surveillance of aspartame, ranged from 1.6 to 2.3 mg/kg body weight/day amongst all ages, and these intakes represented the 90th percentiles. Thus, true average intakes were several-fold less than projected intakes.

Another potential explanation for the low reported intakes of olestra in the OPMSS is that the subjects may have underreported true olestra intakes. Underreporting of actual intakes in observational studies is a recognized problem (Freudenheim, 1993; Prentice, 1996; Willett, 1998; Subar *et al.,* 2003; Novotny *et al.,* 2003). To maintain blinding in the OPMSS, subjects were told that they were participating in a National Nutrition Survey, and not in a study assessing chip consumption. It is well known that subjects tend to report their intakes in a socially desirable way, by eating or reporting less frequently foods considered unhealthful or fattening, like sweets and fried foods (Scagliusi *et al.,* 2003).

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