ORIGINAL SUBMISSION

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

January 20, 2010

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 Olestra Amendment for Additional Food Uses

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 18938 (17 April 1997)], I am submitting in triplicate, as the notifier [The Procter & Gamble Company (P&G), 5299 Spring Grove Ave, Cincinnati, OH 45217], a Notice of the determination, on the basis of scientific procedures, that olestra, produced by P&G, as defined in the enclosed documents, is GRAS under specific conditions of use as a food ingredient in various additional foods, and therefore, is exempt from the premarket approval requirements of the *Federal, Food, Drug and Cosmetic Act*. A previous GRAS notification of olestra for use in pre-packaged ready-to-eat cookies was filed [GRAS Notice No. GRN 000227] upon which FDA had no questions. Information setting forth the basis for the GRAS determination of the amended uses, includes a comprehensive intakes analysis, an updated review of lipid soluble nutrients, and a re-evaluation of the safety data for olestra by an independent panel of experts (the Expert Panel) qualified by scientific training and experience to evaluate the safety of olestra.

I trust that the enclosed Notice is acceptable. An electronic version of this notice is enclosed on the attached CD. Should you have any questions or concerns regarding this GRAS Notice, please do not hesitate to contact me. 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

The Procter & Gamble Company
Ivorydale Technical Center
5299 Spring Grove Ave
Cincinnati, Ohio 45217
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Division of
Biotechnology and
GRAS Notice Review

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Sincerely,

(b) (6)

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

Enclosures

OLESTRA GRAS AMENDMENT NOTIFICATION

Prepared for: Robert L. Martin, Ph.D.
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

Prepared by: The Procter & Gamble Company
Ivorydale Technical Center
5299 Spring Grove Ave.
Cincinnati, Ohio 45217

January 18, 2010

OLESTRA GRAS AMENDMENT NOTIFICATION

Table of Contents

Page

I GRAS EXEMPTION CLAIM 3
- 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)] (U.S. FDA, 1997) 3
- B. Name and Address of Notifier 3
- C. Common Name of the Notified Substance 3
- D. Conditions of Intended Use in Food 4
- E. Basis for the GRAS Determination 5
- F. Availability of Information 6

II. DETAILED INFORMATION REGARDING THE IDENTITY OF THE SUBSTANCE 6
- A. Identity 6
- B. Method of Manufacture 7
- C. Product Specifications 7
- D. Stability of Olestra 7

III. SELF-LIMITING LEVELS OF USE 8

IV. BASIS FOR GRAS DETERMINATION 8
- A. Estimated Intake of Olestra Using CSFII Data 8
  - A.1 Estimated Intake of Olestra Using NHANES Data 13
- B. Overview of Absorption, Distribution, Metabolism, and Excretion (ADME) and Toxicology of Olestra 15
- C. Overview of Nutrition 16
- D. Overview of Post-Marketing Surveillance and Human Experimental Studies of Olestra Intake 20
- E. Carotenoids 23
- F. Lutein and Zeaxanthin 25
- G. Summary 30
- H Conclusion 34

REFERENCES 35

List of Appendices

APPENDIX A EXPERT PANEL CONSENSUS STATEMENT
APPENDIX B INTAKES ASSESSMENT REPORT
APPENDIX C CAROTENOIDS
APPENDIX D PUBLICATION
APPENDIX E LUTEIN AND ZEAXANTHIN

List of Figures and Tables

Figure 1 Structural Representation of Olestra 7
Figure 2 Changes from Baseline in Serum Levels of Lutein and Zeaxanthin Relative to β-Carotene and Lycopene 24
Figure 3 Change from Baseline in Serum Level of Lutein and Zeaxanthin as a Function of Olestra/SPE Intake 29
Figure 4 Increases in Circulating Levels of Lutein and Zeaxanthin with Supplementation 30

Table 1 Summary of the Individual Permitted and Proposed Food-Uses and Levels of Fat Being Replaced by Olestra in the U.S. 9
Table 2 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data) 12
Table 3 Comparison of the Estimated Daily Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII *vs.* 2003-2004, 2005-2006 NHANES Data) 14
Table 4 Distribution of Chip Consumption by Percentile for Subjects in the Olestra Arm of the Movie Theatre Study 22
Table 5 Acute and Chronic Intakes of Olestra from Permitted Uses 23

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)] (U.S. FDA, 1997)

As defined herein, olestra, a sucrose polyester (SPE) that has been developed by The Procter & Gamble Company (P&G) for use as a fat replacement, 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, and on the consensus opinion of an independent panel of experts qualified by scientific training and expertise to evaluate the safety of olestra under the conditions of intended use in food. This is an amendment to a previous GRAS notice for the addition of olestra to cookies. Therefore, the use of P&G's olestra in food as described below is exempt from the requirement of premarket approval (Section 409 of the *Federal Food, Drug and Cosmetic Act*).

Signed,

Robert Enouen
Associate Director - P&G Food Ingredients
The Procter & Gamble Company
11530 Reed Hartman Hwy.
Cincinnati, OH 45241
USA

Date

B. Name and Address of Notifier

Robert Enouen
Associate Director - P&G Food Ingredients
The Procter & Gamble Company
11530 Reed Hartman Hwy.
Cincinnati, OH 45241
USA
enouen.rj@pg.com

C. Common Name of the Notified Substance

Olestra

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)] (U.S. FDA, 1997)

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Signed,

(b) (6)

January 20, 2010

Date

Robert Enouen
Associate Director - P&G Food Ingredients
The Procter & Gamble Company
11530 Reed Hartman Hwy.
Cincinnati, OH 45241
USA

B. Name and Address of Notifier

Robert Enouen
Associate Director - P&G Food Ingredients
The Procter & Gamble Company
11530 Reed Hartman Hwy.
Cincinnati, OH 45241
USA
enouen.rj@pg.com

C. Common Name of the Notified Substance

Olestra

D. Conditions of Intended Use in Food

Olestra is currently permitted for use in pre-packaged ready-to-eat (RTE) savory snacks (*i.e.*, salty or piquant, but not sweet) and pre-packaged ready-to-heat (RTH) unpopped popcorn kernels in place of fats and oils (21 CFR §172.867) (U.S. FDA, 2009). Olestra also is permitted for use in pre-packaged RTE cookies [GRAS No. GRN 000227] (U.S. FDA, 2008). The U.S. Food and Drug Administration (FDA) has issued a letter of no objections following review of the GRAS notification for olestra use in pre-packaged, ready-to-eat cookies.

Olestra is intended for use in the following additional products that are produced only at facilities operating under Good Manufacturing Practice (GMP) and in prepared food products which are intended for sale at retail outlets or vending machines:

- Pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH biscuits and English muffins, pre-packaged RTE & RTH bread, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTH cookies, pre-packaged RTE & RTH cornbread, corn muffins, tortillas and taco shells (hard and soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack type), pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pancakes, crepes, and French toast, pre-packaged RTE & RTH sweet pastries (pastry portion), pre-packaged RTE & RTH sweet pies (pastry portion), pre-packaged RTE & RTH meat and vegetable pies and pastries (pastry portion), pre-packaged RTE & RTH rolls, pre-packaged RTE & RTH sweet rolls and quick breads, and pre-packaged RTE & RTH waffles;

- Natural cheese and processed cheese portion of pre-packaged RTE & RTH prepared foods; NOTE: : “Natural” cheese was included for the purpose of selecting food codes but would not be marketed as “natural” once olestra has been added; it would be marketed as “imitation” or “substitute/alternate” cheese, as per 21 CFR §101.3(e). (U.S. FDA, 2009)

- Pre-packaged RTE frosting and icing;

- Pre-packaged RTE mayonnaise;

- Pre-packaged RTE ice cream, and pre-packaged RTE frozen yogurt;

- Pre-packaged RTE breakfast, granola, and nutritional bars and pre-packaged RTE & RTH pizza crust; and,

- Pre-packaged RTE chocolate confections (chocolate portion).

The maximum proposed use-levels of olestra for the proposed food-uses range from 67 to 100% replacement of added fats. Proposed use-levels of less than 100% will contain blends of

digestible fat (*e.g.*, vegetable oils, shortenings, *etc.*) and olestra. These blends were developed by P&G to provide more palatable products and/or to meet other technical properties of the food matrices.

Products intended for olestra use will solely consist of pre-packaged RTE or RTH foods that will be produced at food manufacturing and packaging establishments operating under GMP. Olestra-containing foods are intended to be sold at retail outlets and vending machines. Olestra will not be distributed for use as a food ingredient to facilities that do not have the capability to produce and package foods according to GMP such as restaurants, cafeterias, or other such facilities. Olestra will not be sold as a food ingredient to food service establishments (even if they operate according to GMP), as the end use is not in pre-packaged form (*i.e.,* such foods are typically sold in eateries, in an unpackaged, ready-to-eat form). This will ensure that the required vitamin restoration levels are met during manufacture of the food, and that all olestra-containing foods will be sold with an ingredients list which clearly indicates the presence of olestra in the food.

Olestra is not intended for use in, and will not be sold for the manufacture of foods that are specifically produced for infants or toddlers. Also, olestra will not be used to replace the fat in milk with the exception of the use of olestra to replace the butter fat in ice cream, frozen yogurt, and the natural and processed cheese used in the production of pre-packaged, RTE and RTH prepared foods. Although natural and processed cheeses are proposed for olestra use, they are proposed only for use in the cheese portion of pre-packaged RTE and RTH prepared foods.

E. Basis for the GRAS Determination

Pursuant to 21 CFR §170.30, olestra has been determined by P&G to be GRAS on the basis of scientific procedures (U.S. FDA, 2009). This GRAS determination is based on data generally available in the public domain pertaining to the safety of olestra for use in food, as discussed herein and in the accompanying documents, and on a consensus among a panel of experts[1] who are qualified by scientific training and experience, who reconvened to evaluate the safety of olestra as a component of food for amended uses. The consensus statement is provided in **Appendix A**.

---

[1] The Panel consisted of the below-signed qualified scientific experts: Dr. G. Harvey Anderson, Ph.D. (Department of Nutritional Sciences, University of Toronto); Dr. Joanne Curran-Celentano, Ph.D. (University of New Hampshire; new Panel member, added based on specific expertise in lutein and zeaxanthin); 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. (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)A copy of the Expert Panel summary is located in appendix A and is titled "EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OLESTRA FOR USE IN VARIOUS PRE-PACKAGED, READY-TO-EAT, AND READY-TO-HEAT FOODS: AN AMENDMENT TO THE GRAS DETERMINATION OF OLESTRA FOR USE IN PRE PACKAGED READY-TO-EAT COOKIES".

F. Availability of Information

Data and information that serve as the basis for this GRAS Notice will be sent to the FDA upon request to:

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

Should the FDA have any questions or additional information requests regarding this Notice, The Procter & Gamble Company, will supply these data and information.

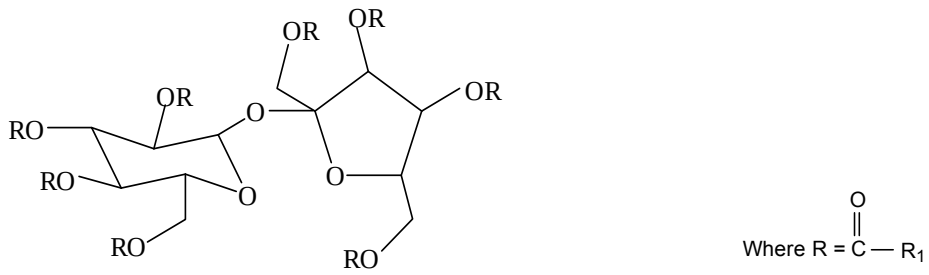
II. DETAILED INFORMATION REGARDING THE IDENTITY OF THE SUBSTANCE

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
Trade Name:	Olean
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_{16} to C_{22}

B. Method of Manufacture

The method of manufacture was detailed in the previous GRAS Notice [GRAS No. GRN 000227] and there have been no changes to this method (U.S. FDA, 2008).

C. Product Specifications

Product specifications for Olestra are published in the Food Chemicals Codex (FCC, 2008).[2] There have been no changes to the specification since the previous GRAS Notice [GRAS No. GRN 000227] (U.S. FDA, 2008).

D. Stability of Olestra

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. The stability of olestra was discussed in detail in the previous GRAS Notice [GRAS No. GRN 000227] (U.S. FDA, 2008).

As a condition of use, foods containing olestra must meet the requirement that vitamins A, D, E, and K be added to the olestra-containing foods at concentrations that meet the conditions specified in 21 CFR §172.867(d) (U.S. FDA, 2009).

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[2] FCC. 2008. Olestra. In: Food Chemicals Codex (6th Ed.). United States Pharmacopeial Convention (USP); Rockville, Maryland, pp. 703-705.

III. SELF-LIMITING LEVELS OF USE

Use of olestra as a fat replacement in pre-packaged, ready-to-eat/ready-to-heat foods will be limited by the added fat content of the food.

IV. BASIS FOR GRAS DETERMINATION

A. Estimated Intake of Olestra Using CSFII Data

An expanded discussion of the proposed uses of olestra, proposed levels of use, the methodology followed to estimate intakes of olestra, and the results are provided in **Appendix B** (Estimated Daily Intake of Olestra by the U.S. Population from Permitted and Proposed Food-Uses) to of this notice. The results of the intakes assessment are summarized, briefly, below while a detailed description is provided in **Appendix B**.

Olestra is a replacement for conventional fats, and products using olestra are intended to be "low-fat", "reduced-fat", or "fat-free". Olestra is currently permitted for use in pre-packaged RTE savory snacks (*i.e.*, salty or piquant, but not sweet) and pre-packaged RTH unpopped popcorn kernels in place of fats and oils (21 CFR §172.867) (U.S. FDA, 2009). Olestra also is permitted for use in pre-packaged RTE cookies. FDA has issued a letter of no objections following review of the GRAS notification for olestra use in pre-packaged, ready-to-eat cookies.

Olestra is currently proposed for use in the following products that are produced only at facilities operating under GMP and in prepared food products which are intended for sale at retail outlets or vending machines:

- Pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH biscuits and English muffins, pre-packaged RTE & RTH bread, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTH cookies, pre-packaged RTE & RTH cornbread, corn muffins, tortillas and taco shells (hard and soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack type), pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pancakes, crepes, and French toast, pre-packaged RTE & RTH sweet pastries (pastry portion), pre-packaged RTE & RTH sweet pies (pastry portion), pre-packaged RTE & RTH meat and vegetable pies and pastries (pastry portion), pre-packaged RTE & RTH rolls, pre-packaged RTE & RTH sweet rolls and quick breads, and pre-packaged RTE & RTH waffles;

- Natural cheese[3] and processed cheese portion of pre-packaged RTE & RTH prepared foods;
- Pre-packaged RTE frosting and icing;
- Pre-packaged RTE mayonnaise;
- Pre-packaged RTE ice cream, and pre-packaged RTE frozen yogurt;
- Pre-packaged RTE breakfast, granola, and nutritional bars and pre-packaged RTE & RTH pizza crust; and,
- Pre-packaged RTE chocolate confections (chocolate portion).

The maximum proposed use-levels of olestra for the proposed food-uses range from 67 to 100% replacement of added fats. Proposed use-levels of less than 100% will contain blends of digestible fat (*e.g.*, vegetable oils, shortenings, *etc.*) and olestra. These blends were developed by P&G to provide more palatable products and/or to meet other technical properties of the food matrices. The fat replacement strategy employed in the assessment of the intake of olestra, and the maximum proposed level of fat replacement based on technical and recipe data from all currently approved and proposed food uses is detailed in Table 1.

Table 1 Summary of the Individual Permitted and Proposed Food-Uses and Levels of Fat Being Replaced by Olestra in the U.S.

Food Category	Food-Uses[a]	Fat Replaced	Maximum Levels of Fat Replacement (%)
Permitted Uses			
Baked Goods and Baking Mixes	Pre-packaged RTE[b] Cookies	Total[c]	100
Snack Foods	Pre-packaged RTH[b] Unpopped Popcorn	Total[c]	100
	Pre-packaged RTE Savory Snacks	Total[c]	100
Proposed Uses			
Baked Goods and Baking Mixes	Pre-packaged RTE & RTH Bagels	Shortening[c]	75
	Pre-packaged RTE & RTH Biscuits and English Muffins	Shortening[d]	75
	Pre-packaged RTE & RTH Bread	Shortening[d]	75
	Pre-packaged RTE & RTH Bread Sticks (hard)	Shortening[d]	75
	Pre-packaged RTE & RTH Bread Sticks (soft)	Shortening[d]	75
	Pre-packaged RTE & RTH Cakes	Shortening[d]	75
	Pre-packaged RTH Cookies	Shortening[d]	75
	Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	Shortening[d]	75
	Pre-packaged RTE & RTH Croissants	Shortening[d]	75

[3] Note: "Natural" cheese was included for the purpose of selecting food codes but would not be marketed as "natural" once olestra has been added; it would be marketed as "imitation" or "substitute/alternate" cheese, as per 21 CFR §101.3(e)

Table 1 Summary of the Individual Permitted and Proposed Food-Uses and Levels of Fat Being Replaced by Olestra in the U.S.

Food Category	Food-Uses[a]	Fat Replaced	Maximum Levels of Fat Replacement (%)
	Pre-packaged RTE & RTH Crackers (not snack type)	Shortening[d]	75
	Pre-packaged RTE & RTH Doughnuts	Frying Oil[c,d,e]	100
	Pre-packaged RTE & RTH Muffins	Shortening[d]	75
	Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	Shortening[d]	75
	Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	Shortening[d]	75
	Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	Shortening[d]	75
	Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	Shortening[d]	75
	Pre-packaged RTE & RTH Rolls	Shortening[d]	75
	Pre-packaged RTE & RTH Sweet Rolls and Quick Breads	Shortening[d]	75
	Pre-packaged RTE & RTH Waffles	Shortening[d]	75
Cheeses	Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	Butter Fat[c]	67
	Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	Butter Fat[c]	67
Confections and Frostings	Pre-packaged RTE Frosting and Icing	Shortening[c]	100
Fats and Oil	Pre-packaged RTE Mayonnaise	Soybean Oil[c]	67
Frozen Dairy Desserts and Mixes	Pre-packaged RTE Ice Cream	Butter Fat[d]	67
	Pre-packaged RTE Frozen Yogurt	Butter Fat[c]	67
Grain Products and Pastas	Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	Shortening[d]	75
	Pre-packaged RTE & RTH Pizza Crust	Shortening[d]	75
Soft Candy	Pre-packaged RTE Chocolate Confections (chocolate portion)	Cocoa Butter	100

[a] Products intended for olestra use can be produced only at GMP-compliant manufacturing and packaging facilities (where it would be possible to meet vitamin restoration requirements) and subsequently sold at retail outlets or vending machines. Olestra will not be distributed for use as a food ingredient to facilities that do not have the capacity to produce and package foods according to GMP such as restaurants, cafeterias, or other such facilities. Infant and toddler foods are not intended for olestra use.
[b] RTE = Ready-to-Eat; RTH = Ready-to-Heat
[c] Fat content was determined from the USDA National Nutrient Database for Standard Reference, Release 17.
[d] The standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000) was used to find the specific contribution of fat from shortening, oil, margarine, or butter fat.
[e] Calculation of fat from frying oil:
Fat from frying oil = (total doughnut fat content) - [shortening portion + (milk portion x average fat content) + (egg portion x average fat content)];
Total doughnut fat content and fat content of milk and eggs were determined from the USDA National Nutrient Database for Standard Reference, Release 17. The proportions of doughnut that are shortening, milk, or egg were determined from the standard recipe file for the CSFII 1994-1996, 1998 survey.

Products intended for olestra use will solely consist of pre-packaged RTE or RTH foods that will be produced at food manufacturing and packaging establishments operating under GMP. Olestra-containing foods are intended to be sold at retail outlets and vending machines. Olestra will not be distributed for use as a food ingredient to facilities that do not have the capability to produce and package foods according to GMP such as restaurants, cafeterias, or other such facilities. Olestra will not be sold as a food ingredient to food service establishments (even if they operate according to GMP), as the end use is not in pre-packaged form (*i.e.,* such foods are typically sold in eateries, in an unpackaged, ready-to-eat form). This will ensure that the required vitamin restoration levels are met during manufacture of the food, and that all olestra-containing foods will be sold with an ingredients list which clearly indicates the presence of olestra in the food.

Olestra is not intended for use in, and will not be sold for the manufacture of foods that are specifically produced for infants or toddlers. Also, olestra will not be used to replace the fat in milk with the exception of the use of olestra to replace the butter fat in ice cream, frozen yogurt, and the natural and processed cheese used in the production of pre-packaged, RTE and RTH prepared foods. Although natural and processed cheeses are proposed for olestra use, they are proposed only for use in the cheese portion of pre-packaged RTE and RTH prepared foods.

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 1998) (USDA, 2000).

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 (USDA, 2000). Individual consumption data were collated by computer and the resulting distributions were analyzed statistically. All-person intake estimates refer 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 estimates refer 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 intake estimates, and percent consuming were performed for various age and population groups. To reflect the conditions of sale for all products containing olestra, these being for sale at retail outlets or vending machines only, the food source code was employed to appropriately modify the CSFII databases. Only foods available for purchase packaged in their final form from retail locations or vending machines, as well as those foods with unknown food sources, were included in the intake analysis.

The estimated intakes of olestra on a per day basis for permitted and proposed uses are summarized in Table 2. In summary, on an all-user basis, the estimated mean and 90th percentile intakes of olestra from the consumption of all permitted and proposed food-uses

combined by the total U.S. population were estimated to be 4.6 g/person/day and 10.6 g/person/day, respectively. These intake estimates are greater than the estimated all-user mean and 90th percentile intakes of olestra by the total population resulting from the consumption of permitted uses, of 3.1 g/person/day and 7.7 g/person/day, respectively.

On an individual population basis, the greatest absolute mean all-user estimate for the intake of olestra from permitted and proposed uses occurred in male teenagers (6.2 g/person/day); the greatest 90th percentile all-user intake estimate for olestra occurred in male adults, aged 31 to 50 years (13.7 g/person/day). These intakes are still well within the range of olestra levels administered in the various human experimental studies.

Table 2 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)*

Age Group	% Users	Actual # of Users	All-Person Consumption (g)		All-Users Consumption (g)	
			Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 Months	14.2	138	0.1	0.3	1.0	2.1
7 to 11 Months	28.6	107	0.2	0.6	0.7	1.6
Toddlers and Children						
1 to 3 Years	89.2	3,436	2.2	5.2	2.5	5.7
4 to 8 Years	93.2	3,508	3.6	8.2	3.9	8.5
9 to 13 Years	92.1	1,055	4.4	9.5	4.7	10.0
Female Teenagers and Adults						
14 to 18 Years	85.7	378	3.7	8.9	4.3	9.6
19 to 30 Years	83.5	685	3.4	8.9	4.1	10.0
31 to 50 Years	89.5	1,471	4.0	9.7	4.4	10.4
51 to 70 Years	90.2	1,385	3.7	9.1	4.1	9.3
71 and Older	90.6	561	3.6	8.4	3.9	8.8
Male Teenagers and Adults						
14 to 18 Years	89.4	397	5.6	13.0	6.2	13.4
19 to 30 Years	83.9	706	4.4	10.8	5.3	12.2
31 to 50 Years	89.2	1,496	5.1	12.8	5.7	13.7
51 to 70 Years	90.4	1,445	4.7	11.0	5.2	11.6
71 and Older	91.2	612	4.6	11.2	5.0	11.3
Total Population						
Total Population	85.2	17,380	4.1	10.1	4.6	10.6

* Intake model refined to only include pre-packaged RTE and/or RTH olestra-containing products purchased at retail outlets or vending machines.

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 including:

- Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently (Anderson, 1988; Lambe and Kearney, 1999);
- The assumption that *all* food products within a food category will contain the ingredient at the *maximum* specified level of use;
- Where the food source was unknown it was assumed that the source was a store or a vending machine and so these food codes were included;
- The assumption that all foods in a food category are *pre-packaged*, even if there was uncertainty that the food was pre-packaged; and
- Where limited data on fat-modified foods were available, regular fat food codes were used in intake estimates, thereby inflating the percentage of the U.S. population who may be users of olestra. Also, amongst population groups that do not typically consume large quantities of fat modified or reduced fat foods, such as infants or young children, the use of regular fat foods as surrogates in the model may greatly over-estimate olestra intakes.

A.1 Estimated Intake of Olestra Using NHANES Data

Since the original undertaking of the original Olestra intake assessment employing the CSFII data, two cycles of the National Health and Nutrition Examination Survey (NHANES) have been released. An update of the original intake assessment was conducted with the NHANES data, using the same proposed food uses, food sources, and population groups, to ensure that changing patterns of consumption would not have significantly altered the estimated intakes derived with the CSFII data. A comparison of the number of identified users and the estimated all-user intakes on an absolute basis is presented in Table 3. A full description of the intake assessment is provided in **Appendix B**.

Table 3 Comparison of the Estimated Daily Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII *vs.* 2003-2004, 2005-2006 NHANES Data)

Population Group	% Users		All-User Consumption (g/day)			
			Mean		90th Percentile	
	CSFII	NHANES	CSFII	NHANES	CSFII	NHANES
Infants						
0 to 6 Months	14.2	15.6	1.0	0.8	2.1	1.8
7 to 11 Months	28.6	60.5	0.7	0.8	1.6	1.8
Toddlers and Children						
1 to 3 Years	89.2	89.7	2.5	2.5	5.7	5.4
4 to 8 Years	93.2	93.4	3.9	4.2	8.5	9.4
9 to 13 Years	92.1	92.1	4.7	5.5	10.0	12.3
Female Teenagers and Adults						
14 to 18 Years	85.7	88.0	4.3	5.2	9.6	11.5
19 to 30 Years	83.5	89.5	4.1	4.7	10.0	11.0
31 to 50 Years	89.5	90.6	4.4	4.8	10.4	10.9
51 to 70 Years	90.2	92.7	4.1	4.6	9.3	10.9
71 and older	90.6	93.8	3.9	4.1	8.8	9.5
Male Teenagers and Adults						
14 to 18 Years	89.4	87.9	6.2	7.0	13.4	16.2
19 to 30 Years	83.9	85.9	5.3	6.0	12.2	16.0
31 to 50 Years	89.2	91.0	5.7	5.9	13.7	13.7
51 to 70 Years	90.4	93.9	5.2	6.4	11.6	14.5
71 and older	91.2	95.6	5.0	5.7	11.3	12.5
Total Population						
Total Population	85.2	87.5	4.6	5.2	10.6	11.9

After comparing the intake estimates derived from the NHANES data to those derived from the CSFII it was evident that the rates of consumption are similar between the 2 surveys while levels of intake increased. This increase was most notable in male teenagers and adults, where the 90th percentile all-user intake estimates increased between 1.24 to 3.75 g/person/day, with a maximum relative increase of 30%. Within the total population the mean and 90th percentile all-user estimates for the intake of olestra increased from 4.6 and 10.6 g/person/day, respectively, to 5.15 and 11.87 g/person/day, respectively, a relative increase of 12% in both cases. Within the infant population groups, the intake of olestra remained relatively constant between the 2 surveys which would be expected as the olestra is not intended for use in infant foods or formula. Within the older population group of infants, those aged 7 to 11 months, the intake remained stable while the percentage of the population identified as potential users increase from 28.7 to 60.7%. The absolute numbers of likely consumers of olestra within this

population group identified in both surveys were similar, equivalent to 107 and 89 individuals in the CSFII and NHANES data sets, respectively.

B. Overview of Absorption, Distribution, Metabolism, and Excretion (ADME) and Toxicology of Olestra

No new metabolism or toxicology studies were identified since the previous olestra GRAS Notice [GRAS No. GRN 000227] (U.S. FDA, 2008). A comprehensive dossier which summarized the absorption, distribution, metabolism, and excretion (ADME) studies and toxicology studies, entitled "Summary of Data Concerning the Safety of Olestra for Use in Pre-Packaged Ready-to-Eat Cookies" was submitted with the previous notice.

In summary, 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 5 or fewer fatty acids (penta- or lower sucrose ester), which accounts for a very low percentage (less 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 these smaller sucrose esters (*i.e*., fatty acids, glucose, and fructose) are subsequently absorbed and processed through common metabolic pathways.

Numerous toxicology studies were conducted on olestra and olestra-like sucrose polyester (SPE) formulations to support the application of olestra for addition to savory snacks.[4] 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*., 1991; Lafranconi *et al*., 1994) to estimates of human consumption, indicates that intake of olestra at

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[4] Olestra differs from other SPE formulations in that it has a thixotropy of ≥50 kPa/s (see Olestra specifications; FCC, 2008), which results in an olestra formulation that is semi-solid, as opposed to liquid, at body temperature. Thixotropy, which is a rheological measure of stiffness, was included in the olestra specifications as later studies indicated that the incidence of anal leakage was significantly attenuated with SPE formulations that had a minimum thixotropy of 50 kPa/s.

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 days (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.

In conclusion, olestra is not absorbed, and has been shown to be non-toxic, non-mutagenic, non-carcinogenic and non-teratogenic. As olestra is not absorbed from the GI tract, there is no greater systemic exposure resulting from the proposed new uses. Furthermore, estimated intakes remain within dose ranges determined to be without adverse effects in toxicology and nutrition studies

C. Overview of Nutrition

No new nutrition studies were identified since the previous olestra GRAS Notice [GRAS No. GRN 000227] (U.S. FDA, 2008). A comprehensive dossier which summarized the nutrition studies, entitled “Summary of Data Concerning the Safety of Olestra for Use in Pre-Packaged Ready-to-Eat Cookies” was submitted with the notice.

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 cholecystokinin

(CCK) and peptide YY[5]. 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 conducted with

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[5] Peptide YY is a short protein that reduces appetite. It is released by cells in the ileum and colon in response to feeding.

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}C-carbon dioxide, ^{14}C-methane, ^{14}C-short-chain fatty acids and ^{14}C-long chain fatty acids) were detected. The effects of olestra on several microbiota-associated characteristics (MACs)[6] 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 short chain fatty acids (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, 2008a). Results from the Olestra Post-Marketing Surveillance Study (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,

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[6] MACs are properties of the indigenous colonic flora and include 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 (hydrogen, methane and carbon dioxide).

2008a). 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, 2008a). Vitamins A, D, E, and K have been added]. The 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. The safety of olestra 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 studies indicated that the incidence of anal leakage was significantly attenuated with SPE formulations that had a minimum thixotropy of 50 kPa/s. These SPE formulations remained semi-solid at body temperature. Thus, a minimum thixotropy of 50 kPa/s was included in the olestra specifications, and studies conducted with olestra formulations meeting the thixoptropy specification confirmed that the problem of anal leakage with the earlier formulations had been resolved.

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 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 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.

D. Overview of Post-Marketing Surveillance and Human Experimental Studies of Olestra Intake

No new human or clinical studies were identified since the previous olestra GRAS Notice [GRAS No. GRN 000227] (U.S. FDA, 2008). A comprehensive dossier which summarized the nutrition studies, entitled "Summary of Data Concerning the Safety of Olestra for Use in Pre-Packaged Ready-to-Eat Cookies" was submitted with the notice.

Briefly, 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.*, 1997, 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).

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 the Market Research Corporation of America (MRCA) from 4,741 individuals from approximately 2,000 households during 1991-1992 (Webb *et al*., 1997). This study found that on average, 69% of savory snack eating occasions were with main meals, while the remainder were consumed as in-between meal snacks. Furthermore, savory snacks were not found to be

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 FDA, approval of olestra for use in savory snacks. The Olestra Post-Marketing Surveillance Study included 2,535 adults and 272 adolescents (aged 12 to 17 years). Study participants were required to complete a 16-item savory snack questionnaire (Neuhouser *et al.,* 2000), which 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] during the previous month. Among users-only, the mean chronic olestra intake for adults and adolescents was 0.78 and 0.74 g/day, respectively, while the 90th percentile chronic intake was 1.8 and 2.1 g/day, respectively (Neuhouser *et al*., 2006).

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 or olestra chips and asked to consume as much (or as little) as they wanted 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); however, some of the subjects consumed in excess of 100 g of olestra as indicated in the following table.

Table 4 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%

The Household Chip Consumption Study was a randomized, double-blind, placebo-controlled study involving 3181 volunteers ages 2 to 89 years. Subjects were provided with unlimited free 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 only 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 (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, and at the 90th percentile, 35 days out of a possible of 42 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 gastrointestinal symptoms. The results of these studies, 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 the following table.

In conclusion, these studies demonstrate that consumption of foods made with olestra does not result in effects that differ from consumption of foods containing triglycerides.

Table 5 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)

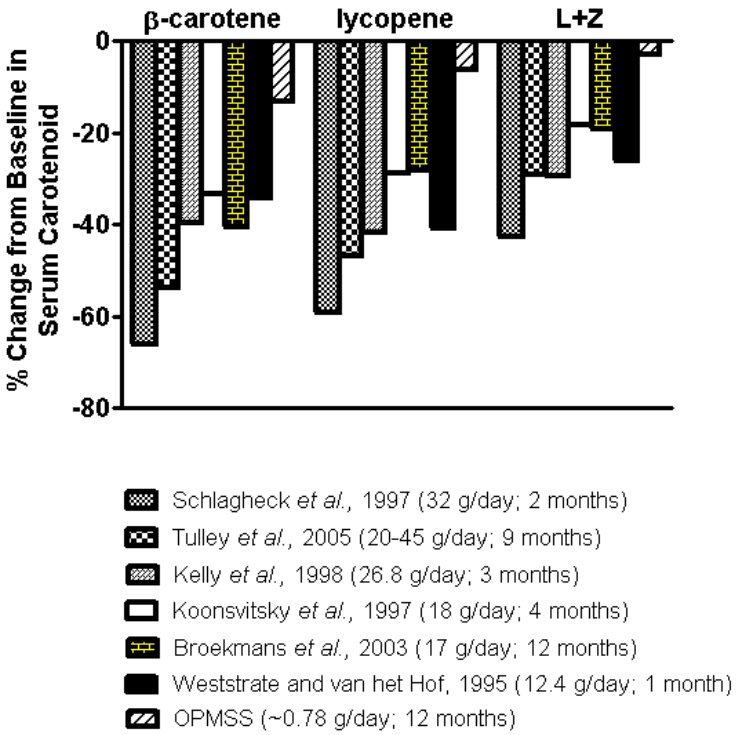
Abbreviations: MRCA, Market Research Corporation of America; OPMSS, Olestra Post-marketing Surveillance Study; USDA CSFII, United States Department of Agriculture Continuing Survey of Food Intakes by Individuals.

E. Carotenoids

Consumption of olestra results in dose-dependent reductions, from baseline, in serum carotenoid levels (Figure 2). Despite reductions in serum carotenoid levels, no apparent ill health effects have been reported in any of the olestra studies. In the longest intervention trial, which was 1 year in duration and included 380 subjects, the consumption of up to 17 g/day olestra+ SPE was not associated with adverse effects on markers of oxidative stress, cardiovascular health, immune status, macular pigment optical density (MPOD), or eye health, despite reductions, from baseline, in serum carotenoid levels of 13 to 33% (Broekmans *et al.,* 2003). Despite these findings, the Panel considered the possibility that reductions in carotenoid levels chronically over one's lifetime may be associated with adverse health effects that would not be captured in a 1-year study. Thus, additional information on the physiological roles of carotenoids was reviewed by the Panel. This additional information included position statements of scientific and regulatory organizations, and relevant scientific studies published in

or subsequent to 2003. Approximately 75 studies were identified of which several looked at associations with more than one carotenoid.

Figure 2 **Changes from Baseline in Serum Levels of Lutein and Zeaxanthin Relative to β-Carotene and Lycopene**



Data points are based on the highest intakes of olestra in each study. Results from Schlagheck *et al.* (1997a,b) at an olestra intake of 32 g/day were averaged; likewise, results from the highest intake levels in the OPMSS (Thornquist *et al.,* 2000; Neuhouser *et al.,* 2006) were averaged. Lutein and zeaxanthin serum levels were reported separately in Weststrate and van het Hof (1995), Broekmans *et al.* (2003), and Thornquist *et al.* (2000), but were combined in the figure above. Where baseline levels were not reported, control levels were used as surrogates.
Abbreviations: L+Z, lutein+zeaxanthin; OPMSS, Olestra Post-Marketing Surveillance Study.

There is strong consensus amongst regulatory and scientific organizations that a diet rich in fruits and vegetables may be beneficial in reducing the risk of cardiovascular disease and cancer; nevertheless, regulatory and scientific organizations cautioned against the use of supplemental forms of carotenoids, stating that it is not possible to discern whether the observed beneficial effects are due to carotenoids, other nutrients in fruits and vegetables, lifestyle factors associated with consumption of fruits and vegetables, a combination of these, or other factors altogether (WHO/IARC, 1998; IOM, 2000; Kushi *et al.*, 2006; WCRF/AICR, 2007). There is no consensus from human observational studies that carotenoids are associated with reduced risk of cancer or cardiovascular disease. The limited numbers of studies reporting significant inverse associations between dietary intakes or circulating levels of β-carotene,

lycopene, β-cryptoxanthin, or α-carotene and risk of cardiovascular disease (CVD) or cancer were case-control. Due to the retrospective nature of case-control studies, they are subject to recall bias and reported associations are generally biased away from the null.

Observational studies are associated with several limitations, and are generally not sufficient for demonstrating causality, particularly when the subject of the claimed effect is a specific nutrient or food constituent as opposed to a category of foods or a food group. No intervention trials assessing the effects of either α-carotene or β-cryptoxanthin on cancer risk were identified. Intervention trials assessing risk of cancer or cardiovascular disease following supplementation with either β-carotene or lycopene did not support attenuations in disease risk. Thus, data from recently published human intervention studies, as well as position statements from authoritative bodies, including the FDA, World Health Organization, American Institute for Cancer Research, and American Cancer Society do not support physiological roles for the carotenoids, outside of the potential importance of the provitamin-A carotenoids (β-carotene, α-carotene, and β-cryptoxanthin) in reducing risk of vitamin A deficiency. Sufficient levels of pre-formed vitamin A are added to olestra, as per 21 CFR §172.867(d), to off-set effects of olestra on vitamin A levels.

The full scientific assessment on carotenoids can be found in **Appendix C**. The results of the scientific assessment on carotenoids were recently accepted for publication in Nutrition Reviews (Musa-Veloso *et al.,* 2009). A reprint of the publication is provided in **Appendix D**.

F. Lutein and Zeaxanthin

It has been demonstrated in non-human primates that the long-term feeding of an xanthophyll-free semi-purified diet results in undetectable levels of xanthophylls in plasma, a loss in yellow pigmentation of the macula, and the development of drusen in the retina, which is an early sign of age-related macular degeneration in humans (Malinow *et al.,* 1980); although, no gross visual disturbances were associated with this long-term diet. Similar observations have been reported in humans on long-term total parenteral nutrition (TPN) (Vinton *et al.,* 1990; Porter *et al.,* 2005), though associated vitamin deficiencies and co-morbidities preclude attribution of these effects to any single nutrient. Lutein and zeaxanthin, collectively referred to as macular pigments, have been hypothesized to play important roles in the maintenance of eye function and in reducing the risks of age-related cataract formation and macular degeneration, based on the following 3 observations:

1. Lutein and zeaxanthin are present in the lens and unlike other carotenoids, are selectively concentrated in the macula of the eye;

2. Lutein and zeaxanthin have an absorbance spectrum which permits filtration of phototoxic blue light; and

3. Lutein and zeaxanthin have antioxidant activity and thus might protect visual tissue from free radical damage and lipid oxidation of the polyunsaturated-rich environment.

Human observational and intervention studies determined to have high methodological quality, as assessed using a quality appraisal tool[7], were critically reviewed to determine whether there are scientific data to support the proposed role of lutein/zeaxanthin in supporting eye health. Three primary endpoints were evaluated separately, including age-related cataract, age-related maculopathy/age-related macular degeneration (ARM/ARMD), and outcomes related to visual performance. The full scientific assessments and detailed descriptions of the methodology can be found in **Appendix E**.

Cataract

The full scientific assessment and a detailed description of the methodology can be found in **Appendix E**.

Of the 9 studies assessing the relationship between dietary intakes of lutein+zeaxanthin and risk of cataract, 7 (77.8%) reported a significant reduction in risk of cataract with increased intake of lutein+zeaxanthin (Brown *et al.,* 1999; Chasan-Taber *et al.,* 1999; Lyle *et al.,* 1999b; Jacques *et al.,* 2001; Vu *et al.,* 2006; Christen *et al.,* 2008; Moeller *et al.,* 2008) and 2 (22.2%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of cataract (Valero *et al.,* 2002; Jacques *et al.,* 2005). Of the 6 studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of cataract, 4 (66.7%) reported a significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin (Gale *et al.,* 2001; Delcourt *et al.,* 2006; Dherani *et al.,* 2008; Moeller *et al.,* 2008) and 2 (33.3%) reported no significant associations between circulating levels of lutein and/or zeaxanthin and risk of cataract (Mares-Perlman *et al.,* 1995; Lyle *et al.,* 1999a).

Data from human observational studies support an association between lutein and zeaxanthin status (dietary intake or circulating levels) and a reduced risk of cataract formation/extraction; however, it could not be established from the observational studies that reductions in cataract risk were due specifically to lutein and zeaxanthin and not to some other nutrient or non-nutrient covariates. Moreover, the biological plausibility for an effect of lutein and zeaxanthin in mitigating risk of cataract formation is weak as although lutein and zeaxanthin are present in the lens, they are not concentrated in the lens as they are in the macula. It is noteworthy that in all studies reporting a decreased risk of cataract with increased intakes of lutein+zeaxanthin, relationships were *always* attenuated and no longer significant when other nutritional covariates (such as vitamin C, vitamin E, and β-carotene) were examined simultaneously with

[7] The quality appraisal tool was developed prior to the review of the study findings, and included criteria relevant to study design and control of potential confounding variables. Two raters independently evaluated the quality of each study. Studies were assigned a quality score based on the number of items accounted for. The critical review was based only on studies with high methodological quality, defined as a score of ≥60%.

lutein+zeaxanthin. These observations suggest that lutein+zeaxanthin are correlated with other nutritional variables that may mitigate risk of cataract, either independently of lutein and zeaxanthin, or in association with lutein and zeaxanthin.

ARM/ARMD

The full scientific assessment and a detailed description of the methodology can be found in **Appendix E**.

Of the 10 observational studies assessing risk of ARM/ARMD as a function of dietary intakes of lutein+zeaxanthin, 5 (50.0%) reported a significant reduction in risk of ARM/ARMD with increased intake of lutein+zeaxanthin (Seddon *et al.,* 1994; Mares-Perlman *et al.,* 2001; Moeller *et al.,* 2006; SanGiovanni *et al.,* 2007; Tan *et al.,* 2008), while 5 (50.0%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD (Mares-Perlman *et al.,* 1996; VandenLangenberg *et al.,* 1998; Cho *et al.,* 2004; van Leeuwen *et al.,* 2005; Morris *et al.,* 2007). Of the 8 observational studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD, 2 (25.0%) reported a significant reduction in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin (Gale *et al.,* 2003; Delcourt *et al.,* 2006) and 6 (75.0%) reported no significant associations between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD (Mares-Perlman *et al.,* 1995; Mares-Perlman *et al.,* 2001; Simonelli *et al.,* 2002; Cardinault *et al.,* 2005; Dasch *et al.,* 2005; Moeller *et al.,* 2006).

Evidence from human observational studies does not support a relationship between lutein and/or zeaxanthin (dietary intake, circulating levels, or macular pigment optical density) and risk of ARM/ARMD.

Visual Performance

The full scientific assessment and a detailed description of the methodology can be found in **Appendix E**.

The majority of human experimental studies assessing the effects of lutein and zeaxanthin on visual performance were found to be of low methodological quality (*i.e.,* these were exploratory in nature and of limited size, analogous to “pilot” studies). One human experimental study [the Veterans Lutein Antioxidant Supplementation Trial (LAST); Richer *et al.,* 2004] was determined to have acceptable methodological quality. Supplementation with 10 mg/day lutein for 1 year resulted in significant improvements in near visual acuity in the left eye. Other endpoints assessed in the study, including distance visual acuity, contrast sensitivity, glare recovery, retinopathy [Age-Related Eye Disease Study (AREDS) staging], lens opacification, and visual quality of life were unaffected. While preliminary results from this human intervention trial suggest that supplementation with lutein may improve near visual acuity, the study was

associated with several deficiencies which limit interpretation of study findings. First, approximately half of the subjects in each group were taking supplemental vitamins and minerals, several of which (*i.e.,* β-carotene, vitamin C, vitamin E, zinc, and copper) have been demonstrated in the AREDS I[8] trial to reduce the rate of visual acuity loss independently of lutein. Second, compared to the lutein group, a significantly higher proportion of placebo subjects had advanced (AREDS Stage IV) disease in the left eye (41.7% *vs.* 9.1%; P=0.0002), which was the only eye in which near visual acuity was significantly improved.

Overall Conclusions

Overall, limited and preliminary data indicate that lutein and zeaxanthin may be important in reducing the risk of cataract and in the maintenance of normal visual performance. Although the totality of evidence is not supportive of a role for lutein and zeaxanthin in reducing the risk of ARM/ARMD, biological plausibility for the claimed effect is strong (*i.e.,* lutein and zeaxanthin are concentrated in the macula to the exclusion of the other carotenoids, and are proposed to filter phototoxic blue light and to have antioxidant activity). Thus, the possible roles of lutein and zeaxanthin in maintaining visual health were considered in the safety assessment.

Olestra, as intended for use in a variety of food categories, is not expected to result in clinically meaningful reductions in lutein and zeaxanthin status. This is based on the following observations:

1. Intake estimates for olestra from permitted and proposed uses combined are exaggerated.

2. Reductions in serum levels of lutein and zeaxanthin are within the background range of those caused by other food ingredients (Riedl *et al.*, 1999; Plat and Mensink, 2001; Amundsen *et al.*, 2004).

3. Lutein and zeaxanthin concentrations in the macula are highly conserved. In a 1-year human intervention study (Broekmans *et al.,* 2003), the consumption of up to 17 g/day olestra+SPE [in the form of chips (7 g/day olestra) and a margarine-like spread (10 g/day SPE)], did not result in reductions in MPOD, despite reductions in serum levels of lutein+zeaxanthin. In lutein and zeaxanthin supplementation trials, macular pigment levels remained stable for up to 6 months following the end of lutein and

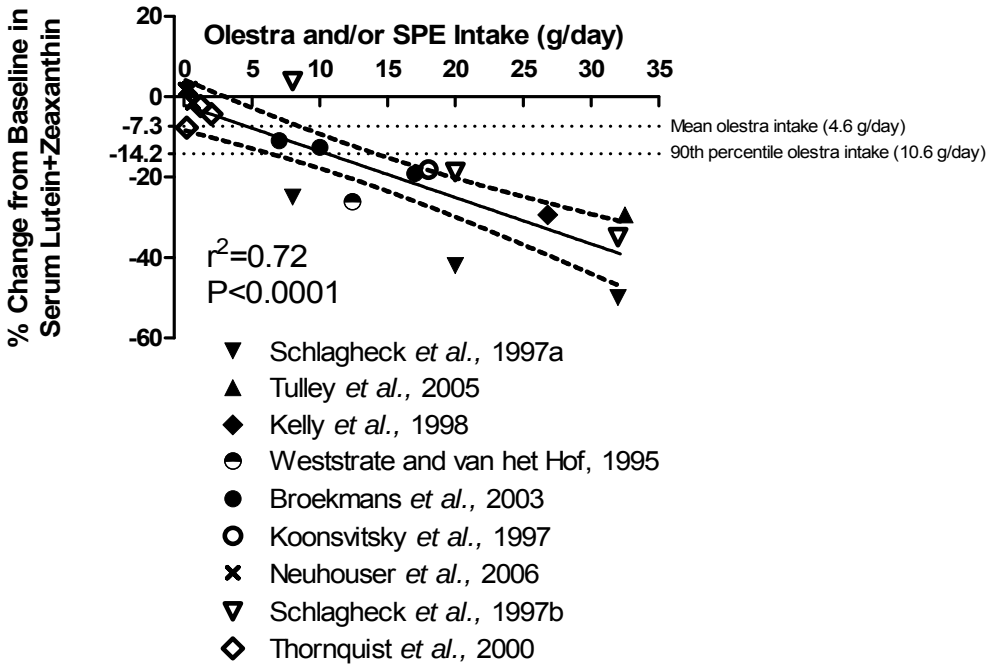
[8] The AREDS is a National Eye Institute-sponsored randomized controlled trial of nutritional factors that may impact the development and progression of ARMD and cataract. In AREDS I, in which the average follow-up was 6.3 years, a formulation containing zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide to prevent potential anemia) and antioxidants (500 mg of vitamin C, 400 IU of vitamin E, 15 mg of β carotene) reduced the likelihood of developing advanced ARMD by approximately 25% in moderate-risk individuals; in addition, overall risk of moderate vision loss (>15 letters on the ETDRS chart) was reduced by 19% at 5 years (AREDS, 2001).

zeaxanthin supplementation, despite reductions in serum levels of lutein and zeaxanthin (Hammond *et al.,* 1997; Johnson *et al.,* 2000; Trieschmann *et al.,* 2007).

4. Lutein and zeaxanthin are hydroxylated carotenoids and their circulating levels are affected least by olestra (Figure 2). At the estimated mean and 90th percentile olestra intakes, serum lutein and zeaxanthin levels are expected to decrease by -7.3 and -14.2%, respectively (Figure 3).

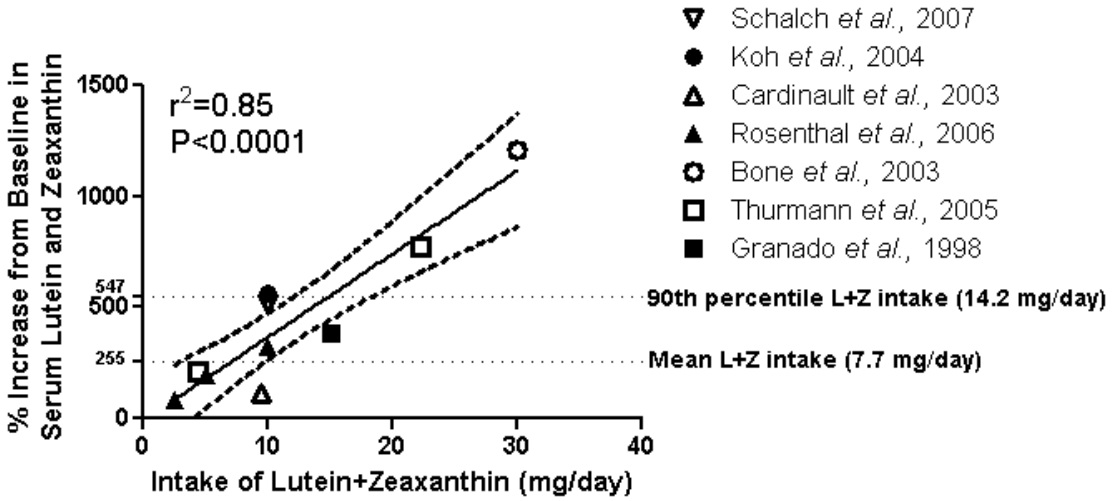
5. Intakes of lutein and zeaxanthin are expected to increase in the US. The estimated intakes of lutein and zeaxanthin at the mean and 90th percentile are 7.7 and 14.2 mg/day, respectively (U.S. FDA, 2004). Associated serum levels of lutein and zeaxanthin are expected to increase by 255 and 547%, respectively (Figure 4), and to overcompensate for reductions attributable to olestra.

Figure 3 Change from Baseline in Serum Level of Lutein and Zeaxanthin as a Function of Olestra/SPE Intake



Results from the clinic cross-section and cohort of the OPMSS at the sentinel site were averaged (Thornquist *et al.,* 2000). Results observed in adults and adolescents from the other 3 sites involved in the OPMSS were averaged (Neuhouser *et al.,* 2006). The slope and y-intercept of the line are -1.151 and -2.048, respectively.
In the study by Schlagheck *et al.* (1997b), serum levels of lutein+zeaxanthin were very high at baseline in all groups (*i.e.,* 0.76 – 1.06 µM). Typical serum levels of lutein and zeaxanthin are approximately 0.30 µM. It is unclear why these levels are so high, and why, in the control group, serum levels of lutein+zeaxanthin doubled by the end of the 8-week study. Neither of these issues was apparent in the Schlagheck *et al.* (1997a) study.
Abbreviations: OPMSS, Olestra Post-Marketing Surveillance Study

Figure 4 Increases in Circulating Levels of Lutein and Zeaxanthin with Supplementation



Ten data points from 7 studies were used in the regression analysis. Since lutein is the predominant xanthophyll in the GRAS formulations and in the diet, studies in which pure zeaxanthin were administered were not included in the regression analysis. The slope and y-intercept of the line are 37.54 and -7.834, respectively. The % increases in serum levels of lutein and zeaxanthin at the projected mean (7.7 mg/day) and 90th percentile (14.2 mg/day) intakes of lutein and zeaxanthin are 255 and 547%, respectively.

For the reasons outlined above, the estimated 15% reduction in serum L/Z levels associated with the estimated 90th percentile olestra intake is not expected to result in any clinically meaningful effects on eye health.

G. Summary

Olestra, meeting the specifications of the *Food Chemicals Codex* (FCC, 2008), is a food additive that has been 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 since 1996 (21 CFR §172.867) (U.S. FDA, 2009). In 2004, the FDA amended the food additive regulations to allow for the safe use of olestra as a replacement for fats and oils in pre-packaged, unpopped popcorn kernels that are ready-to-heat [21 CFR §172.867(c)] (U.S. FDA, 2009). In 2007, olestra was determined to be GRAS, consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*, for use in pre-packaged ready-to-eat cookies (FDA notification).

The current evaluation was undertaken to determine if expanded uses of olestra to include use in all pre-packaged ready-to-heat cookies, all other pre-packaged ready-to-eat, and ready-to-heat baked goods, and pre-packaged ready-to-eat frostings and icings, mayonnaise, ice cream, frozen yogurt, breakfast/granola/nutritional bars, chocolate confections, and the natural or

processed cheese portion of pre-packaged ready-to-eat or ready-to-heat prepared foods intended for sale at retail outlets or vending machines also would be GRAS.

The data and information summarized in this dossier demonstrate that olestra, meeting appropriate food grade specifications and manufactured in accordance with current GMP, would be GRAS based on scientific procedures for use as a food ingredient under the expanded conditions of intended use. This conclusion is conditional on the requirement that vitamins A, D, E, and K be added to the olestra-containing foods at concentrations that meet the conditions specified in 21 CFR §172.867(d).

The determination of GRAS is supported by the following important considerations.

- The total population mean and 90th percentile intakes from proposed (new uses proposed herein) and permitted uses, combined, for all-users, were estimated to be 4.6 and 10.6 g/day, respectively, compared to estimates of 3.1 and 7.7 g/day, respectively, for permitted uses (pre-packaged, ready-to-eat savory snacks and cookies and pre-packaged, unpopped popcorn kernels that are ready to heat). Thus, the proposed uses increase estimated intakes modestly by 1.5 and 2.9 g/day for the mean and 90th percentile, respectively. In comparison, total daily fat intakes at the mean and 90th percentile, are approximately 75 and 114 g/day, respectively, for the total population; thus, for the total population, olestra would replace less than 10% of total fat intake.

- Among infants aged 0 to 6 months, mean and 90th percentile olestra intakes for all-users were estimated to be 1.0 and 2.1 g/day, respectively. (Intakes of olestra among infants are largely attributable to the use of full fat surrogates for foods without reduced fat equivalents.) Total daily fat intakes for this age group are approximately 35 (mean) and 46 g/day (90th percentile); therefore, potential exposure to olestra represents less than 5% of total fat intake. Furthermore, these values are highly likely to be gross overestimates of actual olestra consumption given that infants aged 0 to 6 months primarily consume breast milk and/or infant formula, with the introduction of some solid foods that are most likely to be pre-packaged baby foods (for which olestra is not proposed for use). For infants aged 7 to 12 months, olestra intakes, for all-users, were estimated to be 0.7 and 1.6 g/day at the mean and 90th percentile, while total fat intakes are approximately 40 and 54 g/day, respectively. Thus, olestra intakes would replace less than 3% of total fat intakes for this age group. Moreover, the intakes of olestra estimated for this age group result almost entirely from the required use of food codes representative of regular fat foods that were used as surrogates in the absence of food codes representative of fat modified or reduced fat foods (*e.g.*, most baked goods including bread).

- The 90th percentile all-user intakes of olestra estimated for all population groups are lower than the maximum intake of 17 g/day olestra+SPE employed in the Broekmans *et al.* (2003) 12-month randomized, double-blind, placebo-controlled parallel study which was

not associated with any adverse health or visual effects. This holds true for intake estimates prepared using the CSFII database, as well as for the updated assessment of intakes employing the most recent NHANES dataset.

- The intake modeling methodology conducted for this assessment included the following conservative assumptions, thus actual intakes will likely be much lower:

  - All of the products within food codes that are representative of foods that are permitted and proposed for olestra use were assumed to contain olestra (*i.e.*, 100% market share);
  - All food products were assumed to contain olestra at the maximum specified level of use;
  - All foods in a food category were assumed to be pre-packaged, even if there was uncertainty that the food was pre-packaged; and
  - Where limited data on fat-modified foods were available, regular fat food codes were used in intake estimates, thereby inflating the percentage of the U.S. population who may be users of olestra.

- The Olestra Post-Marketing Surveillance Study [OPMSS; (Thornquist *et al.,* 2000; Neuhouser *et al.,* 2006)], 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 from savory snacks was estimated by Webb *et al.* (1997) 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 from savory snacks was estimated to be 8.1 g/day, while the actual intake was 1.8 g/day].

- 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 (demonstrated in original GRAS evaluation).

  - 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.

- As olestra is not absorbed from the gastrointestinal tract, it is not associated with systemic toxicity. This has been demonstrated in numerous standard toxicology studies including chronic studies in mice, rats, and dogs, a 2-generation reproductive and developmental toxicity study in rats, and a 4-year study in primates. Olestra was not associated with systemic toxicity when administered to experimental animals at dietary levels of up to 10%, the highest dose level tested (demonstrated in original GRAS evaluation).

- Studies in humans have demonstrated that consumption of up to 40 g/day olestra is not associated with adverse GI effects (demonstrated in original GRAS evaluation).

- The results of the Movie Theatre study indicated no differences in gastrointestinal effects between olestra chips and triglyceride chips, following single event consumption (over 2 hours) even at the very highest intakes in excess of 100 g olestra.

- Sufficient vitamin A is added to olestra containing products to offset effects of olestra on serum vitamin A levels. Other than the provitamin A activity of α-carotene, β-carotene, and β-cryptoxanthin, the current state of scientific evidence is equivocal regarding the roles of carotenoids in maintaining health or preventing disease.

- Required vitamin restoration levels will compensate for reductions in the absorption of fat-soluble vitamins given that restoration levels were calculated for olestra intakes up to 32 g/day, a level well in excess of the estimated 90th percentile takes for users-only.

- Olestra intakes, for permitted and proposed uses, at the mean (*i.e.,* 4.6 g/day) and 90th percentile (*i.e.,* 10.6 g/day) were estimated to result in reductions, from baseline, in serum levels of lutein and zeaxanthin of -7.3% and -14.2%, respectively. As discussed above, actual chronic olestra intakes, and therefore, actual reductions in serum lutein and zeaxanthin levels are expected to be less than predicted.

- Based on the following observations, these reductions in circulating levels of lutein and zeaxanthin are not expected to be clinically meaningful:

    - Intake estimates for olestra from permitted and proposed food uses combined are exaggerated;
    - Reductions in serum levels of lutein and zeaxanthin are within the background range of those caused by other food ingredients such as fiber or plant sterols/stanols;
    - Intakes of lutein and zeaxanthin are expected to increase in the U.S.;
    - Lutein and zeaxanthin concentrations in the macula are highly conserved;
    - While data from observational studies suggest that increased intakes of lutein and zeaxanthin are associated with a reduced risk of cataract, specificity of effect

could not be established – in all studies assessing associations with lutein and zeaxanthin independently of other nutritional covariates, relationships were always attenuated and no longer significant;

- There are limited data from one human intervention study that supplementation with lutein and zeaxanthin may improve visual performance; however, the study was based on a small sample size and had several limitations, including confounding nutritional variables, more severe disease in placebo subjects, relative to treatment subjects, at study initiation, in the left eye where efficacy was demonstrated; these deficiencies limit interpretation of the study findings;
- Although there is strong biological plausibility for a role for these xanthophylls in reducing ARMD risk, data from epidemiological studies are equivocal with respect to the association between lutein and zeaxanthin and risk of ARMD;
- Causality could not be established for any of the exposure biomarkers assessed (intake, circulating levels, or MPOD).

H Conclusion

Based on the data and information summarized above, it can be concluded olestra is GRAS for the intended uses in food products as described herein based on scientific procedures. This conclusion is based on the following conditions: (i) olestra must meet current food grade specifications published in the Food Chemical Codex; (ii) vitamins A, D, E & K must be added to olestra containing foods at concentrations specified in 21 CFR §172.867(d); (iii) all foods must be produced at facilities operating under current Good Manufacturing Practice (cGMP), essential to ensure vitamin restoration; (iv) all foods are to be pre-packaged and suitable for retail outlets & vending machines.

Therefore, the use of olestra in food as described herein is exempt from the requirement of premarket approval (Section 409 of the *Federal Food, Drug and Cosmetic Act*).

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Table of CFR Sections Referenced (Title 21—Food and Drugs)

Part	Section §	Section Title
101—Food labeling	101.3	Identity labeling of food in packaged form
170—Food additives	170.30	Eligibility for classification as generally recognized as safe (GRAS).
172—Food additives permitted for direct addition to food for human consumption	172.867	Olestra

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OLESTRA AMENDMENT GRAS NOTICE

APPENDIX A:

EXPERT PANEL CONSENSUS STATEMENT

January 18, 2010

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OLESTRA FOR USE IN VARIOUS PRE-PACKAGED, READY-TO-EAT, AND READY-TO-HEAT FOODS: AN AMENDMENT TO THE GRAS DETERMINATION OF OLESTRA FOR USE IN PRE-PACKAGED READY-TO-EAT COOKIES

April 14, 2009

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 July 14, 2008, 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 various pre-packaged ready-to-eat and ready-to-heat foods, intended to be marketed as reduced-fat, low-fat, or fat-free, would be Generally Recognized as Safe (GRAS), based on scientific procedures. This is an amendment to a prior GRAS determination which supported the use of olestra in all pre-packaged, ready-to-eat cookies marketed as reduced-fat, low-fat, or fat-free. The expanded uses for olestra considered in this GRAS amendment include use in reduced fat versions of all pre-packaged ready-to-heat cookies, all other pre-packaged ready-to-eat and ready-to-heat baked goods, the natural[1] cheese and processed cheese portion of pre-packaged ready-to eat and ready-to-heat prepared foods, and pre-packaged ready-to-eat frostings and icings, mayonnaise, ice cream, frozen yogurt, breakfast/granola/nutritional bars, pizza crust, and chocolate confections.

The Panel consisted of the following qualified scientific experts: Dr. G. Harvey Anderson, Ph.D. (Department of Nutritional Sciences, University of Toronto); Dr. Joanne Curran-Celentano, Ph.D. (University of New Hampshire; new Panel member, added based on specific expertise in lutein and zeaxanthin); 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. (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.

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[1] Note: "Natural" cheese was included for the purpose of selecting food codes but would not be marketed as "natural" once olestra has been added; it would be marketed as "imitation" or "substitute/alternate" cheese, as per 21 CFR §101.3(e). (U.S. FDA, 2008b)

In the original GRAS determination, the Panel[2], 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, as well as 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[3] and proposed uses. Metabolic studies in humans and experimental animals were evaluated to assess absorption, metabolism and excretion of olestra and other sucrose polyesters. The determination of safety involved evaluation of a comprehensive database of toxicology studies performed with heated and unheated olestra, as well as other sucrose polyesters, and studies addressing nutritional issues such as gastrointestinal (GI) physiology and function, olestra's interaction in the digestive tract with lipophilic compounds, effects on appetite regulation, and the absorption of nutrients. In addition, the results of human clinical studies 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.

Currently, olestra is permitted for use as a 100% fat substitute in savory snacks, pre-packaged ready-to-heat popcorn, and pre-packaged ready-to-eat cookies. It was previously demonstrated, from dietary intake assessments, that approximately 90% of eating occasions for popcorn and two-thirds of eating occasions for savory snacks and cookies are as snacks; thus, the potential for reductions in carotenoid absorption was determined to be low, since olestra is known to cause reductions in serum levels of carotenoids when *co-consumed* with carotenoid-rich meals (Daher *et al.,* 1997). In the current GRAS amendment, olestra is intended to be used in several categories of foods that are expected to be consumed as components of main meals. Because the potential for reductions in carotenoids is greater with the proposed new uses, for this GRAS amendment, the primary focus of the evaluation was to assess potential impacts that the proposed new uses for olestra would have on total olestra consumption and to determine the clinical significance of olestra-related reductions in circulating levels of carotenoids. These data are summarized below. Comprehensive details are provided in the GRAS dossier [Documentation Supporting the Evaluation of Olestra as Generally Recognized as Safe (GRAS) for Use in Various Pre-packaged Ready-to-eat and Ready-to-heat Foods: An Amendment to the GRAS Use of Olestra in Pre-packaged Ready-to-eat Cookies].

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[2] Original panel consisted of all of the current panel members with the exception of Dr. Curran-Celentano. Dr. Curran-Celentano was requested to join the panel for the purpose of the amendment given her expertise in lutein and zeaxanthin.

[3] For the purpose of this report, permitted food uses include uses specified in the Code of Federal Regulations (popcorn and savory snacks; 21 CFR §172.867) and also uses determined to be Generally Recognized as Safe (cookies) as per the Substances Generally Recognized as Safe; Proposed Rule (62 FR 18938) (U.S. FDA, 1997).

FOOD INTAKE EVALUATION

Olestra is a replacement for conventional fats, and products using olestra are intended to be marketed as “low-fat”, “reduced-fat”, or “fat-free”. Olestra is currently permitted for use in pre-packaged ready-to-eat (RTE) savory snacks (*i.e.*, salty or piquant, but not sweet) and pre-packaged ready-to-heat (RTH) unpopped popcorn kernels in place of fats and oils (21 CFR §172.867) (U.S. FDA, 2008a). Olestra also is permitted for use in pre-packaged RTE cookies. FDA has issued a letter of no objections following review of the GRAS notification for olestra use in pre-packaged, ready-to-eat cookies.

Olestra is currently proposed for use in the following products that are produced only at facilities operating under Good Manufacturing Practice (GMP) and in prepared food products which are intended for sale at retail outlets or vending machines:

- Pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH biscuits and English muffins, pre-packaged RTE & RTH bread, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTH cookies, pre-packaged RTE & RTH cornbread, corn muffins, tortillas and taco shells (hard and soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack type), pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pancakes, crepes, and French toast, pre-packaged RTE & RTH sweet pastries (pastry portion), pre-packaged RTE & RTH sweet pies (pastry portion), pre-packaged RTE & RTH meat and vegetable pies and pastries (pastry portion), pre-packaged RTE & RTH rolls, pre-packaged RTE & RTH sweet rolls and quick breads, and pre-packaged RTE & RTH waffles;

- Natural cheese (see footnote on page 1) and processed cheese portion of pre-packaged RTE & RTH prepared foods;

- Pre-packaged RTE frosting and icing;

- Pre-packaged RTE mayonnaise;

- Pre-packaged RTE ice cream, and pre-packaged RTE frozen yogurt;

- Pre-packaged RTE breakfast, granola, and nutritional bars and pre-packaged RTE & RTH pizza crust; and,

- Pre-packaged RTE chocolate confections (chocolate portion).

The maximum proposed use-levels of olestra for the proposed food-uses range from 67 to 100% replacement of added fats. Proposed use-levels of less than 100% will contain blends of digestible fat (*e.g.*, vegetable oils, shortenings, *etc.*) and olestra. These blends were developed

by P&G to provide more palatable products and/or to meet other technical properties of the food matrices.

Products intended for olestra use will solely consist of pre-packaged ready-to-eat (RTE) or ready-to-heat (RTH) foods that will be produced at food manufacturing and packaging establishments operating under GMP. Olestra-containing foods are intended to be sold at retail outlets and vending machines. Olestra will not be distributed for use as a food ingredient to facilities that do not have the capability to produce and package foods according to GMP such as restaurants, cafeterias, or other such facilities. Olestra will not be sold as a food ingredient to food service establishments (even if they operate according to GMP), as the end use is not in pre-packaged form (*i.e.,* such foods are typically sold in eateries, in an unpackaged, ready-to-eat form). This will ensure that the required vitamin restoration levels are met during manufacture of the food, and that all olestra-containing foods will be sold with an ingredients list which clearly indicates the presence of olestra in the food.

Olestra is not intended for use in, and will not be sold for the manufacture of foods that are specifically produced for infants or toddlers. Also, olestra will not be used to replace the fat in milk with the exception of the use of olestra to replace the butter fat in ice cream, frozen yogurt, and the natural and processed cheese used in the production of pre-packaged, RTE and RTH prepared foods. Although natural and processed cheeses are proposed for olestra use, they are proposed only for use in the cheese portion of pre-packaged RTE and RTH prepared foods.

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).

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 (USDA, 2000). 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.

The estimated intakes of olestra on a per day basis for permitted and proposed uses are summarized in Table 1. In summary, on an all-user basis, the estimated mean and 90th percentile intakes of olestra from the consumption of all permitted and proposed food-uses combined by the total U.S. population were estimated to be 4.6 g/person/day and 10.6 g/person/

day, respectively. These intake estimates are greater than the estimated all-user mean and 90th percentile intakes of olestra by the total population resulting from the consumption of permitted uses, of 3.1 g/person/day and 7.7 g/person/day, respectively.

On an individual population basis, the greatest absolute mean all-user intake of olestra from permitted and proposed uses occurred in male teenagers (6.2 g/person/day); the greatest 90th percentile all-user intake of olestra occurred in male adults, aged 31 to 50 years (13.7 g/person/day). These intakes are still well within the range of olestra levels administered in the various human experimental studies.

Table 1 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)*

Age Group	Sex	% Users	Total Number of Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Infants (0 to 6 Months)	Male and female	14.2	138	0.1	0.3	1.0	2.1
Infants (7 to 12 Months)	Male and female	28.6	107	0.2	0.6	0.7	1.6
Toddlers (1 to 3 Years)	Male and female	89.2	3,436	2.2	5.2	2.5	5.7
Children (4 to 8 Years)	Male and female	93.2	3,508	3.6	8.2	3.9	8.5
Children (9 to 13 Years)	Male and female	92.1	1,055	4.4	9.5	4.7	10.0
Teenagers (14 to 18 Years)	Female	85.7	378	3.7	8.9	4.3	9.6
Teenagers (14 to 18 Years)	Male	89.4	397	5.6	13.0	6.2	13.4
Adults (19 to 30 Years)	Female	83.5	685	3.4	8.9	4.1	10.0
Adults (19 to 30 Years)	Male	83.9	706	4.4	10.8	5.3	12.2
Adults (31 to 50 Years)	Female	89.5	1,471	4.0	9.7	4.4	10.4
Adults (31 to 50 Years)	Male	89.2	1,496	5.1	12.8	5.7	13.7
Adults (51 to 70 Years)	Female	90.2	1,385	3.7	9.1	4.1	9.3
Adults (51 to 70 Years)	Male	90.4	1,445	4.7	11.0	5.2	11.6
Adults (71 and Up)	Female	90.6	561	3.6	8.4	3.9	8.8
Adults (71 and Up)	Male	91.2	612	4.6	11.2	5.0	11.3
Total Population	Male and female	85.2	17,380	4.1	10.1	4.6	10.6

*Intake model refined to only include pre-packaged RTE and/or RTH olestra-containing products purchased at retail outlets or vending machines.

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 including:

- Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently (Anderson, 1988; Lambe and Kearney, 1999);
- The assumption that *all* food products within a food category will contain the ingredient at the *maximum* specified level of use;
- The assumption that all foods in a food category are *pre-packaged*, even if there was uncertainty that the food was pre-packaged; and
- Where limited data on fat-modified foods were available, regular fat food codes were used in intake estimates, thereby inflating the percentage of the U.S. population who may be users of olestra. Also, amongst population groups that do not typically consume large quantities of fat modified or reduced fat foods, such as infants or young children, the use of regular fat foods as surrogates in the model may greatly over-estimate olestra intakes.

OVERVIEW OF TOXICOLOGY AND NUTRITION

Since olestra was last reviewed in 2007, no significant new data pertaining to the toxicology or other nutritional considerations were identified, and the specifications and other chemistry and manufacturing information for olestra are unchanged. The toxicology and nutritional data evaluated in the original GRAS determination were reassessed to determine if the increase in intakes from the proposed new uses would be supported. The Panel determined that the increase in intakes from the proposed new food uses was still well within the dose ranges determined to be without adverse effects in toxicology and clinical studies. In particular, the 90th percentile all-user intakes of olestra estimated for all population groups (see Table 1) are lower than the maximum intake of 17 g/day employed in the Broekmans *et al*. (2003) 12-month randomized, double-blind, placebo-controlled parallel study, which was not associated with any adverse health or visual effects. The resultant intakes from the addition of the proposed new uses of olestra also are well below oral doses of olestra evaluated in short-term studies (up to 40 g/day), which were not associated with GI effects. Moreover, as olestra is not absorbed from the gastrointestinal tract, there is no greater systemic exposure resulting from the proposed new uses. The lack of systemic exposure, and hence systemic toxicity, with olestra has been demonstrated in standard toxicology studies including carcinogenicity, and reproductive and developmental toxicity studies (the above nutrition and toxicology studies were discussed in great detail in the original GRAS evaluation and are not repeated here).

CAROTENOIDS EVALUATION

The scientific literature has been critically reviewed to determine the roles of carotenoids in the maintenance of health and prevention of disease, and to determine whether olestra-associated reductions in serum carotenoid levels might be associated with adverse health effects.

β-Carotene, Lycopene, β-Cryptoxanthin, and α-Carotene

Overview

There is strong agreement amongst human intervention studies that consumption of olestra results in reductions, from baseline, in serum carotenoid levels. Despite reductions in serum levels of β-carotene, lycopene, β-cryptoxanthin, and α-carotene, no apparent ill health effects have been reported in any of the studies. In the longest intervention trial, which was 1 year in duration and included 380 subjects, the consumption of up to 17 g/day olestra+sucrose polyesters (SPE) was not associated with adverse effects on markers of oxidative stress, cardiovascular health, immune status, macular pigment optical density (MPOD), or eye health, despite reductions, from baseline, in serum carotenoid levels of 13 to 33% (Broekmans *et al.,* 2003). Despite these findings, the Panel considered that reductions in carotenoid levels chronically over one's lifetime may be associated with adverse health effects that would not be captured in a 1-year study. Thus, additional information on the physiological roles of carotenoids was reviewed by the Panel. This additional information included position statements of scientific and regulatory organizations (9 in total), and relevant scientific studies published in or subsequent to 2003. Approximately 75 studies were identified of which several looked at associations with more than one carotenoid.

There is strong consensus amongst regulatory and scientific organizations that a diet rich in fruits and vegetables may be beneficial in reducing the risk of cardiovascular disease and cancer; nevertheless, regulatory and scientific organizations cautioned against the use of supplemental forms of carotenoids, stating that it is not possible to discern whether the observed beneficial effects are due to carotenoids, other nutrients in fruits and vegetables, lifestyle factors associated with consumption of fruits and vegetables, a combination of these, or other factors altogether (WHO/IARC, 1998; IOM, 2000; Kushi *et al.*, 2006; WCRF/AICR, 2007). There is no consensus from human observational studies that carotenoids are associated with reduced risk of cancer or cardiovascular disease. The limited number of studies reporting significant inverse associations between dietary intakes or circulating levels of β-carotene, lycopene, β-cryptoxanthin, or α-carotene and risk of cardiovascular disease (CVD) or cancer were case-control studies. Due to the retrospective nature of case-control studies, they are subject to recall bias and reported associations are generally biased away from the null.

Observational studies are associated with several limitations, and are generally not sufficient for demonstrating causality, particularly when the subject of the claimed effect is a specific nutrient

or food constituent as opposed to a category of foods or a food group. No intervention trials assessing the effects of either α-carotene or β-cryptoxanthin on cancer risk were identified. A limited number of carotenoid supplementation trials in humans were identified in which the effects of β-carotene or lycopene on risk of CVD or cancer were assessed.

β-Carotene and Cancer Risk

Five publications were identified (1 review, 1 meta-analysis, 1 primary intervention trial, and 2 follow-up studies to primary intervention trials) in which the effects of β-carotene supplementation on the risk of cancer were assessed. Based on the results from 4 intervention trials, in which β-carotene was provided at doses of 20 to 50 mg daily or on alternate days for up to 12.9 years, Dagnelie *et al.* (2004) concluded that prostate cancer risk is unaffected by β-carotene supplementation. The authors went on to note that β-carotene supplementation may reduce prostate cancer risk in men with low baseline β-carotene levels and increase risk in men with high baseline β-carotene levels. In a meta-analysis of 5 intervention trials, β-carotene supplementation (15 to 50 mg daily or every other day for 1 to 12 years), had no effect on risks of esophageal, gastric, colorectal, or pancreatic cancers or mortality (Bjelakovic *et al.,* 2004). In a placebo-controlled intervention study [the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study], supplementation with 20 mg/day β-carotene for 5 to 8 years had no effect on risk of cancers of the oral cavity, pharynx, esophagus, or larynx (Wright *et al.,* 2007). In a follow-up to the ATBC Study, no significant increases or reductions in the incidences of lung, prostate, urothelial, stomach, kidney, or pancreatic cancers were observed at any time during the 6-year follow-up period; however, risk of colorectal cancer was significantly increased for subjects in the β-carotene group during the period covering years 4 through 6 of follow-up but not during the period covering years 1 through 3 of follow-up (Virtamo *et* al., 2003). In a follow-up to the Beta-carotene and Retinol Efficacy Trial (CARET), the risk of lung cancer was significantly increased in smokers and former asbestos workers supplementing with beta-carotene (Goodman *et al.,* 2004).

Thus, data from recently published human intervention studies, as well as position statements from authoritative bodies, including the U.S. Food and Drug Administration (FDA), World Health Organization, American Institute for Cancer Research, and American Cancer Society do not support a role for β-carotene supplementation in attenuating cancer risk.

β-Carotene and CVD Risk

Three publications were identified (1 review, 1 meta-analysis, and 1 secondary intervention trial) in which the effects of β-carotene supplementation on the risk of CVD were assessed. Voutilainen *et al.* (2006) conducted a review of 7 human intervention trials (5 primary prevention trials and 2 secondary prevention trials), in which subjects were supplemented daily with 20 to 50 mg β-carotene for 4 to 12 years. In 3 of the 5 primary prevention trials, subjects supplemented with β-carotene had an increased incidence of ischemic heart disease, stroke

mortality, first major coronary event, or CVD mortality. Of the 2 secondary prevention trials, β-carotene supplementation was associated with a significant increase in the risk of a fatal coronary event in 1 study. In none of the studies reviewed was β-carotene supplementation associated with a reduction in CVD risk. In a meta-analysis of 8 β-carotene supplementation trials (Vivekananthan *et al.,* 2003), in which subjects consumed 15 to 50 mg/day β-carotene for 2.1 to 12.0 years, risk of death from CVD was slightly increased with β-carotene supplementation (OR=1.1; CI, 1.03-1.17; P=0.003). In a secondary prevention trial, supplementation of female health professionals with 50 mg β-carotene on alternate days for a mean duration of 9.4 years had no effect on CVD risk (Cook *et al.,* 2007).

Data from recently published human intervention trials do not support a role for β-carotene in reducing risk of CVD; in contrast, in some studies, there is a suggestion that β-carotene supplementation may increase risk of CVD. Thus, consistent with the position statements of scientific and regulatory organizations, β-carotene supplementation is not associated with a reduced risk of CVD.

Lycopene and Cancer Risk

In the one intervention study identified investigating the effect of lycopene supplementation on prostate-specific antigen (PSA) serum levels, 77 men with elevated prostate cancer risk (*i.e.,* subjects had high-grade prostatic intraepithelial neoplasia, atypical foci, or repeated non-cancerous biopsies) were randomized to receive, for 4 months, a multivitamin alone or in combination with 30 mg/day lycopene (Bunker *et al.,* 2007). After 1 month of treatment, serum PSA levels declined from baseline in both groups (lycopene+multivitamin, 10% decline, not significant; multivitamin alone, 13% decline, P<0.001). After 4 months of treatment, serum PSA levels returned to baseline in both groups. Thus, supplementation with lycopene had no effect on serum PSA levels in males with high prostate cancer risk.

Conclusions

Consistent with the position statements of several regulatory and scientific organizations, human data published in or subsequent to 2003 do not support roles for β-carotene, lycopene, β-cryptoxanthin, and α-carotene in mitigating the risk of CVD or cancer. Thus, olestra-associated reductions in circulating levels of these carotenoids are not expected to be associated with adverse health effects.

Lutein and Zeaxanthin

It has been demonstrated in non-human primates that the long-term feeding of an xanthophyll-free semi-purified diet results in undetectable levels of xanthophylls in plasma, a loss in yellow pigmentation of the macula, and the development of drusen in the retina, which is an early sign of age-related macular degeneration in humans (Malinow *et al.,* 1980); although, no gross visual

disturbances were associated with this long-term diet. Similar observations have been reported in humans on long-term total parenteral nutrition (TPN) (Vinton *et al.,* 1990; Porter *et al.,* 2005), though associated vitamin deficiencies and co-morbidities preclude attribution of these effects to any single nutrient. Lutein and zeaxanthin, collectively referred to as macular pigments, have been hypothesized to play important roles in the maintenance of eye function and in reducing the risks of age-related cataract formation and macular degeneration, based on the following 3 observations:

1. Lutein and zeaxanthin are present in the lens and unlike other carotenoids, are selectively concentrated in the macula of the eye;

2. Lutein and zeaxanthin have an absorbance spectrum which permits filtration of phototoxic blue light; and

3. Lutein and zeaxanthin have antioxidant activity and thus might protect visual tissue from free radical damage and lipid oxidation of the polyunsaturated-rich environment.

Human observational and intervention studies determined to have high methodological quality, as assessed using a quality appraisal tool[4], were critically reviewed to determine whether there are scientific data to support the proposed role of lutein/zeaxanthin in supporting eye health. Three primary endpoints were evaluated separately, including age-related cataract, ARM/ARMD, and outcomes related to visual performance.

Age-Related Cataract and Macular Degeneration (ARMD)

Human observational and intervention studies in which risk of cataract/ARMD was assessed as a function of lutein/zeaxanthin status were critically reviewed. A study was considered to support a significant reduction in risk of cataract/ARMD with increased status of lutein and/or zeaxanthin if significant inverse associations were reported for at least 1 outcome measure in at least 1 subgroup of the population studied. The study was considered to support a significant reduction in risk of cataract/ARMD with increased status of lutein and/or zeaxanthin if it reported a significant inverse trend, significantly lower levels in cases *versus* controls, or a significant reduction in risk in 1 category of lutein and/or zeaxanthin status *versus* the lowest category of lutein and/or zeaxanthin status.

[4] The quality appraisal tool was developed prior to the review of the study findings, and included criteria relevant to study design and control of potential confounding variables. Two raters independently evaluated the quality of each study. Studies were assigned a quality score based on the number of items accounted for. The critical review was based only on studies with high methodological quality, defined as a score of ≥60%.

Age-Related Cataract

Of the 9 studies assessing the relationship between dietary intakes of lutein+zeaxanthin and risk of cataract, 7 (77.8%) reported a significant reduction in risk of cataract with increased intake of lutein+zeaxanthin (Brown *et al.,* 1999; Chasan-Taber *et al.,* 1999; Lyle *et al.,* 1999b; Jacques *et al.,* 2001; Vu *et al.,* 2006; Christen *et al.,* 2008; Moeller *et al.,* 2008) and 2 (22.2%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of cataract (Valero *et al.,* 2002; Jacques *et al.,* 2005). Of the 6 studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of cataract, 4 (66.7%) reported a significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin (Gale *et al.,* 2001; Delcourt *et al.,* 2006; Dherani *et al.,* 2008; Moeller *et al.,* 2008) and 2 (33.3%) reported no significant associations between circulating levels of lutein and/or zeaxanthin and risk of cataract (Mares-Perlman *et al.,* 1995; Lyle *et al.,* 1999a).

Data from human observational studies corroborate a role for lutein and zeaxanthin in reducing the risk of cataract formation. Several causality criteria, including consistency, explanation of opposing/neutral evidence, dose-response, and temporality were satisfied by the available data; however, effect of dechallenge and alternate explanations (*i.e.,* that reductions are due specifically to lutein and zeaxanthin and not to some other nutrient or non-nutrient covariates) could not be established because all of the studies identified were observational. Moreover, although lutein and zeaxanthin are present in the lens, they are not concentrated in the lens as they are in the macula, and so the biological plausibility for an effect of lutein+zeaxanthin in reducing the risk of cataract is weaker. It is noteworthy that in all studies reporting a decreased risk of cataract with increased intakes of lutein+zeaxanthin, relationships were *always* attenuated and no longer significant when other nutritional covariates (such as vitamin C, vitamin E, and β-carotene) were examined simultaneously with lutein+zeaxanthin. These observations suggest that lutein+zeaxanthin are correlated with other nutritional variables that may mitigate risk of cataract, either independently of lutein and zeaxanthin or in association with lutein and zeaxanthin.

Given that the totality of evidence on lutein and zeaxanthin status and risk of cataract is from observational studies, there is some suggestion in the literature that lutein and zeaxanthin may reduce the risk of cataract. However, the totality of evidence would not meet the FDA standard of significant scientific agreement (SSA) (http://www.cfsan.fda.gov/~dms/hclmgui6.html - U.S. FDA, 2009). To meet the SSA standard, the level of agreement amongst qualified scientific experts regarding the validity of the claim must be high, and new and emerging science must be regarded as highly unlikely to cause a reversal in the claimed effect. Because the totality of evidence for lutein and zeaxanthin and cataract risk is from observational studies, the SSA standard cannot be satisfied; rather, the current evidence is considered exploratory and preliminary. Nevertheless, to be conservative, the suggested role that lutein and zeaxanthin may play in reducing the risk of cataract was considered in the safety assessment of olestra.

ARM, ARMD

Of the 10 observational studies assessing risk of ARM/ARMD as a function of dietary intakes of lutein+zeaxanthin, 5 (50.0%) reported a significant reduction in risk of ARM/ARMD with increased intake of lutein+zeaxanthin (Seddon *et al.,* 1994; Mares-Perlman *et al.,* 2001; Moeller *et al.,* 2006; SanGiovanni *et al.,* 2007; Tan *et al.,* 2008), while 5 (50.0%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD (Mares-Perlman *et al.,* 1996; VandenLangenberg *et al.,* 1998; Cho *et al.,* 2004; van Leeuwen *et al.,* 2005; Morris *et al.,* 2007). Of the 8 observational studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD, 2 (25.0%) reported a significant reduction in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin (Gale *et al.,* 2003; Delcourt *et al.,* 2006) and 6 (75.0%) reported no significant associations between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD (Mares-Perlman *et al.,* 1995; Mares-Perlman *et al.,* 2001; Simonelli *et al.,* 2002; Cardinault *et al.,* 2005; Dasch *et al.,* 2005; Moeller *et al.,* 2006).

Evidence from human observational studies is equivocal regarding the relationship between lutein and/or zeaxanthin (as assessed *via* dietary intakes, circulating levels, or MPOD) and risk of ARM/ARMD. Although there exists a biologically plausible mechanism for the potential roles of lutein and zeaxanthin in reducing ARMD risk, several other causality criteria could not be established, including consistency, temporality, dose-response, effect of dechallenge and alternate explanations.

Future intervention trials in patients with ARM/ARMD will likely be required, from an ethical perspective, to administer the Age-Related Eye Disease Study I (AREDS I) formula (β-carotene, vitamin C, vitamin E, zinc, copper) to all patients, as this formula has been demonstrated to significantly reduce the progression of ARM and the rate of visual acuity loss. Additional nutrients of interest will have to be added to the AREDS formulation as add-ons. In the AREDS II trial, one of the treatment arms will receive lutein/zeaxanthin (10 mg/2 mg) in addition to the original AREDS formulation. Fundoscopic examinations in patients receiving long-term TPN suggest that these patients have macular changes that are consistent with early ARM; thus, well controlled intervention studies in these patients may be useful in understanding the roles of lutein and zeaxanthin in reducing the risk of ARMD.

With some observational studies supporting a reduction in risk of ARM/ARMD with increased status of lutein and/or zeaxanthin and other studies failing to demonstrate such an association, a definitive relationship between increased status of lutein and/or zeaxanthin and reduced risk of ARM/ARMD could not be established; nonetheless, the selective uptake of lutein and zeaxanthin in the macula to the exclusion of the other carotenoids, as well as the biological plausibility, warranted that potential protective effects be considered in the current safety assessment of olestra.

Visual Performance

The majority of human experimental studies assessing the role of lutein and zeaxanthin in visual performance were found to be of low methodological quality (*i.e.,* these were exploratory in nature and of limited size, analogous to "pilot" studies). One human experimental study [the Veterans Lutein Antioxidant Supplementation Trial (LAST); Richer *et al.,* 2004] was determined to have acceptable methodological quality. In this study, subjects were randomized to receive either 10 mg/day lutein or a maltodextrin placebo for 12 months (an additional group was administered 10 mg/day lutein plus an antioxidant formula, but the discussion of results is restricted to the former 2 groups). Several endpoints were measured, both at baseline and at the completion of the 12-month intervention, including MPOD, visual performance (near visual acuity, distance visual acuity, contrast sensitivity, glare recovery), retinopathy [Age-Related Eye Disease Study (AREDS) staging], lens opacification, and visual quality of life.

Mean (average of right and left eyes) MPOD increased by 36% in the lutein group, but decreased in the placebo group ($P<0.05$ between groups). Near visual acuity in the left eye, but not in the right eye, and averaged over both eyes increased a mean of 5.4 Snellen equivalent letters (about 1 line of visual acuity) in the lutein group (95% CI, 2.5 to 8.2) but decreased by 0.2 Snellen equivalent letters in the placebo group (95% CI, -3.0 to 2.7). Near visual acuity over time was significantly different between the lutein and placebo groups for the left eye ($P=0.01$) but not for the right eye. None of the other endpoints assessed were significantly different between the lutein and placebo groups.

While preliminary results from this human intervention trial suggest that supplementation with lutein may improve near visual acuity, the study was associated with several deficiencies which limit interpretation of study findings.

1. Approximately half of the subjects in each group were taking supplemental vitamins and minerals. As demonstrated in the AREDS I, which was a National Eye Institute-sponsored randomized controlled trial of nutritional factors that may impact the development and progression of ARMD and cataract (approximate follow-up, 6.3 years), the progression of age-related maculopathy and the rate of visual acuity loss can be reduced by supplementing with β-carotene, vitamin C, vitamin E, zinc, and copper, and so use of supplemental forms of vitamins and minerals may confound study results.

2. Subjects in the placebo and lutein groups were not comparable at baseline with respect to severity of retinopathy in the left eye. Compared to the lutein group, a significantly higher proportion of subjects in the placebo group had advanced (AREDS Stage IV) disease in the left eye (41.7% *vs.* 9.1%; $P=0.0002$). The only statistically significant difference between the lutein and placebo groups was an improvement in near visual acuity in the lutein group in the left eye; however, given that the 2 subject groups were not comparable with respect to disease severity in the left eye, the validity of the

comparison is questionable. For the right eye, the proportion of subjects with AREDS Stage IV was similar in the lutein and placebo groups (31.8% *vs.* 32.0%), and there were no significant between-group differences in near visual acuity in the right eye, indicating a probable effect of the severity of the disease at study initiation on the final outcome.

In addition to these study limitations, several causality criteria, including consistency, dose-response, and effect of dechallenge could not be demonstrated due to insufficient scientific evidence. As well, the physiological relevance of the reported improvements in near visual acuity to quality of life measures are unclear, given that subjects in the lutein group did not report significant improvements relative to the placebo group in parameters such as night driving or in AREDS staging.

The Effects of Olestra on Lutein and Zeaxanthin Status: Safety Assessment

While the data on lutein and zeaxanthin fall short of the standard of significant scientific agreement required for authorized health claims in the U.S., limited and preliminary data indicate that lutein and zeaxanthin *may* be important in reducing the risk of cataract and in the maintenance of normal visual performance. Although the totality of evidence is not supportive of a role for lutein and zeaxanthin in reducing the risk of ARM/ARMD, biological plausibility for the claimed effect is strong (*i.e.,* lutein and zeaxanthin are concentrated in the macula to the exclusion of the other carotenoids, and are proposed to filter phototoxic blue light and to have antioxidant activity).

Olestra, as intended for use in a variety of food categories, is not expected to result in clinically meaningful reductions in lutein and zeaxanthin status. This is based on the following observations:

1. Because lutein and zeaxanthin are hydroxylated carotenoids (referred to as xanthophylls), circulating levels of lutein and zeaxanthin are only modestly affected by olestra compared with unhydroxylated carotenoids such as α-carotene, β-carotene, and lycopene (referred to as carotenes) which are much more lipophilic.

2. Serum levels of lutein and zeaxanthin are highly variable depending on the other components of the diet. For example, certain fibers may result in reductions in the absorption of xanthophylls, with a subsequent decrease in serum levels, while meals rich in vegetables or eggs would be expected to increase serum levels. Thus, serum levels of xanthophylls following consumption of foods containing olestra (at estimated olestra intakes from the permitted and proposed new uses, which represent up to 10% of the total daily fat intake based on the 90th percentile all-user total population) would be expected to be within the background variability of serum lutein and zeaxanthin associated with variations in the diet. The long-term (*i.e.,* 1 year) consumption of up to 17 g/day olestra+SPE, which was found not to affect lutein and zeaxanthin status in the

macula, is supportive of absorbed lutein and zeaxanthin still being sufficient at this level of intake (Broekmans *et al*., 2003).

3. Macular pigment has a very low turnover.

4. Consumption of lutein and zeaxanthin is expected to increase in the U.S.

5. Intake estimates for olestra from permitted and proposed uses combined are exaggerated.

Each of these observations is discussed in detail in the following sections.

1) Effects of Olestra on Circulating Levels of Lutein and Zeaxanthin

Several studies have been conducted to study the effects of olestra or other SPEs on serum carotenoid levels. Cumulatively, these studies suggest that:

i) Of the carotenoids studied, serum levels of lutein and zeaxanthin are generally least affected by olestra/other SPEs (Figure 1); and

ii) Effects of olestra/other SPEs on serum levels of lutein and zeaxanthin are dose-dependent (Figure 2).

Because lutein and zeaxanthin are hydroxylated carotenoids, they are less lipophilic than the unhydroxylated carotenes. Specifically, lutein and zeaxanthin are 630 and 398 times, respectively, less lipophilic than the carotenes and lycopene (Cooper *et al.,* 1997). In Figure 1, the percentage change from baseline in serum levels of lutein+zeaxanthin, β-carotene, and lycopene in studies assessing the effects of olestra/other SPEs on serum carotenoid levels are depicted. As can be observed from this figure, serum levels of lutein and zeaxanthin are generally least affected by olestra/other SPEs.

Olestra-induced reductions in serum levels of lutein and zeaxanthin are dose-dependent and predictable based on human studies, in some of which olestra was fed with meals in such a way as to maximize co-consumption with these phytochemicals (Figure 2). Using the equation of the line depicted in Figure 2 (slope = -1.151; y intercept = -2.048), the percent decrease in serum levels of lutein+zeaxanthin at the total population mean (4.6 g/day) and 90th percentile (10.6 g/day) estimated intakes of olestra from permitted and proposed uses combined (amongst users only) are estimated to be -7.3% and -14.2%, respectively. These reductions in serum levels of lutein and zeaxanthin are not considered to be biologically significant, given that similar reductions have been observed with other food ingredients, macular pigment has a very low turnover, intakes of lutein and zeaxanthin are expected to increase in the U.S., and estimated intakes of olestra from permitted and proposed uses, combined, are exaggerated.

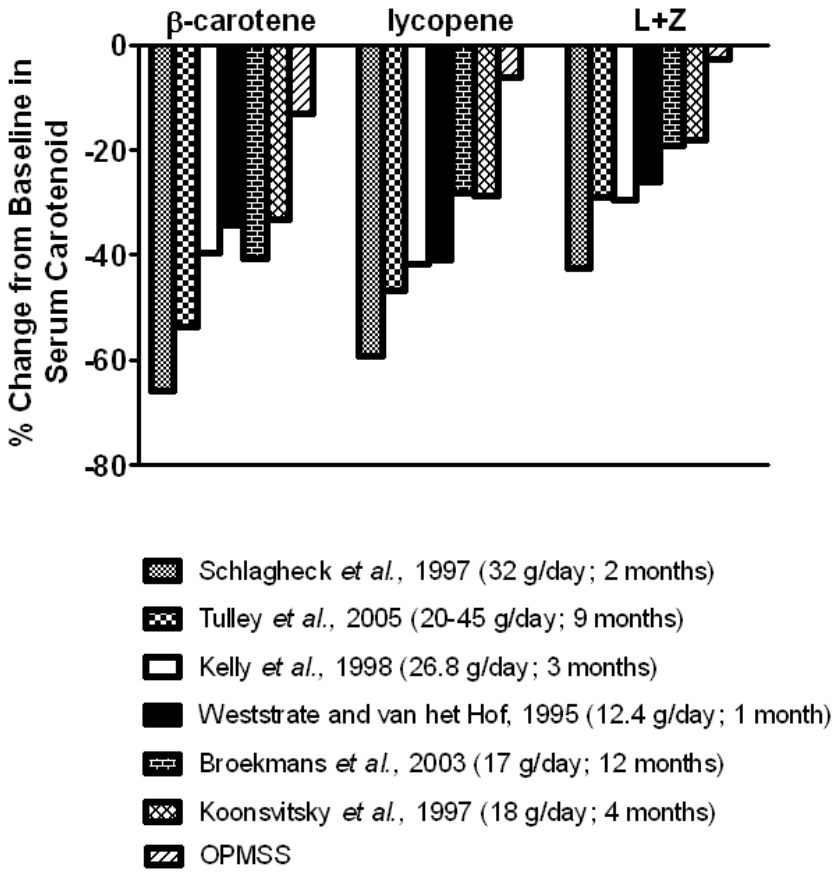

Figure 1 Changes from Baseline in Serum Levels of Lutein and Zeaxanthin Relative to β-Carotene and Lycopene

Data points are based on the highest intakes of olestra in each study. Results from Schlagheck *et al.* (1997a,b) at an olestra intake of 32 g/day were averaged; likewise, results from the highest intake levels in the OPMSS (Thornquist *et al.,* 2000; Neuhouser *et al.,* 2006) were averaged. Lutein and zeaxanthin serum levels were reported separately in Weststrate and van het Hof (1995), Broekmans *et al.* (2003), and Thornquist *et al.* (2000), but were combined in the figure above. Where baseline levels were not reported, control levels were used as reference values.
Abbreviations: L+Z, lutein+zeaxanthin; OPMSS, Olestra Post-Marketing Surveillance Study.

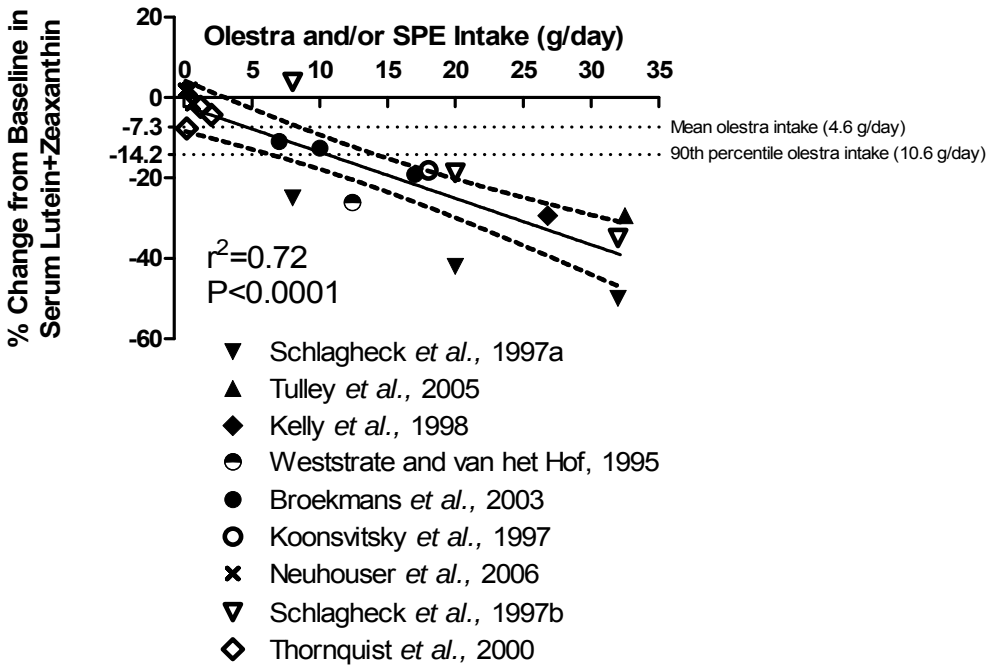

Figure 2 Change from Baseline in Serum Level of Lutein and Zeaxanthin as a Function of Olestra/SPE Intake

Results from the clinic cross-section and cohort of the OPMSS at the sentinel site were averaged (Thornquist *et al.,* 2000). Results observed in adults and adolescents from the other 3 sites involved in the OPMSS were averaged (Neuhouser *et al.,* 2006). The slope and y-intercept of the line are -1.151 and -2.048, respectively.
In the study by Schlagheck *et al.* (1997b), serum levels of lutein+zeaxanthin were very high at baseline in all groups (*i.e.,* 0.76 – 1.06 µM). Typical serum levels of lutein and zeaxanthin are approximately 0.30 µM. It is unclear why these levels are so high, and why, in the control group, serum levels of lutein+zeaxanthin doubled by the end of the 8-week study. Neither of these issues was apparent in the Schlagheck *et al.* (1997a) study.
Abbreviations: OPMSS, Olestra Post-Marketing Surveillance Study

2) Effect of Olestra on Circulating Levels of Lutein and Zeaxanthin are within Range of Background Variability Observed with Dietary Fiber and Stanol/Sterols

It has been estimated that olestra intakes at the mean (*i.e.,* 4.6 g/day) and 90th percentile (*i.e.,* 10.6 g/day) will result in reductions, from baseline, in serum levels of lutein and zeaxanthin of -7.3% and -14.2%, respectively. However, levels of lutein and zeaxanthin in serum that would result from the co-consumption of olestra containing food products is still expected to be within the normal variability of serum levels following co-consumption of xanthophyll containing foods with other dietary components.

For example, similar reductions in serum levels of lutein and zeaxanthin have been observed with certain fibers. Fibers naturally present in fruits and vegetables have been reported to

reduce the bioavailability of carotenoids. To test this hypothesis, the effects of various fibers on carotenoid bioavailability were assessed in 6 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). Plasma lutein area under the curve concentrations (AUC_{24h}) were reduced by all tested fibers by 40 to 74% ($P<0.05$). Thus, when consumed in reasonable amounts [*i.e.,* 7.8 to 10.4 g/meal, generally representing about one-third of the dietary reference intakes (DRIs) for dietary fibers (30 g/day)], dietary fiber interferes with the absorption of carotenoids to a greater extent as that observed with the consumption of olestra. The authors concluded that the fiber content of fruits and vegetables likely limits carotenoid bioavailability from these foods. Similarly, Plat and Mensink (2001) demonstrated that the consumption of margarines and shortenings containing 3.8 g vegetable oil-based plant stanols or 4.0 g wood-based stanols for 8 weeks resulted in reductions in oxygenated carotenoids (*i.e.,* sum of lutein+zeaxanthin+β-cryptoxanthin) of -13.2% and -17.4%, respectively. In another study, consumption of approximately 1.5 g/day plant sterols for 26 weeks in subjects with familial hypercholesterolemia resulted in a 7.3% reduction in serum levels of lutein (Amundsen *et al.,* 2004). The recommended intake of stanols for cholesterol-lowering is 2.0 to 2.5 g/day [http://www.proactivscience.com/index.cfm/page/31 – (Becel, 2008)].

3) Macular Pigment Has a Very Low Turnover

The effects of olestra or other SPEs on lutein and zeaxanthin status in the macula have been investigated in 2 studies. In an observational study at the sentinel site of the Olestra Post-Marketing Surveillance Study, MPOD was measured cross-sectionally during a single clinic visit in 280 subjects (81 of whom reported consuming olestra) (Cooper *et al.,* 2000). There were no significant differences noted between olestra consumers and non-consumers in MPOD. Olestra mean, median, and 90th percentile intakes amongst consumers were 1.09, 0.34, and 2.43 g/day, respectively (Cooper *et al.,* 2000). At the time of this study, olestra had been on the market for approximately 1 year.

In a 1-year human intervention study, the consumption of up to 17 g/day olestra+SPE [in the form of chips (7 g/day olestra) and a margarine-like spread (10 g/day SPE)], did not result in reductions in MPOD, despite reductions in serum levels of lutein+zeaxanthin. Median changes in MPOD in all groups changed in a positive direction (Broekmans *et al.,* 2003). In this study, it was estimated that approximately 20 to 25% of participants used the spread on bread or on their vegetables (indicating potential consumption with main meals). The highest amount of olestra+SPE (*i.e.,* 17 g/day) administered in this study is 6.4 g (or 37.6%) greater than the estimated users-only 90th percentile intake of olestra (*i.e.,* 10.6 g/day) from current and proposed uses, combined.

Although serum levels of lutein and zeaxanthin are predicted to be reduced by 7.3% and 14.2%, respectively, at the mean and 90th percentile intakes of olestra from all permitted and proposed uses, combined, these predicted reductions are not expected to result in changes in MPOD. This fact is supported by the cross-sectional and human intervention studies already discussed, as well as by the finding that macular pigment has a very low turnover, with levels remaining stable for up to 6 months following the end of lutein and zeaxanthin supplementation, despite reductions in serum levels of lutein and zeaxanthin (Hammond *et al.,* 1997; Johnson *et al.,* 2000; Trieschmann *et al.,* 2007). Thus, it appears that lutein and zeaxanthin concentrations in the macula are highly conserved.

4) Lutein and Zeaxanthin Intakes in the U.S. Diet are Expected to Increase

Although consumption data for lutein and zeaxanthin are limited, it is estimated that the average dietary intake of these xanthophylls from food sources ranges from 2 to 4 mg/person/day (U.S. FDA, 2004). However, intakes of lutein and zeaxanthin are likely to increase in the U.S., given the increasing public perception of the potential roles of these carotenoids in the maintenance of healthy visual function. In anticipation of consumer demand, three GRAS notices have been filed with the FDA for addition to foods of crystalline lutein and zeaxanthin (U.S. FDA, 2004); lutein and zeaxanthin esters (U.S. FDA, 2003) and suspended lutein (U.S. FDA, 2007). The FDA had no questions on the notifications allowing for foods fortified with these carotenoids to be made available to the U.S. consumer. (Note: The third notice for suspended lutein was filed regarding the GRAS status of lutein for use in infant formula. However, there is no intention to add olestra to formula or other foods intended specifically for infants and toddlers.)

The FDA responded to the notices with letters of no objection. For the first two notifications, the intended uses of lutein and zeaxanthin included a number of food categories, including baked goods and baking mixes, soy milk, beverages and beverage bases, breakfast cereals, chewing gum, dairy product analogs, egg products and egg substitutes, fats and oils, frozen dairy desserts and mixes, gravies and sauces, hard candy, fruit snacks, infant and toddler foods, soft candy, soups and soup mixes, milk products, and processed fruit and fruit juices. Intakes of lutein and zeaxanthin were estimated to range from approximately 0.3 to 3.0 mg/reference amount customarily consumed. In one notice, estimated intakes of lutein+zeaxanthin from the intended uses were 7.7 mg/person/day at the mean and 14.2 mg/person/day at the 90th percentile (U.S. FDA, 2004). These estimated intakes, which do not account for use of supplemental forms of lutein and zeaxanthin, are approximately 3.9 to 7.1-fold greater than background intakes of lutein and zeaxanthin from plant sources.

Several lutein and zeaxanthin supplementation trials have been identified in the literature, and data from these studies were used to estimate % increases from baseline in serum levels of lutein and zeaxanthin with different intakes of these xanthophylls. A total of 7 studies and 10 data points were used in the regression analysis; the studies included healthy subjects, elderly

subjects, as well as subjects with ARMD; in addition, the lengths of supplementation varied from 5 weeks to 6 months, and supplementation doses ranged from 2.5 to 30 mg/day.

At the total population mean and 90th percentile intakes of olestra from all permitted and proposed uses combined, serum levels of lutein and zeaxanthin are expected to be reduced by 7.3 and 14.2%, respectively (Figure 2). In comparison, the percent increase in serum levels of lutein and zeaxanthin at the estimated mean (7.7 mg/day) and 90th percentile (14.2 mg/day) intakes of lutein and zeaxanthin was determined to be 255 and 547%, respectively. These percent increases are several-fold higher than the predicted decreases in serum levels of lutein and zeaxanthin at the mean and 90th percentile intakes of olestra from all permitted and proposed uses, combined. Thus, reductions in serum levels of lutein and zeaxanthin with intakes of olestra from the permitted and proposed uses combined are likely to be compensated for by increases in the intakes of these carotenoids from proposed new food uses.

While this evaluation is crude in that projected lutein and zeaxanthin intakes (and corresponding increases in serum levels of lutein and zeaxanthin) are likely over-estimates, given that intakes are calculated by assuming that all foods in relevant food categories will contain the maximum levels of lutein and zeaxanthin, the same is true for olestra. For these same reasons, projected olestra intake estimates (and corresponding reductions in serum levels of lutein and zeaxanthin) from all permitted and proposed uses combined also are exaggerated. The USDA 1994-1996 CSFII and the 1998 Supplemental Children's Survey were used in the derivation of both lutein and zeaxanthin intakes and olestra intakes; thus, despite intake estimates being exaggerated, the intake estimates are more comparable than if different intake databases were used (USDA, 2000).

5) Olestra Intake Estimates are Exaggerated

It has been estimated that intakes of olestra from permitted and proposed uses, combined, are 4.6 g/day and 10.6 g/day at the mean and 90th percentile, respectively. Associated reductions in serum levels of lutein and zeaxanthin are -7.3% and -14.2%, respectively. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently (Anderson, 1988; Lambe and Kearney, 1999). Moreover, several conservative assumptions are made in the derivation of estimated intakes, and these result in an exaggeration in the estimated intakes of olestra from permitted and proposed food uses. These assumptions are discussed below:

- It was assumed that *all* food products within a food category contain olestra at the *maximum* specified level of use;
- The proposed uses are for foods which are prepackaged. Thus, it was assumed that all foods in a food category are pre-packaged, even if there was uncertainty that the food was

pre-packaged (foods not pre-packaged and not produced according to GMP to ensure vitamin restoration, would not be made with olestra); and

- Where limited data on fat-modified foods were available, regular fat food codes were used in intake estimates, thereby inflating the percentage of the U.S. population who may be users of olestra.

Prior to the market introduction of olestra, intakes of olestra were predicted by Webb et al., (1997) to be 3.1 and 6.9 g/day at the mean and 90th percentile, respectively. In the Olestra Post-Marketing Surveillance Study (OPMSS), mean olestra intakes were 0.78±1.39 g/day in adults and 0.74±1.0 g/day in adolescents (Neuhouser *et al.,* 2006). Thus, estimated intakes of olestra were approximately 4-fold greater than actual intakes of olestra. Olestra is associated with dose-dependent reductions in circulating levels of lutein and zeaxanthin; since actual olestra intakes will likely be lower than estimated olestra intakes, reductions in serum levels of lutein and zeaxanthin also will be lower.

Conclusions Regarding Carotenoids

Olestra is being proposed for use in several food categories, and some of these foods may be consumed as/with main meals. Co-consumption of olestra with carotenoid-rich meals results in a reduction in circulating carotenoid levels. To ensure that reductions in circulating levels of β-carotene, lycopene, β-cryptoxanthin, and α-carotene will not be associated with adverse health effects, position statements and recommendations of scientific and regulatory organizations were reviewed and data from human studies published in or subsequent to 2003 were critically evaluated. The limited numbers of studies reporting cancer risk reductions with increased intakes/circulating levels of carotenoids were case-control studies. Case-control studies are retrospective and subject to recall bias and findings are confounded by possible effects of the disease itself on carotenoid status. The main conclusion of this evaluation, based on the current scientific evidence and consistent with the recent findings of the IOM and other authoritative bodies, is that the essentiality of β-carotene, lycopene, β-cryptoxanthin, and α-carotene for the maintenance of human health and/or prevention of disease cannot be corroborated by the current scientific evidence.[5]

Because the research area pertaining to lutein and zeaxanthin is continuously evolving, a critical review of the literature relating to the effects/associations of lutein and zeaxanthin and risk of cataract, ARM/ARMD, and visual performance has been conducted to determine whether olestra-related reductions in serum levels of lutein and zeaxanthin will be associated with adverse visual outcomes.

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[5] The IOM identified the roles of the provitamin A carotenoids (β-carotene, β-cryptoxanthin, and α-carotene) as sources of vitamin A; however, the DRIs for vitamin A do not require any fraction to come from the provitamin A carotenoids.

Data from methodologically good observational studies *suggest* that increased intakes of lutein and zeaxanthin may reduce the risk of age-related cataract. Several causality criteria were supported by the available data – with the exception of effect of dechallenge, strong biological plausibility, and the ruling out of alternate explanations. *All* studies reporting significant reductions in risk of cataract with increased intakes of lutein+zeaxanthin reported attenuations in the relationships when other nutritional variables also associated with reduced risk of cataract were assessed simultaneously with lutein+zeaxanthin. Moreover, although lutein and zeaxanthin have antioxidant activity and are known to filter phototoxic blue light, they are not particularly concentrated in the lens as they are in the macula, thereby reducing biological plausibility.

Observational studies – including prospective cohort studies – are associated with several limitations (see Table 2) and history has shown that while observational studies are hypothesis-generating, often, claimed effects cannot be verified in human intervention trials. For example, in the early 1980s, observational studies reported that risk of lung cancer was significantly reduced in people who consumed diets rich in fruits and vegetables, and with closer examination, β-carotene was hypothesized to be the active ingredient (Flagg *et al.,* 1995). Subsequent human intervention trials demonstrated that risk of lung cancer actually increased with β-carotene supplementation in smokers or former asbestos workers (Albanes *et al.,* 1995; Omenn *et al.,* 1996a,b; Goodman *et al.,* 2004).

Thus, although observational studies support a reduction in risk of cataract with increased intake of lutein and zeaxanthin, and although this proposed claimed effect has been considered in the current safety review, definitive supporting data are lacking, and based on historical experiences, *caution should be exercised in inferring causality from correlations*.

Table 2 Limitations Associated with Observational Studies

Limitation	Description
Measurement error	Inaccuracy in measurement of biomarkers or in classification of subjects.
Participation bias	Healthier people are more likely to participate in health studies, and if more subjects with age-related eye diseases refused to participate in the study or were lost to follow-up, associations will be biased towards the null.
Selective mortality bias	Age-related eye diseases are associated with other chronic diseases, such as cardiovascular disease. If death is more prevalent amongst subjects with age-related eye diseases, associations will be biased towards the null.
Sampling bias	Error resulting from differences in the characteristics between members of a reference population and those selected/invited to participate in an ancillary study.
Recall bias	Typically a problem in retrospective, case-control, and cross-sectional studies; occurs when subjects with age-related eye diseases report their dietary intakes inaccurately. Recall bias tends to bias associations away from the null.
Diet instability	Subjects developing age-related eye diseases or other diseases may alter their diets, in which case, dietary intakes/plasma levels of lutein and zeaxanthin assessed either prospectively or retrospectively will not be reflective of chronic dietary intakes.
Confounding bias	Confounders are variables that are considered risk factors for age-related eye diseases and that are associated with lutein and zeaxanthin intakes. Insufficient control of dietary and non-dietary confounding variables can result in inaccurate diet-disease relationships, thereby biasing associations away from the null.
Residual confounding	Arises when a confounding variable has not been identified or when a confounding variable cannot be measured with sufficient precision.
Rare diseases	In populations where risk of age-related eye diseases is low, the number of events may be too small to discern associations, thereby biasing associations towards the null.
Publication bias	Most studies reporting null effects are less likely to be published. The totality of published evidence is biased away from the null.
Other	In longitudinal studies, effects of several variables, including historical, political, and economic events, cannot be accounted for. In addition, methodologies change over time, as outdated measurement tools are replaced with more modern ones, making comparisons of baseline and follow-up measures difficult.

The evidence is equivocal with respect to the relationship between the status of lutein and/or zeaxanthin (as assessed *via* dietary intakes, circulating levels, or MPOD) and risk of ARM/ARMD. In one study, subjects with a family history of ARM/ARMD were reported to have significantly lower MPODs than subjects without a family history of ARM/ARMD (Nolan *et al.,* 2007). In this same study, dietary intakes and serum levels of lutein and zeaxanthin were reported to be similar, irrespective of family history of ARM/ARMD. Thus, it appears that while dietary intakes and plasma levels of lutein and zeaxanthin are “normal” in subjects with a family history of ARM/ARMD, retinal uptake of lutein and zeaxanthin may be compromised. Further research is needed to understand whether MPOD is inversely associated with risk of ARM/ARMD, and whether MPOD can be increased in *all* subjects at risk for ARM/ARMD. “Retinal non-responders” (*i.e.,* subjects who, upon lutein+zeaxanthin supplementation, demonstrate increases in serum levels of lutein+zeaxanthin but not in MPOD) have been described in some supplementation trials (Hammond *et al.*, 1996; Trieschmann *et al.,* 2007).

There is preliminary evidence from a single human intervention trial (the Veterans LAST; Richer *et al.,* 2004) that supplementation with lutein and zeaxanthin may improve near visual acuity unilaterally (*i.e.,* in the left eye). Interpretation of study findings is confounded by the prevalent use, in both groups, of multivitamin and mineral supplements. In addition, compared to the lutein group, a significantly higher proportion of subjects in the placebo group had severe (AREDS Stage IV)[6] retinopathy in the left eye at baseline (41.7% *vs.* 9.1%; P=0.0002). Given that the two subject groups were not comparable at baseline with respect to severity of retinopathy in the left eye, a comparison of improvements in visual performance across the groups for the left eye may be invalid. For the right eye, the proportion of subjects with AREDS Stage IV was similar in the lutein and placebo groups at baseline (31.8% *vs.* 32.0%), and there were no significant between-group differences in near visual acuity in the right eye, indicating that baseline severity of retinopathy probably influences the final outcome. Given these study limitations, a cause and effect relationship could not be established between consumption of lutein and zeaxanthin and improvements in visual performance. Additionally, as subjects in the lutein group did not experience significant improvements, relative to the placebo group, in measures of quality of life (activities of daily living, night driving, and glare recovery), the physiological relevance of a mild improvement in near visual acuity in one eye is unclear.

Despite the inability to demonstrate that reductions in risk of cataract or ARM/ARMD and improvements in visual performance are causally related to lutein and zeaxanthin, to be conservative, the potential role of lutein and zeaxanthin in the maintenance of visual health was considered in the current safety evaluation of olestra, as olestra is being proposed for use in several food categories which may result in a reduction in the absorption of these xanthophylls. The overall conclusion from this safety assessment is that reductions in lutein and zeaxanthin are unlikely to be clinically meaningful. This conclusion is supported by 4 observations:

- Predicted reductions in serum levels of lutein and zeaxanthin at the mean and 90th percentile intakes of olestra from permitted and proposed food uses combined are small in magnitude and similar to those caused by typical intakes of fibers or plant sterols/stanols.

- Estimated intakes of olestra, and corresponding reductions in serum levels of lutein and zeaxanthin, are exaggerated. In deriving intake estimates, *all foods in a given food category* were assumed to contain olestra, and use-levels were assumed to be *the maximum proposed*. As fat-soluble vitamins are required to be added to olestra-containing products [21 CFR 172.867(d)] (U.S. FDA, 2008a), products containing olestra will be restricted to those that are pre-packaged and produced in GMP-compliant facilities; nevertheless, in the derivation of intake estimates, all foods in the proposed

[6] The macular status of the subjects ranged from essentially no macular abnormality in either eye (ARMD Stage 1), to advanced ARMD or lesions of ARMD with visual acuity less than 20/32 in only 1 eye (ARMD Stage 4) (AREDS, 2001).

food categories were included, despite the inability to discern whether all were pre-packaged. In addition, in the absence of fat modified food codes, regular-fat food codes were used, thereby inflating the percentage of the U.S. population that consumes fat-modified foods.

- Olestra, at the 90th percentile intake, is unlikely to have any effect on MPOD, the best measure of lutein and zeaxanthin status in the eye. Despite reductions in serum levels of lutein and zeaxanthin, MPOD remained stable for up to 1 year of consuming up to 17 g/day olestra+SPE (Broekmans *et al.,* 2003), which is approximately 6.4 g higher than the total population users-only 90th percentile intake of olestra from permitted and proposed uses, combined.

- Intakes of lutein and zeaxanthin are projected to increase in the U.S., and increases in serum levels of lutein and zeaxanthin are expected to more than compensate for olestra-related reductions in serum levels of lutein and zeaxanthin.

Based on these findings, addition of olestra at the use-levels and food categories proposed herein are not expected to be associated with adverse visual outcomes.

SUMMARY

Olestra, meeting the specifications of the *Food Chemicals Codex* (FCC, 2008), is a food additive that has been 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 since 1996 (21 CFR §172.867) (U.S. FDA, 2008a). In 2004, the FDA amended the food additive regulations to allow for the safe use of olestra as a replacement for fats and oils in pre-packaged, unpopped popcorn kernels that are ready-to-heat [21 CFR §172.867(c)] (U.S. FDA, 2008a). In 2007, olestra was determined to be GRAS, consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*, for use in pre-packaged ready-to-eat cookies (FDA notification).

The current evaluation was undertaken to determine if expanded uses of olestra to include use in all pre-packaged ready-to-heat cookies, all other pre-packaged ready-to-eat, and ready-to-heat baked goods, and pre-packaged ready-to-eat frostings and icings, mayonnaise, ice cream, frozen yogurt, breakfast/granola/nutritional bars, chocolate confections, and the natural or processed cheese portion of pre-packaged ready-to-eat or ready-to-heat prepared foods intended for sale at retail outlets or vending machines also would be GRAS.

The data and information summarized in this dossier demonstrate that olestra, meeting appropriate food grade specifications and manufactured in accordance with current GMP, would be GRAS based on scientific procedures for use as a food ingredient under the expanded conditions of intended use. This conclusion is conditional on the requirement that vitamins A, D,

E, and K be added to the olestra-containing foods at concentrations that meet the conditions specified in 21 CFR §172.867(d).

The determination of GRAS is supported by the following important details.

- The total population mean and 90th percentile intakes *from proposed* (new uses proposed herein) *and permitted uses,* combined, for all-users, were estimated to be 4.6 and 10.6 g/day, respectively, compared to estimates of 3.1 and 7.7 g/day, respectively, *for permitted uses* (pre-packaged, ready-to-eat savory snacks and cookies and pre-packaged, unpopped popcorn kernels that are ready to heat). Thus, the proposed uses increase estimated intakes modestly by 1.5 and 2.9 g/day for the mean and 90th percentile, respectively. In comparison, total daily fat intakes at the mean and 90th percentile, are approximately 75 and 114 g/day, respectively, for the total population; thus, for the total population, olestra would replace less than 10% of total fat intake.

- Among infants aged 0 to 6 months, mean and 90th percentile olestra intakes for all-users were estimated to be 1.0 and 2.1 g/day, respectively. (Intakes of olestra among infants are largely attributable to the use of full fat surrogates for foods without reduced fat equivalents.) Total daily fat intakes for this age group are approximately 35 (mean) and 46 g/day (90th percentile); therefore, potential exposure to olestra represents less than 5% of total fat intake. Furthermore, these values are highly likely to be gross overestimates of actual olestra consumption given that infants aged 0 to 6 months primarily consume breast milk and/or infant formula, with the introduction of some solid foods that are most likely to be pre-packaged baby foods (for which olestra is not proposed for use). For infants aged 7 to 12 months, olestra intakes, for all-users, were estimated to be 0.7 and 1.6 g/day at the mean and 90th percentile, while total fat intakes are approximately 40 and 54 g/day, respectively. Thus, olestra intakes would replace less than 3% of total fat intakes for this age group. Moreover, the intakes of olestra estimated for this age group result almost entirely from the required use of food codes representative of regular fat foods that were used as surrogates in the absence of food codes representative of fat modified or reduced fat foods (*e.g.,* most baked goods including bread).

- The 90th percentile all-user intakes of olestra estimated for all population groups are lower than the maximum intake of 17 g/day olestra+SPE employed in the Broekmans *et al.* (2003) 12-month randomized, double-blind, placebo-controlled parallel study which was not associated with any adverse health or visual effects.

- The intake modeling methodology conducted for this assessment included the following conservative assumptions, thus actual intakes will likely be much lower:

- All of the food codes that are representative of foods that are permitted and proposed for olestra use were assumed to contain olestra (*i.e.*, 100% market share);
- All food products were assumed to contain olestra at the maximum specified level of use;
- All foods in a food category were assumed to be pre-packaged, even if there was uncertainty that the food was pre-packaged; and
- Where limited data on fat-modified foods were available, regular fat food codes were used in intake estimates, thereby inflating the percentage of the U.S. population who may be users of olestra.

- The Olestra Post-Marketing Surveillance Study [OPMSS; (Thornquist *et al.,* 2000; Neuhouser *et al.,* 2006)], 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 from savory snacks was estimated by Webb *et al.* (1997) 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 from savory snacks was estimated to be 8.1 g/day, while the actual intake was 1.8 g/day].

- 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 (demonstrated in original GRAS evaluation).

  - 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.

- As olestra is not absorbed from the gastrointestinal tract, it is not associated with systemic toxicity. This has been demonstrated in numerous standard toxicology studies including chronic studies in mice, rats, and dogs, a 2-generation reproductive and developmental toxicity study in rats, and a four year study in primates. Olestra was not associated with systemic toxicity when administered to experimental animals at dietary levels of up to 10%, the highest dose level tested (demonstrated in original GRAS evaluation).

- Studies in humans have demonstrated that consumption of up to 40 g/day olestra is not associated with adverse GI effects (demonstrated in original GRAS evaluation).

- Sufficient vitamin A is added to olestra containing products to offset effects of olestra on serum vitamin A levels. Other than the provitamin A activity of α-carotene, β-carotene, and β-cryptoxanthin, the current state of scientific evidence is equivocal regarding the roles of carotenoids in maintaining health or preventing disease.

- Fat-soluble restoration levels will compensate for reductions in the absorption of fat-soluble vitamins given that restoration levels were calculated for olestra intakes up to 32 g/day, a level well in excess of the estimated 90th percentile takes for users-only.

- Olestra intakes, for permitted and proposed uses, at the mean (*i.e.,* 4.6 g/day) and 90th percentile (*i.e.,* 10.6 g/day) were estimated to result in reductions, from baseline, in serum levels of lutein and zeaxanthin of -7.3% and -14.2%, respectively.

- Based on the following observations, these reductions in circulating levels of lutein and zeaxanthin are not expected to be clinically meaningful:

    - Intake estimates for olestra from permitted and proposed food uses combined are exaggerated;
    - Reductions in serum levels of lutein and zeaxanthin are within the background range of those caused by other food ingredients such as fiber or plant sterols/stanols;
    - Intakes of lutein and zeaxanthin are expected to increase in the U.S.;
    - Lutein and zeaxanthin concentrations in the macula are highly conserved;
    - While data from observational studies suggest that increased intakes of lutein and zeaxanthin are associated with a reduced risk of cataract, specificity of effect could not be established – in all studies assessing associations with lutein and zeaxanthin independently of other nutritional covariates, relationships were always attenuated and no longer significant;
    - There are limited data from one human intervention study that supplementation with lutein and zeaxanthin may improve visual performance; however, the study was based on a small sample size and had several limitations, including more severe disease in placebo subjects, relative to treatment subjects, at study initiation, in the left eye where efficacy was demonstrated; these deficiencies limit interpretation of the study findings;
    - Although there is strong biological plausibility for a role for these xanthophylls in reducing ARMD risk, data from epidemiological studies are equivocal with respect to the association between lutein and zeaxanthin and risk of ARMD;
    - Causality could not be established for any of the exposure biomarkers assessed (intake, circulating levels, or MPOD).

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 described herein. This conclusion is conditional on the requirement that vitamins A, D, E, and K be added to the olestra-containing foods at concentrations that meet the conditions specified in 21 CFR §172.867(d).

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New member of panel included to contribute expertise to lutein and zeaxanthin evaluation

4-27-09
Date

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OLESTRA AMENDMENT GRAS NOTICE

ATTACHMENT 1 TO APPENDIX A:

CURRICULA VITAE OF EXPERT PANEL MEMBERS

January 18, 2010

Pages 000084-000229 removed in accordance with the Privacy Act of 1974.

OLESTRA AMENDMENT GRAS NOTICE

APPENDIX B:

ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM PERMITTED AND PROPOSED FOOD-USES

January 18, 2010

ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM PERMITTED AND PROPOSED FOOD-USES

Table of Contents

		Page
1.0	INTRODUCTION	B-1
2.0	FOOD CONSUMPTION SURVEY DATA	B-2
2.1	Survey Description	B-2
2.2	Statistical Methods	B-3
2.3	Statistical Reliability	B-3
3.0	FOOD USAGE DATA	B-4
3.1	Permitted and Proposed Food-Uses and Use-Levels for Olestra	B-4
3.2	Identifying Representative Food Codes for All Permitted and Proposed Food-Uses	B-7
3.3	Determining Fat Content of Permitted and Proposed Food-Uses	B-8
3.4	Restriction to Retail Store or Vending Machine Purchased, Pre-Packaged, Ready-To-Eat or Ready-To-Heat Products	B-9
4.0	DAILY OLESTRA INTAKE FROM ALL PERMITTED FOOD-USES	B-10
4.1	Estimated Daily Olestra Intake from All Permitted Food-Uses	B-10
5.0	DAILY OLESTRA INTAKE FROM ALL PERMITTED AND PROPOSED FOOD-USES	B-11
5.1	Estimated Daily Intake of Olestra from All Permitted and Proposed Food-Uses	B-11
5.2	All-Person Intakes of Individual Permitted and Proposed Food-Uses of Olestra	B-14
5.3	All-User Intakes of Individual Permitted and Proposed Food-Uses of Olestra	B-15
6.0	OLESTRA INTAKES RELATIVE TO TOTAL FAT INTAKES	B-19
7.0	DETERMINATION OF PERCENT CONSUMERS OF FAT MODIFIED PRODUCTS	B-20
8.0	OLESTRA AND SPECIFIC POPULATION GROUPS	B-22
8.1	Infants	B-22
8.2	Pregnant and Lactating Women	B-22
8.3	Special Supplemental Nutrition Program for Women, Infants and Children	B-23
9.0	PREDICTING OLESTRA INTAKE: A CONSERVATIVE APPROACH	B-24

10.0 CONCLUSIONS B-25

11.0 REFERENCES B-26

List of Attachments

Attachment I Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Different Population Groups Within the United States

Attachment 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

Attachment III Representative CSFII 1994-1996, 1998 Food Codes for All Permitted and Proposed Food-Uses of Olestra in the United States

Attachment IV Representative CSFII 1994-1996, 1998 Food Codes for All Fat Modified Products

Attachment V Estimated Daily Intake of Olestra by the U.S. Population from All Permitted and Proposed Food-Uses (NHANES 2003-2004, 2005-2006)

List of Tables

Table 3.1-1 Summary of the Individual Permitted and Proposed Food-Uses and Levels of Fat Being Replaced by Olestra in the U.S. B-5

Table 3.2-1 Food Codes Representative of Fat-Modified Products *Versus* Regular Fat Products B-8

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) B-10

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) B-11

Table 5.1-1 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data) B-12

Table 5.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data) B-13

Table 6-1 Comparison of Estimated Olestra Intake from All Permitted and Proposed Food Uses with Total Fat Intake in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data) B-19

Table 7-1 Summary of the Estimated Percentage of the U.S. Population that Consumes Fat Modified Products (1994-1996, 1998 USDA CSFII Data) B-21

Table 8.2-1 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses by Pregnant and Lactating Women in the U.S. (1994-1996, 1998 USDA CSFII Data) B-23

Table 8.2-2	Summary of the Estimated Daily Per Kilogram Body Weight Intake of Olestra from Permitted and Proposed Food-Uses by Pregnant and Lactating Women in the U.S. (1994-1996, 1998 USDA CSFII Data)	B-23
Table 8.2-3	Summary of the Estimated Percentage of Pregnant and Lactating Women of the U.S. Population that Consumes Fat Modified Products[1] (1994-1996, 1998 USDA CSFII Data)	B-23
Table I-1	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-1
Table I-2	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-4
Table I-3	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-7
Table I-4	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-10
Table I-5	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-13
Table I-6	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-16
Table I-7	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-19
Table I-8	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-22
Table I-9	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-25
Table I-10	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-28
Table I-11	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-31
Table I-12	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-34
Table I-13	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-37
Table I-14	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-40
Table I-15	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-43

Table I-16	Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population Within the United States (1994-1996, 1998 USDA CSFII Data)	BI-46
Table II-1	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-1
Table II-2	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-4
Table II-3	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-7
Table II-4	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-10
Table II-5	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-13
Table II-6	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-16
Table II-7	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-19
Table II-8	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-22
Table II-9	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-25
Table II-10	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-28
Table II-11	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-31
Table II-12	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-34
Table II-13	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 Years Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-37

Table II-14	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-40
Table II-15	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-43
Table II-16	Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population Within the United States (1994-1996, 1998 USDA CSFII Data)	BII-46
Table 2-1	Estimated Daily Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (NHANES 2003-2004, 2005-2006 Data)	V-4
Table 2-2	Estimated Daily per Kilogram Body Weight Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (NHANES 2003-2004, 2005-2006 Data)	V-5
Table 3-1	Comparison of the Estimated Daily Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII *vs.* 2003-2004, 2005-2006 NHANES Data)	V-6
Table 3-2	Comparison of the Estimated Daily Per Kilogram Body Weight Daily Intake of Olestra From All Proposed Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII *vs.* 2003-2004, 2005-2006 NHANES Data)	V-7

ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM PERMITTED AND PROPOSED FOOD-USES

1.0 INTRODUCTION

The following is an assessment of the consumption of olestra from all permitted and proposed food-uses by the United States (U.S.) population. Olestra is a replacement for conventional fats, and products using Olestra are intended to be marketed as “low-fat”, “reduced-fat”, or “fat-free”. Olestra is currently permitted for use in pre-packaged ready-to-eat (RTE) savory snacks (*i.e.*, salty or piquant, but not sweet) and pre-packaged ready-to-heat (RTH) unpopped popcorn kernels in place of fats and oils (21 CFR §172.867) (CFR, 2008a). Olestra also is permitted for use in pre-packaged RTE cookies. Olestra is currently proposed for use in the following products that are produced at facilities operating under Good Manufacturing Practice (GMP) and are intended for sale at retail outlets or vending machines: baked goods and baking mixes [pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH biscuits and English muffins, pre-packaged RTE & RTH bread, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTH cookies, pre-packaged RTE & RTH cornbread, corn muffins, tortillas and taco shells (hard and soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack type), pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pancakes, crepes, and French toast, pre-packaged RTE & RTH sweet pastries (pastry portion), pre-packaged RTE & RTH sweet pies (pastry portion), pre-packaged RTE & RTH meat and vegetable pies and pastries (pastry portion), pre-packaged RTE & RTH rolls, pre-packaged RTE & RTH sweet rolls and quick breads, and pre-packaged RTE & RTH waffles], cheeses (natural cheese portion of pre-packaged RTE & RTH prepared foods, processed cheese portion of pre-packaged RTE & RTH prepared foods), confections and frostings (pre-packaged RTE frosting and icing), fats and oils (pre-packaged RTE mayonnaise), frozen dairy desserts and mixes (pre-packaged RTE ice cream, and pre-packaged RTE frozen yogurt), grain products and pastas (pre-packaged RTE breakfast, granola, and nutritional bars, and pre-packaged RTE & RTH pizza crust), and soft candy [pre-packaged RTE chocolate confections (chocolate portion)]. Foods specifically marketed as infant or toddler products are not proposed for olestra use.

Estimates for the intake of olestra were based on the level of fat replaced by olestra in permitted and proposed food-uses in the U.S. 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, aged 0 to 6 months and 7 to 11 months;
- toddlers, aged 1 to 3 years;
- children, aged 4 to 8 years and 9 to 13 years;
- female teenagers, aged 14 to 18 years;
- male teenagers, aged 14 to 18 years;
- female adults, aged 19 to 30 years, 31 to 50 years, 51 to 70 years, and 71 years and up;
- male adults, aged 19 to 30 years, 31 to 50 years, 51 to 70 years, and 71 years and up and,
- total population (all age and gender groups combined).

Within the infant population group, the older infants were divided into those aged 7 to 11 months as opposed to the tradition grouping of 7 to 12 months as a result of the criteria by which age was documented in the CSFII data set. For all individuals aged 1 year and older age was described by years, whereas in the individuals aged younger than 1 year age was described in months. As a result an 11 months old infant has an age of 11 months while any infant or toddler between the ages of 12 and 23 months has an age of 1 year. This classification renders it impossible to separate out infants 12 months of age and therefore, the category was capped at 11 months of age.

2.0 FOOD CONSUMPTION SURVEY DATA

2.1 Survey Description

USDA, CSFII 1994-1996 provides food consumption data on persons of all ages; while, CSFII 1998 is specifically focused on children from birth through 9 years of age. The permitted and proposed food-uses for olestra include many products that are highly consumed by children. Thus, although nationwide dietary intake data for the years 2003-2004 are now available for public use (National Health and Nutrition Examination Survey 2003-2004); CSFII 1994-1996, 1998 survey data were used for the intake assessment on olestra because of the substantially greater number of children included in this survey (USDA, 2000; 2008). CSFII 1994-1996, 1998 surveys provide the most appropriate data for evaluating food-use and food consumption patterns for olestra in the U.S., 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 2 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) or the sample size is less than 30 respondents. 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

3.1 Permitted and Proposed Food-Uses and Use-Levels for Olestra

The individual permitted and proposed food-uses and levels of fat being replaced by olestra employed in the current intake analysis are summarized in Table 3.1-1. The method used for selecting appropriate food codes is summarized in Section 3.2, the determination of use-levels is presented in Section 3.3, and the method for restricting the place of purchase for the assessment is described in Section 3.4.

Food codes representative of each of the permitted and proposed food-uses were chosen from the CSFII 1994-1996, 1998 (USDA, 2000). The use of olestra results in products that are intended to be marketed as “reduced-fat”, “low-fat”, or “fat-free”; therefore, intakes of olestra were estimated using food codes representing reduced-fat, low-fat, and fat-free products, if available. If the fat-modified version was not available, food codes representative of the regular version were used as surrogates (see Section 3.2). The proposed use-levels of olestra for the proposed food-uses range from 67% to 100% replacement of added fats. Proposed use-levels of less than 100% will contain blends of digestible fat (*e.g.,* vegetable oils, shortenings, *etc.*) and olestra. These blends were developed by The Procter & Gamble Company to provide palatable products and/or to meet other technical properties of the food matrices.

Products intended for olestra use will be <u>pre-packaged</u> ready-to-eat (RTE) or ready-to-heat (RTH) that will be produced at food manufacturing and packaging establishments operating under GMP. Olestra-containing foods are intended to be sold at retail outlets or vending machines. Olestra will not be distributed for use as a food ingredient to facilities that do not have the capability to produce and package foods according to GMP such as restaurants, bakeries, cafeterias, or other such facilities. Olestra will not be sold as a food ingredient to food service establishments (even if they operate according to GMP), as the end use is not in pre-packaged form (*i.e.,* such foods are typically sold in eateries, in an <u>unpackaged</u>, ready-to-eat form). This will ensure that the required vitamin restoration levels are met and that all olestra-containing foods will indicate olestra in the ingredients list.

Olestra is not intended for use in foods that are specifically produced for infants or toddlers. Also, olestra will not be used to replace the fat in milk, with the exception of the use of olestra to

replace the butter fat in ice cream, frozen yogurt, and the natural and processed cheese portion of RTE and RTH prepared foods. Additionally, olestra is not intended for use in products in which it is difficult to predict the amount and manner in which the product may be used by consumers, such as cooking oils, and block or shredded cheese. Although natural and processed cheeses are proposed for olestra use, they are only proposed for use in the cheese portion of pre-packaged RTE and RTH prepared foods (Table 3.1-1).

Food codes were grouped in food-use categories according to Title 21, Section §170.3 of the Code of Federal Regulations (CFR, 2008b). Product-specific adjustment factors were developed based on data provided in the standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000; herein referred to as standard recipe file). All food codes included in the current intake assessment are listed in **Appendix III**.

To provide conservative estimates of possible olestra intakes, two assumptions were built into the model:

1. All foods in which olestra is permitted and proposed for olestra use would contain olestra (*i.e.*, 100% market share); and
2. All permitted and proposed food uses would contain olestra at the maximum proposed levels of use specified in Table 3.1-1.

Table 3.1-1 Summary of the Individual Permitted and Proposed Food-Uses and Levels of Fat Being Replaced by Olestra in the U.S.

Food Category	Food-Uses[a]	Fat Replaced	Levels of Fat Replacement (%)
Permitted Uses			
Baked Goods and Baking Mixes	Pre-packaged RTE[b] Cookies	Total[c]	100
Snack Foods	Pre-packaged RTH[b] Unpopped Popcorn	Total[c]	100
	Pre-packaged RTE Savory Snacks	Total[c]	100
Proposed Uses			
Baked Goods and Baking Mixes	Pre-packaged RTE & RTH Bagels	Shortening[c]	75
	Pre-packaged RTE & RTH Biscuits and English Muffins	Shortening[d]	75
	Pre-packaged RTE & RTH Bread	Shortening[d]	75
	Pre-packaged RTE & RTH Bread Sticks (hard)	Shortening[d]	75
	Pre-packaged RTE & RTH Bread Sticks (soft)	Shortening[d]	75
	Pre-packaged RTE & RTH Cakes	Shortening[d]	75
	Pre-packaged RTH Cookies	Shortening[d]	75
	Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	Shortening[d]	75
	Pre-packaged RTE & RTH Croissants	Shortening[d]	75
	Pre-packaged RTE & RTH Crackers (not snack type)	Shortening[d]	75

Table 3.1-1 Summary of the Individual Permitted and Proposed Food-Uses and Levels of Fat Being Replaced by Olestra in the U.S.

Food Category	Food-Uses[a]	Fat Replaced	Levels of Fat Replacement (%)
	Pre-packaged RTE & RTH Doughnuts	Frying Oil[c,d,e]	100
	Pre-packaged RTE & RTH Muffins	Shortening[d]	75
	Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	Shortening[d]	75
	Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	Shortening[d]	75
	Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	Shortening[d]	75
	Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	Shortening[d]	75
	Pre-packaged RTE & RTH Rolls	Shortening[d]	75
	Pre-packaged RTE & RTH Sweet Rolls and Quick Breads	Shortening[d]	75
	Pre-packaged RTE & RTH Waffles	Shortening[d]	75
Cheeses	Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	Butter Fat[c]	67
	Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	Butter Fat[c]	67
Confections and Frostings	Pre-packaged RTE Frosting and Icing	Shortening[c]	100
Fats and Oil	Pre-packaged RTE Mayonnaise	Soybean Oil[c]	67
Frozen Dairy Desserts and Mixes	Pre-packaged RTE Ice Cream	Butter Fat[d]	67
	Pre-packaged RTE Frozen Yogurt	Butter Fat[c]	67
Grain Products and Pastas	Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	Shortening[d]	75
	Pre-packaged RTE & RTH Pizza Crust	Shortening[d]	75
Soft Candy	Pre-packaged RTE Chocolate Confections (chocolate portion)	Cocoa Butter	100

[a] Products intended for olestra use can be produced only at GMP-compliant manufacturing and packaging facilities (where it would be possible to meet vitamin restoration requirements) and subsequently sold at retail outlets or vending machines. Olestra will not be distributed for use as a food ingredient to facilities that do not have the capacity to produce and package foods according to GMP such as restaurants, cafeterias, bakeries, or other such facilities. Infant and toddler foods are not intended for olestra use.

[b] RTE = Ready-to-Eat; RTH = Ready-to-Heat

[c] Fat content was determined from the USDA National Nutrient Database for Standard Reference, Release 17.

[d] The standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000) was used to find the specific contribution of fat from shortening, oil, margarine, or butter fat.

[e] Calculation of fat from frying oil:
Fat from frying oil = (total doughnut fat content) - [shortening portion + (milk portion x average fat content) + (egg portion x average fat content)];
Total doughnut fat content and fat content of milk and eggs were determined from the USDA National Nutrient Database for Standard Reference, Release 17. The proportions of doughnut that are shortening, milk, or egg were determined from the standard recipe file for the CSFII 1994-1996, 1998 survey.

3.2 Identifying Representative Food Codes for All Permitted and Proposed Food-Uses

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

Amongst the foods proposed for olestra use, food codes that were representative of pre-packaged RTE products and specified “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light”, or “diet” were identified for the proposed food-uses of cheese (the processed and natural cheese portion of pre-packaged RTE and RTH prepared foods), frozen yogurt, mayonnaise, and ice cream.

For all remaining proposed food-uses, food codes representative of fat-modified versions of a proposed food-use were either not identified or there were too few to appropriately estimate the potential intake of olestra. Thus, for these proposed food-uses, food codes representative of the regular versions were used. Regular versions of food codes representative of pre-packaged RTE and pre-packaged RTH products were chosen for the proposed food-uses of bagels, biscuits and English muffins, bread, bread sticks (hard and soft), cakes, cornbread, corn muffins, tortillas and taco shells (hard and soft), croissants, crackers (not snack type), muffins, pancakes, crepes, French toast, sweet pastries (pastry portion), sweet pies (pastry portion), meat and vegetable pies and pastries (pastry portion), rolls, sweet rolls and quick breads, waffles, and pizza crust. Food codes representing regular versions of pre-packaged RTH cookies were chosen for this proposed food-use, while food codes representing regular versions of pre-packaged RTE products were chosen for the proposed food-uses of frostings and icing, breakfast, granola, and nutritional bars, and chocolate confections (chocolate portion).

The proportion of food codes representative of fat modified products *versus* regular fat products that were used in the intake model are summarized in Table 3.2-1. Additionally, the numbers of food codes that were identified are also provided in this table.

Table 3.2-1 Food Codes Representative of Fat-Modified Products *Versus* Regular Fat Products

Food Codes Representative of Fat-Modified Products Used		Food Codes Representative of Regular Fat Products Used
• RTE Cookies • RTE Savory Snacks • RTH Unpopped Popcorn • Natural Cheese Portion of Pre-Packaged RTE & RTH Prepared Foods • Processed Cheese Portion of Pre-Packaged RTE & RTH Prepared Foods Yogurt • Mayonnaise • Ice Cream • Frozen Yogurt		• RTE& RTH Bagels • RTE& RTH Biscuits and English Muffins • RTE& RTH Bread • RTE& RTH Bread Sticks • RTE& RTH Cakes • RTE& RTH Cornbread • RTE& RTH Corn Muffins • RTE& RTH Tortillas and Taco Shells (hard and soft)RTE& RTH Croissants • RTE& RTH Crackers (not snack type) • RTE& RTH Muffins • RTE& RTH Pancakes • RTE& RTH Crepes • RTE& RTH French Toast • RTE& RTH Sweet Pastries (pastry portion) • RTE& RTH Sweet Pies (pastry portion) • RTE& RTH Meat and Vegetable Pies and Pastries (pastry portion) • RTE& RTH Rolls • RTE& RTH Sweet Rolls and Quick Breads • RTE& RTH Waffles • RTE& RTH Pizza Crust. • RTH Cookies • RTE Frostings and Icing • RTE Breakfast, Granola, and Nutritional Bars • Chocolate Confections
Total	**182**	**1,207**
Percent of Total	**13%**	**87%**

3.3 Determining Fat Content of Permitted and Proposed Food-Uses

For permitted food-uses, 100% replacement of fat is based on the total 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 products also was assumed to be the same as the fat content of their full-fat counterparts. The total fat content of the regular products used in this assessment was determined from the USDA National Nutrient Database for Standard Reference, Release 17 (herein referred to as Nutrient Database).

Although the food codes representative of fat modified foods were chosen for cheese (the processed and natural portion of pre-packaged RTE and RTH prepared foods), mayonnaise, ice cream and frozen yogurt, the fat content of their full-fat counterparts were used for this assessment. For cheese (the processed and natural cheese portion of pre-packaged RTE and RTH prepared foods), mayonnaise, and frozen yogurt the fat contents of their full-fat

counterparts were determined from the Nutrient Database. For ice cream the fat content of its full-fat counterpart was determined from the standard recipe file.

The standard recipe file was reviewed to find the specific contribution of fat from shortening, oil, margarine, or butter fat for the majority of proposed food-uses (see Table 3.1-1). The fat contribution from all foods within a given food-use was determined from the standard recipe file. For the foods that did not have a recipe breakdown, the proportions of fat from the foods within the same food-use that did include a specified contribution were averaged, and this average value was applied to those foods that did not have recipe information. This average value for fat content also was applied to the food codes representing mixtures and meals.

For the bagels, and frostings and icings categories, there was no information on fat contribution available in the standard recipe file. The Nutrient Database provided proportions of fat for a few foods within each food-use; thus average values for fat content were determined for each food-use, and this average value was applied to those foods that did not have information on fat content. For chocolate confections, olestra will replace the fat from cocoa butter. An assessment by Millar and Hall (2004) provided the breakdown of chocolate, which determined the content of cocoa butter in milk, dark, and white chocolate to be 21.5, 18, and 20%, respectively. These values were used to calculate the fat replacement by olestra in chocolate confections in the current assessment.

3.4 Restriction to Retail Store or Vending Machine Purchased, Pre-Packaged, Ready-To-Eat or Ready-To-Heat Products

Products intended for olestra use will be pre-packaged RTE or RTH that will be produced at food manufacturing and packaging establishments operating under GMP and subsequently sold at retail stores or in vending machines. As much as possible, these criteria were integrated in the model used to estimate olestra intake from all permitted and proposed food uses.

For the most part, it was not possible to determine whether a food code was representative of a pre-packaged RTE or RTH product. In some cases, foods were described as, for example, “homemade” or “purchased at bakery”. In these cases, the food codes were reserved from the analyses. For the remaining food codes, it was assumed that they represented products that were pre-packaged and RTE or RTH, even if their source was not entirely clear. Inclusion of these food codes would be expected to over estimate rather than under estimate intakes.

To further refine the estimated olestra intakes, the model was honed to only include pre-packaged RTE or RTE products that were purchased at either a store or vending machine. Thus, all foods that were reported to have been obtained at sources such as a restaurant, fast food place, cafeteria, child care centre, residential dining facility or any other source outside of retail stores or vending machines were reserved from the analyses. Although these excluded

sources may follow food quality standards, they are not GMP in that vitamin restoration would not be possible.

4.0 DAILY OLESTRA INTAKE FROM ALL PERMITTED FOOD-USES

Estimates for the total daily intake of olestra from permitted food-uses (pre-packaged RTE cookies, pre-packaged RTE savory snacks, and pre-packaged RTH unpopped 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/person/day) 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 I** and Tables II-1 to II-7 of **Attachment II**.

4.1 Estimated Daily Olestra Intake from All Permitted Food-Uses

Approximately 11.7% of the total U.S. population was identified as consumers of pre-packaged RTE savory snacks, pre-packaged RTH popcorn, and/or pre-packaged RTE cookies (2,419 actual users). Consumption of foods in which olestra is permitted for use by the total U.S. population resulted in estimated mean all-person intakes of olestra of 0.4 g/person/day (7.1 mg/kg body weight/day), and mean and 90th percentile all-user intakes of 3.1 g/person /day (54.8 mg/kg body weight/day) and 7.71 g/person/day (132.72 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)
Infants	0-2	8.9	318	0.1	NA	1.2	2.8
Children	3-11	13.5	849	0.2	NA	2.1	4.8
Female Teenagers	12-19	12.3	86	0.4	NA	3.4	7.4
Male Teenagers	12-19	9.8	68	0.4	NA	3.7	8.5
Female Adults	20 and Up	13.6	622	0.5	NA	3.1	8.0
Male Adults	20 and Up	10.0	476	0.4	NA	3.6	9.3
Total Population	All Ages	11.7	2,419	0.4	NA	3.1	7.7

NA = Not available

On an individual population basis, female adults report the greatest percentage of users of permitted food-uses of olestra, at 13.6%. Also on an individual population basis, female adults were determined to have the greatest absolute mean all-person intake, with a value of 0.5 g/person/day (7.2 mg/kg body weight/day). Male teenagers were determined to have the

greatest mean all-user intake, 3.7 g/person/day (62.4 mg/kg body weight/day), while male adults had the greatest 90th percentile all-user intake, with a value of 9.3 g/person/day (98.8 mg/kg body weight/day). Infants had the lowest all-person intake on an absolute basis, with a mean value of 0.1 g/person/day. Infants also had the lowest all-user intakes, with mean and 90th percentile values of 1.2 and 2.8 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 97.7 and 215.7 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)
Infants	0-2	8.9	318	10.2	NA	97.7	215.7
Children	3-11	13.5	849	11.3	NA	81.7	192.7
Female Teenagers	12-19	12.3	86	7.8	NA	58.5	144.1
Male Teenagers	12-19	9.8	68	6.6	NA	62.4	133.6
Female Adults	20 and Up	13.6	622	7.2	NA	48.6	131.8
Male Adults	20 and Up	10.0	476	4.8	NA	43.5	98.8
Total Population	All Ages	11.7	2,419	7.1	NA	54.8	132.7

NA = Not available

5.0 DAILY OLESTRA INTAKE FROM ALL PERMITTED AND PROPOSED FOOD-USES

Estimates for the total daily intake of olestra from permitted and proposed food-uses (see Table 3.1-1) in the U.S. by population group are provided in Tables 5.1-1 and 5.1-2 on a per person (g/person/day) and per kilogram body weight (mg/kg body weight/day) basis, respectively. Estimates for daily intake on an absolute (g/person/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 I** and Tables II-1 to II-7 of **Attachment II**.

5.1 Estimated Daily Intake of Olestra from All Permitted and Proposed Food-Uses

Approximately 85.2 % of the total U.S. population were identified as potential consumers of the permitted and proposed food-uses (17,380 actual users). Consumption of permitted and proposed food-uses for olestra by the total U.S. population resulted in estimated mean and 90th

percentile all-person intakes of olestra of 4.1 g/person/day (75 mg/kg body weight/day) and 10.1 g/person/ day (184 mg/kg body weight/day), respectively, and mean and 90th percentile all-user intakes of 4.6 g/person/day (85 mg/kg body weight/day) and 10.6 g/person/day (195 mg/kg body weight/day), respectively (Tables 5.1-1 and 5.1-2).

Table 5.1-1 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)*

Age Group	% Users	Actual # of Total Users	All-Person Consumption (g)		All-User Consumption (g)	
			Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 Months	14.2	138	0.1	0.3	1.0	2.1
7 to 11 Months	28.6	107	0.2	0.6	0.7	1.6
Toddlers and Children						
1 to 3 Years	89.2	3,436	2.2	5.2	2.5	5.7
4 to 8 Years	93.2	3,508	3.6	8.2	3.9	8.5
9 to 13 Years	92.1	1,055	4.4	9.5	4.7	10.0
Female Teenagers and Adults						
14 to 18 Years	85.7	378	3.7	8.9	4.3	9.6
19 to 30 Years	83.5	685	3.4	8.9	4.1	10.0
31 to 50 Years	89.5	1,471	4.0	9.7	4.4	10.4
51 to 70 Years	90.2	1,385	3.7	9.1	4.1	9.3
71 and Older	90.6	561	3.6	8.4	3.9	8.8
Male Teenagers and Adults						
14 to 18 Years	89.4	397	5.6	13.0	6.2	13.4
19 to 30 Years	83.9	706	4.4	10.8	5.3	12.2
31 to 50 Years	89.2	1,496	5.1	12.8	5.7	13.7
51 to 70 Years	90.4	1,445	4.7	11.0	5.2	11.6
71 and Older	91.2	612	4.6	11.2	5.0	11.3
Total Population						
Total Population	85.2	17,380	4.1	10.1	4.6	10.6

*Intake model refined to pre-packaged RTE and/or RTH olestra-containing products purchased at retail stores or vending machines.

In contrast to the results of analyses of olestra intake resulting from permitted food-uses that indicate that of the population groups surveyed, female adults had the greatest percentage of users, with the inclusion of proposed food-uses to the analyses, children aged 4 to 8 years reported the greatest percentage of users of permitted and proposed food-uses of olestra, at 93.2%. On an individual population basis, male teenagers (aged 14 to 18 years) were determined to have the greatest absolute mean and 90th percentile all-person intakes, with

values of 5.6 g/person/day (85 mg/kg body weight/day) and 13.0 g/person/day (210 mg/kg body weight/day), respectively. Male teenagers aged 14 to 18 years also were determined to have the greatest absolute mean all-user intakes of olestra, with a value of 6.2 g/person/day (94 mg/kg body weight/day), while male adults aged 31 to 50 years were determined to have the greatest absolute 90th percentile all-user intakes, with a value of 13.7 g/person/day (161 mg/kg body weight/day), respectively. Infants (aged 0 to 6 months) had the lowest all-person intakes on an absolute basis, with mean and 90th percentile values of 0.1 and 0.3 g/person/day, respectively. Infants (aged 7 to 11 months) had the lowest all-user intakes, with mean and 90th percentile values of 0.7 and 1.6 g/person/ day, respectively. On a per kilogram body weight basis, toddlers (aged 1 to 3 years) had the highest all-user mean and 90th percentile intakes, with values of 178 and 400 mg/kg body weight/day, respectively.

Table 5.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Olestra from Permitted and Proposed Food-Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)*

Age Group	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)		All-Users Consumption (mg/kg)	
			Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 Months	14.2	138	15	42	96	194
7 to 11 Months	28.6	107	18	59	76	162
Toddlers and Children						
1 to 3 Years	89.2	3,436	157	373	178	400
4 to 8 Years	93.2	3,508	163	357	175	365
9 to 13 Years	92.1	1,055	110	246	118	254
Female Teenagers and Adults						
14 to 18 Years	85.7	378	64	156	75	167
19 to 30 Years	83.5	685	55	142	66	159
31 to 50 Years	89.5	1,471	61	147	68	156
51 to 70 Years	90.2	1,385	55	132	60	137
71 and Older	90.6	561	56	134	62	141
Male Teenagers and Adults						
14 to 18 Years	89.4	397	85	210	94	214
19 to 30 Years	83.9	706	57	139	69	153
31 to 50 Years	89.2	1,496	61	151	68	161
51 to 70 Years	90.4	1,445	57	131	63	138
71 and Older	91.2	612	61	151	66	152
Total Population						
Total Population	85.2	17,380	75	184	85	195

*Intake model refined to pre-packaged RTE and/or RTH olestra-containing products purchased at retail stores or vending machines.

In comparison to the results presented in Section 4.1 that present the estimated olestra intake from permitted food-uses only, the all-users 90th percentile total population olestra intake increased from 7.7 g/person/day (132.7 mg/kg body weight/day) (Tables 4.1-1 and 4.1-2), to 10.6 g/person/day (195 mg/kg body weight/day) (Tables 5.1-1 and 5.1-2) with the addition of the proposed food-uses.

The values presented are likely to be highly conservative estimates of olestra intake given that it was assumed that all of the food codes that are representative of all foods that are permitted and proposed for olestra use would contain olestra and that all foods would contain olestra at the maximum proposed levels of use. In particular, the percentage of the U.S. population who may be users of olestra is likely grossly overestimated given that food codes representative of regular fat foods were used where limited data on fat-modified foods were available (see Section 7.0).

5.2 All-Person Intakes of Individual Permitted and Proposed Food-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/person/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 significant consumers of pre-packaged RTE & RTH bread with 60.8% users (12,397 actual users), and substantial consumers of pre-packaged RTE & RTH rolls with 16.9% users (3,456 actual users), and pre-packaged RTE frosting and icing with 12.1% users (2,464 actual users). Consumption of pre-packaged RTE & RTH bread provided the largest mean all-person intakes of olestra at 0.8 g/person/day (15 mg/kg body weight/day).

The consumption of pre-packaged RTE & RTH bread resulted in the highest mean all-person intakes of olestra in all population groups (Tables I-1 to I-15). The highest mean all-person intakes of olestra, on an absolute basis, were reported in male adults (aged 71 years old and up) consuming pre-packaged RTE & RTH bread, at 1.1 g/person/day (15 mg/kg body weight/day). The highest 90th percentile all-person intakes of olestra were reported in male adults (aged 71 years old and up) consuming pre-packaged RTE & RTH pies, sweet (pastry portion), at 3.5 g/person/day (44 mg/kg body weight/day). On a body weight basis, toddlers (aged 1 to 3 years) had the highest mean and 90th percentile all-person intakes of olestra, respectively, resulting from the consumption of pre-packaged RTE & RTH bread, with values of 37 and 95 mg/kg body weight/day, respectively.

5.3 All-User Intakes of Individual Permitted and Proposed Food-Uses of Olestra

Tables I-16 and II-16 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. For all-user intakes, the impact of each food category on the overall intake is examined by the food category making the largest contribution to the all-user intake. The contribution of a food category is based on the estimated intake of olestra resulting from the consumption of the food, as well as the percentage of users identified as consumers of the food. For example, for the total population, the consumption of pre-packaged RTE & RTH meat and vegetable pies and pastries (pastry portion) resulted in an estimated mean all-user olestra intake of 7.4 g/person/day; however, only 355 users (1.7% of the total population) of pre-packaged RTE & RTH meat and vegetable pies and pastries (pastry portion) were identified, and therefore, the contribution of this category to the mean all-user intake of olestra was not as important as the contribution from pre-packaged RTE & RTH bread.

Consumers of pre-packaged RTE & RTH bread were identified as having the greatest contribution to the mean and 90th percentile all-user intakes of olestra at 1.3 g/person/day (24 mg/kg body weight/day) and 2.4 g/person/day (50 mg/kg body weight/day), respectively, on a total population basis. Pre-packaged RTE & RTH doughnuts 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 6.3 g/person/day (121 mg/kg body weight/day) and 11.9 g/person/day (224 mg/kg body weight/day), respectively. As well, pre-packaged RTE chocolate confections (chocolate portion) 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 2.7 g/person/day (51 mg/kg body weight/day) and 5.6 g/person/day (103 mg/kg body weight/day), respectively.

On an individual population group basis, the consumption of pre-packaged RTE & RTH bread tended to make the most significant contribution to the mean and 90th percentile all-user intakes of olestra for all population groups (Tables I-1 to I-15, and II-1 to II-15). Male adults (71 years old and up) consuming pre-packaged RTE & RTH bread made the greatest contribution to the mean and 90th percentile all-user intake of olestra, with values of 1.5 g/ person/day (20 mg/kg body weight/day) and 2.8 g/person/day (38 mg/kg body weight/day), respectively. On a body weight basis, toddlers (aged 1 to 3 years) consuming pre-packaged RTE & RTH doughnuts had the highest mean and 90th percentile all-user intakes with values of 311 and 603 mg/kg body weight/day, respectively.

The estimated intakes of olestra were considered statistically unreliable if the CV was equal to or greater than 30% or if the sample size was determined to be less than 30 respondents. The results of an assessment of the CV and number of respondents for all-user intake estimates in infants (aged up to 6 months) indicate that the values obtained for the following food-uses were

unreliable: pre-packaged RTH cookies, pre-packaged RTH unpopped popcorn, pre-packaged savory snacks, pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH biscuits & english muffins, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH cakes, pre-packaged RTE & RTH cornbread, corn muffins, tortillas, and taco shells (hard and soft), pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pancakes, crepes, and French toast, pre-packaged RTE & RTH pasties, sweet (pastry portion), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged RTE & RTH rolls, pre-packaged RTE & RTH sweet rolls & quick breads, pre-packaged RTE & RTH waffles, natural cheese portion of pre-packaged RTE & RTH prepared foods, processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE frozen yogurt, pre-packaged RTE breakfast, granola, and nutritional bars, pre-packaged RTE & RTH pizza crust, and pre-packaged RTE chocolate confections (chocolate portion). In infants (aged 7 to 11 months), the intake estimates for the following food uses were determined to be unreliable: pre-packaged RTE cookies, pre-packaged RTE savory snacks, pre-packaged RTE & RTH bagels pre-packaged RTE & RTH biscuits & english muffins, pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTE & RTH cornbread, corn muffins, tortillas and taco shells (hard and soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH pancakes, crepes and French toast, pre-packaged RTE & RTH pastries, sweet (pastry portion), pre-packaged RTE & RTH pies, sweet (pastry portion), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged RTE & RTH rolls, pre-packaged RTE & RTH sweet rolls & quick breads, pre-packaged RTE & RTH waffles, natural cheese portion of pre-packaged RTE & RTH prepared foods, processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE frosting and icing, pre-packaged RTE ice cream, pre-packaged RTE breakfast, granola, and nutritional bars, and pre-packaged RTE & RTH pizza crust.

In toddlers (aged 1 to 3 years) the all-user intake assessments were determined to be unreliable for pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTH cookies, pre-packaged RTE & RTH croissants, and pre-packaged RTE & RTH crackers (not snack-type). In children (aged 4 to 8 years), the all-user intake assessments were determined to be unreliable for pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTH cookies, pre-packaged RTE & RTH croissants, and pre-packaged RTE & RTH crackers (not snack-type). Among children (aged 9 to 13 years) the intake estimates for the following food-uses were determined to be unreliable: pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTH cookies, pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack-type), pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pies, sweet (pastry portion), pre-packaged RTE & RTH pies and pasties, meat and vegetable (pastry portion,

processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE ice cream, and pre-packaged RTE frozen yogurt.

In female teenagers (aged 14 to 18 years), the intake values for the following food-uses were determined to be unreliable: pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE savory snacks, pre-packaged RTE & RTH biscuits & english muffins, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pastries, sweet (pastry portion), pre-packaged RTE & RTH pies, sweet (pastry portion), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged RTE & RTH sweet rolls & quick breads, pre-packaged RTE & RTH waffles, processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE mayonnaise, pre-packaged RTE ice cream, pre-packaged RTE frozen yogurt, and pre-packaged RTE breakfast, granola, and nutritional bars. Among male teenagers (aged 14 to 18 years), the intake values for the following food-uses were determined to be unreliable: pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH bread, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pastries, sweet (pastry portion), pre-packaged RTE & RTH pies, sweet (pastry potion), pre-packaged RTE & RTH pies and pasties, meat and vegetable (pastry portion), pre-packaged RTE & RTH sweet rolls and quick breads, pre-packaged RTE & RTH waffles, processed cheese portion of RTE & RTE prepared foods, pre-packaged RTE mayonnaise, pre-packaged RTE ice cream, pre-packaged RTE frozen yogurt, and pre-packaged RTE breakfast, granola, and nutritional bars.

In female adults (aged 19 to 30 years), the intake values for pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH biscuits & english muffins, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH pancakes, crepes and French toast, pre-packaged RTE & RTH pies, sweet (pastry portion), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged RTE & RTH waffles, processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE mayonnaise, pre-packaged RTE ice cream, and pre-packaged frozen yogurt were determined to be unreliable. In males adults (aged 19 to 30 years), the values for pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH biscuits & English muffins, pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack-type), pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pies, sweet (pastry portion), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged RTE & RTH waffles, processed cheese portion of pre-packaged RTE & RTH prepared foods,

pre-packaged RTE mayonnaise, pre-packaged RTE ice cream, and pre-packaged RTE frozen yogurt were determined to be unreliable. Among female adults (aged 31 to 50 years), the intake values for the following food-uses were determined to be unreliable: pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH pies and pasties, meat and vegetable (pastry portion), processed cheese portion of pre-packaged RTE & RTH prepared foods, and pre-packaged RTE ice cream. In male adults (aged 31 to 50 years), the intake values for the following food-uses were determined to be unreliable: pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH cakes, pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack-type), and processed cheese portions of pre-packaged RTE & RTH prepared foods. In female adults (aged 51 to 70 years), the intake values for the pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers (not snack-type), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), processed cheese portion of pre-packaged RTE & RTH prepared foods, and pre-packaged RTE breakfast, granola, and nutritional bars were determined to be unreliable. In male adults (aged 51 to 70 years), the intake values for pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), processed cheese portion of pre-packaged RTE & RTH prepared foods, and pre-packaged RTE breakfast, granola, and nutritional bars were determined to be unreliable.

Among female adults (aged 71 years and older), the intake values for pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE savory snacks, pre-packaged RTE & RTH bagels, pre-packaged RTE &RTH biscuits and english muffins, pre-packaged RTE & RTH bread sticks (hard), pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH doughnuts, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pancakes, crepes, and French toast, pre-packaged RTE & RTH pastries, sweet (pastry portion), pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged RTE & RTH waffles, natural cheese portion of pre-packaged RTE & RTH prepared foods, processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE ice cream, pre-packaged RTE frozen yogurt, pre-packaged RTE breakfast, granola and nutritional bars, and pre-packaged RTE & RTH pizza crust were determined to be unreliable. In male adults (aged 71 years and older), the intake values for the following food-uses were determined to be unreliable: pre-packaged RTE cookies, pre-packaged RTH unpopped popcorn, pre-packaged RTE & RTH bagels, pre-packaged RTE & RTH bread sticks (soft), pre-packaged RTE & RTH croissants, pre-packaged RTE & RTH crackers, pre-packaged RTE & RTH muffins, pre-packaged RTE & RTH pies and pastries, meat and vegetable (pastry portion), pre-packaged

RTE & RTH waffles, natural cheese portion of pre-packaged RTE & RTH prepared foods, processed cheese portion of pre-packaged RTE & RTH prepared foods, pre-packaged RTE ice cream, pre-packaged RTE frozen yogurt, pre-packaged RTE breakfast, granola, and nutritional bars, and pre-packaged RTE & RTH pizza crust. In the total population, only the intakes for pre-packaged RTH cookies were determined to be unreliable.

6.0 OLESTRA INTAKES RELATIVE TO TOTAL FAT INTAKES

To provide some perspective on the intakes of olestra, Table 6-1 presents the all-user estimates of olestra intake from all permitted and proposed food uses in comparison to the intake of total fat from all sources in the diet. These data show that despite all the conservative assumptions inherent in the model (see Section 3.0), olestra would replace as little as 3.0% of fat in infants and up to a maximum of 12.6% in elderly women, at the 90th percentile. For the total population, olestra would replace less than 10% of total fat intake. Consequently, regular fat consumption can be considered to be a significant contributor to obtaining required fat soluble vitamins and minerals

Table 6-1 Comparison of Estimated Olestra Intake from All Permitted and Proposed Food Uses with Total Fat Intake in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Age Group	All-Users Olestra Consumption (g)		Total Fat Intake (g)		Olestra Intake as a Percentage of Fat Intake (%)	
	Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 Months	1.0	2.1	34.8	46.2	2.9	4.5
7 to 11 Months	0.7	1.6	39.5	53.5	1.8	3.0
Toddlers and Children						
1 to 3 Years	2.5	5.7	54	69.9	4.6	8.2
4 to 8 Years	3.9	8.5	65.4	86.0	6.0	9.9
9 to 13 Years	4.7	10.0	69.5 (F); 84.0 (M)	92.0 (F); 108.0 (M)	6.7 (F); 5.6 (M)	10.8 (F); 9.2 (M)
Female Teenagers and Adults						
14 to 18 Years	4.3	9.6	68.7	91.0	6.3	10.5
19 to 30 Years	4.1	10.0	64.6	92.0	6.3	10.9
31 to 50 Years	4.4	10.4	63.6	89.0	6.9	11.7
51 to 70 Years	4.1	9.3	56.5	81.0	7.3	11.5
71 and Older	3.9	8.8	49.4	70	7.9	12.6
Male Teenagers and Adults						
14 to 18 Years	6.2	13.4	105.6	149.0	5.9	9.0
19 to 30 Years	5.3	12.2	103.7	147.0	5.1	8.3
31 to 50 Years	5.7	13.7	97.4	141.0	5.9	9.7

Table 6-1 Comparison of Estimated Olestra Intake from All Permitted and Proposed Food Uses with Total Fat Intake in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Age Group	All-Users Olestra Consumption (g)		Total Fat Intake (g)		Olestra Intake as a Percentage of Fat Intake (%)	
	Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
51 to 70 Years	5.2	11.6	82.6	122.0	6.3	9.5
71 and Older	5.0	11.3	67.9	100.0	7.4	11.3
Total Population						
Total Population	4.6	10.6	74.7	114.0	6.2	9.3

[1] IOM, 2005

7.0 DETERMINATION OF PERCENT CONSUMERS OF FAT MODIFIED PRODUCTS

Products using olestra as a replacement for conventional fats are intended to be marketed as “low-fat”, “reduced-fat”, or “fat-free”. As such, the approach used to estimate the intake of olestra from all permitted and proposed food-uses was to include all food codes that were representative of “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light”, or “diet” foods. However, for the majority of the proposed food-uses, including many commonly consumed foods, it was not possible to employ this approach because food codes representative of fat-modified versions of the proposed food-use were either not identified or there were too few food codes to appropriately estimate olestra intake. For these proposed food-uses, food codes representative of regular fat products were included in the assessment. Using this approach resulted in an inflated estimate of the percentage of the U.S. population who may be consumers of olestra.

To more accurately estimate the percentage of the U.S. population that is likely to consume olestra, an assessment was conducted to determine the percentage of the U.S. population that consumes any fat-modified product(s). Food codes representative of any product identified as “reduced-fat”, “low-fat”, “fat-free”, “low-calorie”, “light”, or “diet” were chosen from the CSFII 1994-1996, 1998 (USDA, 2000) database. This assessment was run using two different scenarios: (1) the inclusion of all applicable food codes; and (2) the inclusion of applicable food codes with the exception of fat modified milks, yogurts and cheeses. The analyses were conducted using these two different scenarios because milk products are staple foods and fat-modified versions may not be generally viewed as “low-fat” products *per se*. All food codes included in these assessments are listed in **Appendix IV**.

The results of these analyses are presented in Table 7-1. In comparison to the percentage of users estimated for all permitted and proposed food-uses of olestra for the total population,

91.4% (Table 5.1-1), the estimated percentage of the total population that consumes fat-modified products is only 42.1%, while the exclusion of fat modified milks further reduces the percent consumers to 31.2%. The population group with the lowest percent users of fat-modified products is infants 0 to 6 months of age.

Table 7-1 Summary of the Estimated Percentage of the U.S. Population that Consumes Fat Modified Products[1] (1994-1996, 1998 USDA CSFII Data)

Age Group	% Users	
	All types of Fat Modified Products[1]	Excluding Fat Modified Milk Products[2]
Infants		
0 to 6 Months	4.6	2.3
7 to 11 Months	9.3	5.1
Toddlers and Children		
1 to 3 Years	38.6	22.5
4 to 8 Years	44.7	23.2
9 to 13 Years	48.6	23.2
Female Teenagers and Adults		
14 to 18 Years	34.2	20.4
19 to 30 Years	42.3	29.0
31 to 50 Years	49.8	34.4
51 to 70 Years	57.1	39.6
71 and Older	53.5	35.8
Male Teenagers and Adults		
14 to 18 Years	39.7	20.4
19 to 30 Years	37.9	27.9
31 to 50 Years	42.1	29.7
51 to 70 Years	47.6	34.6
71 and Older	50.3	35.5
Total Population		
Total Population	42.1	26.2

[1] Foods considered to be fat-modified include those described as reduced-fat, low-fat, fat-free, low-calorie, light, or diet.
[2] Fat modified milk products excluded include fluid milks (part skim, skimmed), and fat-modified yogurts and cheeses.

8.0 OLESTRA AND SPECIFIC POPULATION GROUPS

8.1 Infants

The World Health Organization recommends "as a global public health recommendation, infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health" (WHO, 2002). As would be expected, the total all-users 90th percentile estimated olestra intake for all proposed food uses is only 2.1 g/person/day for infants 0 to 6 months of age and 1.6 g/person/day for infants 7 to 11 months of age.

The proposed food uses most frequently reported to be consumed by infants 0 to 6 months of age include pre-packaged RTE and RTH bread (9.2%), pre-packaged RTE and RTH cornbread, corn muffins, tortillas, and taco shells (2.5%), and prepackaged RTE and RTH pancakes, crepes, and French toast (2.0%). While these are the most frequently reported consumed, estimated all-user 90th percentile intakes of olestra by infants 0 to 6 months of age from each of these proposed food uses are all below 1 g/person/day (Table I-1). These proposed food uses were also most frequently reported consumed amongst infants 7 to 11 months of age, with 17.9% users of prepackaged RTE and RTH bread, 3.2 % users of prepackaged RTE and RTH pancakes, crepes, and French toast, and 2.7% users of pre-packaged RTE and RTH cornbread, corn muffins, tortillas, and taco shells (Table I-2). All-user 90th percentile intakes from each of these food uses also were also all below 1 g/person/day.

It is expected that the percentage of users of olestra-containing products and the intakes of olestra-containing foods would be far less than the estimates generated from this assessment for several reasons:

- Olestra is not proposed for use in infant and toddler foods.
- For infants that are introduced to solid foods, it is not expected that parents would intentionally select fat-modified foods. This is supported by the low percentage of consumers of fat modified products amongst infants 0 to 6 months of age (4.6%) and infants 7 to 11 months of age (9.3%) (Table 7-1).

Furthermore, other high fat foods commonly consumed by infants/children such as milk, yoghurt and cheese (block or shredded) would not contain olestra.

8.2 Pregnant and Lactating Women

The estimated olestra intakes by pregnant and lactating women from all permitted and proposed food uses are summarized in Tables 8.2-1 and 8.2-2 on a per person (g/person/day) and per kilogram body weight basis (mg/kg body weight/day), respectively. It is highly likely that these values greatly overestimate intakes, particularly in pregnant women, as the percentage of users

of fat modified products, excluding fat modified milks is only 18.6 % (Table 8.2-3), which is less than a third of the estimated percentage of users of all permitted and proposed olestra food uses (63 %; Table 8.2-1). Additionally, the increased consumption of energy to meet increased needs during pregnancy (American Dietetic Association, 2008) also decreases the likelihood that a pregnant woman will choose an olestra-containing food that contains less energy than its full-fat counterpart.

Table 8.2-1 Summary of the Estimated Daily Intake of Olestra from Permitted and Proposed Food-Uses by Pregnant and Lactating Women in the U.S. (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)
Pregnant Women	14-50	63.0	90.0	5.1	11.3	5.7	15.6
Lactating Women	14-50	92.7	38	4.1	7.9	4.4	7.9

Table 8.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Olestra from Permitted and Proposed Food-Uses by Pregnant and Lactating Women in the U.S. (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)
Pregnant Women	14-50	63.0	90.0	78.2	178.8	86.9	304.1
Lactating Women	14-50	92.7	38	64.1	107.9	68.1	107.9

Table 8.2-3 Summary of the Estimated Percentage of Pregnant and Lactating Women of the U.S. Population that Consumes Fat Modified Products[1] (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	
		All Fat Modified Products	Excluding Fat Modified Milk Products
Pregnant Women	14-50	40.0	18.6
Lactating Women	14-50	56.1	35.6

8.3 Special Supplemental Nutrition Program for Women, Infants and Children

The Special Supplemental Nutrition Program for Women, Infants and Children (WIC) provides nutritious foods to low-income pregnant, postpartum and breastfeeding women, infants and

children up to age 5 who are at risk of nutrition deficiency (7 CFR §246.1 - CFR, 2008; http://www.fns.usda.gov/wic/). Foods are selected for the program if they are rich in one or more of the nutrients protein, calcium, iron, vitamin A, and vitamin C. Specifically, the following foods are WIC-eligible: adult cereal, infant cereal, adult and infant juice, milk, cheese, eggs, beans, peas, peanut butter, carrots, tuna, infant formula, exempt infant formula, and medical foods. All of these foods must comply with the U.S. Food and Drug Administration (FDA) Standards of Identity and also have to meet additional Federal requirements (7 CFR §246.10 - CFR, 2008). Amongst the foods that are WIC-eligible, cheese is the only food that is proposed for olestra use; however, cheese is proposed for olestra use only as a component of pre-packaged RTE and RTH prepared foods and thus, would likely not be eligible. Combined with the fact that the cost of a food is a factor that is considered when authorizing foods for WIC use, it is highly unlikely that olestra-containing foods would be part of the WIC program.

9.0 PREDICTING OLESTRA INTAKE: A CONSERVATIVE APPROACH

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, including:

- Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently (Anderson, 1988; Lambe and Kearney, 1999);
- The assumption that *all* food codes representative of a permitted or proposed food use contain olestra at the *maximum* specified level of use;
- The assumption that all foods in a food category are *pre-packaged*, even if there was uncertainty that the food was pre-packaged; and
- Where limited data on fat-modified foods were available, regular fat food codes were used in intake estimates, thereby inflating the percentage of the U.S. population who may be users of olestra.

The results of post marketing surveillance studies demonstrate that in fact, these assumptions inherent in the model result in intake values that highly overestimate actual intakes. Prior to the approval of olestra as a food additive for use in savory snacks, potential chronic olestra intakes were estimated using menu census data collected by Market Research Corporation of America (MRCA; Webb *et al*., 1997). Estimates of olestra intake derived from these data indicated that the 90th percentile eaters-only intake of olestra from savory snacks by the total population would

be 6.9 g/day, with the highest intakes coming from adult males at 11 g/day (Webb *et al*., 1997). As part of the 1996 Food and Drug Administration approval of olestra, active post marketing surveillance was required, which enabled actual olestra intake by the U.S. population to be evaluated. Data from the Olestra Post-Marketing Surveillance Study show that the 90th percentile olestra intake from savory snacks is 1.8 g/day in adults and 2.1 g/day in adolescents (Neuhouser *et al*., 2006).

These data suggest that the conservative assumptions inherent in the model result in predicted values of olestra intake that are likely to overestimate actual olestra intake.

10.0 CONCLUSIONS

In summary, on an all-user basis, the estimated mean and 90th percentile intakes of olestra from the consumption of all permitted and proposed food-uses by the total U.S. population were estimated to be 4.6 g/person/day (85 mg/kg body weight/day) and 10.6 g/person/day (195 mg/kg body weight/day), respectively. These intake estimates are higher than the estimated all-user mean and 90th percentile intakes of olestra by the total population resulting from the consumption of permitted food-uses, of 3.1 g/person/day (54.8 mg/kg body weight/day) and 7.7 g/person/day (132.7 mg/kg body weight/day), respectively. In comparison, the total fat intakes for the total population at the mean and 90th percentile, are 74.7 g/person/day and 114 g/person/day, respectively.

On an individual population basis, the greatest mean and 90th percentile all-user intakes of olestra from permitted and proposed food-uses occurred in male teenagers, at 6.2 g/person/day (94 mg/kg body weight/day) and 13.4 g/person/day (214 mg/kg body weight/day), respectively. Likewise, male teenagers have the highest total fat mean and 90th percentile intake estimates of 74.7 and 114.0 g/person/day, respectively.

11.0 REFERENCES

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ATTACHMENT I TO APPENDIX B

Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Different Population Groups Within the United States

Table I-1 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	0.1	1	< 0.1*	na	10.0*	10.0*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.2	2	< 0.1*	na	0.5*	0.8*
Pre-packaged RTE Savory Snacks	1.1	11	< 0.1*	na	0.4*	1.1*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	0.5	5	< 0.1*	na	0.2*	0.2*
Pre-packaged RTE & RTH Biscuits & English Muffins	0.1	1	< 0.1*	na	0.1*	0.1*
Pre-packaged RTE & RTH Bread	9.2	90	< 0.1	na	0.4	0.8
Pre-packaged RTE & RTH Bread Sticks (hard)	0.1	1	< 0.1*	na	< 0.1*	< 0.1*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cakes	0.3	3	< 0.1*	na	0.7*	1.5*
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	2.5	24	< 0.1*	na	0.2*	0.3*
Pre-packaged RTE & RTH Croissants	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Crackers (not snack type)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Doughnuts	0.2	2	< 0.1*	na	4.4*	6.3*
Pre-packaged RTE & RTH Muffins	0.2	2	< 0.1*	na	0.5*	0.6*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	2.0	19	< 0.1*	na	0.5*	0.9*

Table I-1 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	0.3	3	< 0.1*	na	1.0*	1.7*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	0.1	1	< 0.1*	na	2.3*	2.3*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	0.3	3	< 0.1*	na	4.3*	8.2*
Pre-packaged RTE & RTH Rolls	1.1	11	< 0.1*	na	0.4*	0.7*
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	0.1	1	< 0.1*	na	0.4*	0.4*
Pre-packaged RTE & RTH Waffles	0.6	6	< 0.1*	na	1.0*	1.5*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.0	10	< 0.1*	na	0.2*	0.4*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.1	1	< 0.1*	na	0.9*	0.9*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	1.1	11	< 0.1*	na	1.2*	3.9*
Fats and Oils						
Pre-packaged RTE Mayonnaise	0.0	0	na	na	na	na
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.0	0	na	na	na	na
Pre-packaged RTE Frozen Yogurt	0.1	1	< 0.1*	na	0.7*	0.7*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	0.3	3	< 0.1*	na	0.6*	0.5*
Pre-packaged RTE & RTH Pizza Crust	1.0	10	< 0.1	na	0.3*	0.4*

Table I-1 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	0.3	3	< 0.1*	na	0.7*	0.9*

na = not applicable
* 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 I-2 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	0.3	1	< 0.1*	na	0.7*	0.7*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.0	0	na	na	na	na
Pre-packaged RTE Savory Snacks	1.9	7	< 0.1*	na	0.2*	0.4*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	2.1	8	< 0.1*	na	0.2*	0.3*
Pre-packaged RTE & RTH Biscuits & English Muffins	0.3	1	< 0.1*	na	0.1*	0.1*
Pre-packaged RTE & RTH Bread	17.9	67	< 0.1	0.2	0.4	0.9
Pre-packaged RTE & RTH Bread Sticks (hard)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Bread Sticks (soft)	0.8	3	< 0.1*	na	0.6*	1.5*
Pre-packaged RTE & RTH Cakes	0.8	3	< 0.1*	na	0.7*	1.7*
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	2.7	10	< 0.1*	na	0.1*	0.3*
Pre-packaged RTE & RTH Croissants	0.3	1	< 0.1*	na	0.6*	0.6*
Pre-packaged RTE & RTH Crackers (not snack type)	1.1	4	< 0.1*	na	0.2*	0.6*
Pre-packaged RTE & RTH Doughnuts	0.8	3	< 0.1*	na	3.1*	4.7*
Pre-packaged RTE & RTH Muffins	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	3.2	12	< 0.1*	na	0.4*	0.9*

CANTOX HEALTH SCIENCES INTERNATIONAL

Table I-2 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	1.1	4	< 0.1*	na	0.8*	1.0*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	0.3	1	< 0.1*	na	0.5*	0.5*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	0.3	1	< 0.1*	na	1.7*	1.7*
Pre-packaged RTE & RTH Rolls	1.9	7	< 0.1*	na	0.3*	0.3*
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	0.8	3	< 0.1*	na	0.4*	0.4*
Pre-packaged RTE & RTH Waffles	0.8	3	< 0.1*	na	0.9*	1.2*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.5	2	< 0.1*	na	0.3*	0.4*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.8	3	< 0.1*	na	1.1*	1.7*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	1.6	6	< 0.1*	na	0.3*	0.5*
Fats and Oils						
Pre-packaged RTE Mayonnaise	0.0	0	na	na	na	na
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.3	1	< 0.1*	na	0.1*	0.2*
Pre-packaged RTE Frozen Yogurt	0.0	0	na	na	na	na
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	0.5	2	< 0.1	na	1.8*	1.8*
Pre-packaged RTE & RTH Pizza Crust	0.8	3	< 0.1*	na	0.9*	2.3*

Table I-2 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	0.0	0	na	na	na	na

na = not applicable
* 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 I-3 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.1	80	< 0.1	na	2.0	3.6
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.5	56	< 0.1	na	1.1	2.0
Pre-packaged RTE Savory Snacks	10.2	391	0.1	< 0.1	1.1	2.3
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	4.5	173	< 0.1	na	0.2	0.3
Pre-packaged RTE & RTH Biscuits & English Muffins	2.1	80	< 0.1	na	0.8	1.9
Pre-packaged RTE & RTH Bread	64.3	2,478	0.5	1.3	0.8	1.6
Pre-packaged RTE & RTH Bread Sticks (hard)	0.6	24	< 0.1*	na	0.2*	0.4*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.6	24	< 0.1*	na	0.6*	1.5*
Pre-packaged RTE & RTH Cakes	5.0	191	< 0.1	na	1.3	2.8
Pre-packaged RTH Cookies	0.1	2	< 0.1*	na	2.0*	3.0*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.3	511	< 0.1	0.1	0.5	0.9
Pre-packaged RTE & RTH Croissants	0.3	13	< 0.1*	na	2.2*	4.2*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	11	< 0.1*	na	0.4*	0.5*
Pre-packaged RTE & RTH Doughnuts	5.6	216	0.2	na	4.5	9.3
Pre-packaged RTE & RTH Muffins	2.6	102	< 0.1	na	1.0	1.6
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	12.5	483	< 0.1	0.3	0.8	1.7

Table I-3 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	6.6	254	0.1	na	2.1	3.9
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.2	47	< 0.1	na	2.9	5.6
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.0	77	< 0.1	na	3.4	7.7
Pre-packaged RTE & RTH Rolls	13.5	519	< 0.1	0.4	0.6	1.1
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.5	136	< 0.1	na	1.3	2.4
Pre-packaged RTE & RTH Waffles	8.9	342	< 0.1	na	1.1	1.8
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	8.7	335	< 0.1	na	0.7	1.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	2.1	80	< 0.1	na	1.6	3.5
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	11.9	458	0.1	0.2	0.9	2.0
Fats and Oils						
Pre-packaged RTE Mayonnaise	1.7	67	< 0.1	na	1.4	4.1
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.1	42	< 0.1*	na	0.6	1.0
Pre-packaged RTE Frozen Yogurt	0.9	34	< 0.1	na	0.9	1.8
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	5.2	201	< 0.1	na	1.1	2.1
Pre-packaged RTE & RTH Pizza Crust	6.7	258	< 0.1	na	0.9	1.8

Table I-3 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	10.0	387	0.2	na	1.7	3.8

na = not applicable
* 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 I-4 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.9	70	< 0.1	na	3.0	5.1
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.4	54	< 0.1	na	1.8	3.0
Pre-packaged RTE Savory Snacks	8.3	313	0.1	na	1.7	4.1
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.2	196	< 0.1	na	0.3	0.6
Pre-packaged RTE & RTH Biscuits & English Muffins	2.7	103	< 0.1	na	1.3	4.5
Pre-packaged RTE & RTH Bread	67.8	2,551	0.7	1.7	1.1	2.0
Pre-packaged RTE & RTH Bread Sticks (hard)	0.6	21	< 0.1*	na	0.2*	0.4*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	17	< 0.1*	na	1.0*	1.7*
Pre-packaged RTE & RTH Cakes	6.3	238	0.1	na	1.5	3.3
Pre-packaged RTH Cookies	0.0	1	< 0.1*	na	12.1*	12.1*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.8	521	< 0.1	0.2	0.7	1.5
Pre-packaged RTE & RTH Croissants	0.3	11	< 0.1*	na	9.3*	16.7*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	13	< 0.1*	na	0.8*	1.2*
Pre-packaged RTE & RTH Doughnuts	7.0	264	0.4	na	5.6	9.9
Pre-packaged RTE & RTH Muffins	2.6	98	< 0.1	na	1.4	2.6
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	11.7	440	0.1	0.6	1.2	2.0

Table I-4 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	7.9	297	0.2	na	3.0	5.3
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.5	56	0.1	na	6.0	12.8
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.8	68	< 0.1	na	5.4	7.7
Pre-packaged RTE & RTH Rolls	18.8	709	0.2	0.7	0.8	1.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.9	148	< 0.1	na	1.4	2.4
Pre-packaged RTE & RTH Waffles	8.9	335	0.1	na	1.5	2.9
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	10.6	400	0.1	0.2	1.1	2.3
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.6	62	< 0.1	na	1.7	3.5
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	15.3	577	0.2	0.6	1.3	2.4
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.4	92	< 0.1	na	2.1	4.1
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.8	67	< 0.1	na	1.2	4.0
Pre-packaged RTE Frozen Yogurt	0.8	31	< 0.1	na	2.1	4.0
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	4.8	181	< 0.1	na	1.2	2.1
Pre-packaged RTE & RTH Pizza Crust	8.7	329	0.1	na	1.3	2.7

Table I-4 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	13.2	497	0.3	0.9	2.3	4.6

na = not applicable
* 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 I-5 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.8	21	0.1*	na	5.1*	9.8*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.9	22	< 0.1*	na	4.2*	13.2*
Pre-packaged RTE Savory Snacks	6.6	75	0.2	na	2.3	6.6
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	7.1	81	< 0.1	na	0.4	0.6
Pre-packaged RTE & RTH Biscuits & English Muffins	3.2	37	< 0.1	na	1.3	3.8
Pre-packaged RTE & RTH Bread	61.5	704	0.8	1.9	1.3	2.4
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	4	< 0.1*	na	0.2*	0.2*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.4	5	< 0.1*	na	0.6*	1.5*
Pre-packaged RTE & RTH Cakes	7.7	88	0.1	na	1.7	3.9
Pre-packaged RTH Cookies	0.1	1	< 0.1*	na	8.0*	8.0*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.4	154	0.1	0.2	1.0	2.4
Pre-packaged RTE & RTH Croissants	0.6	7	< 0.1*	na	3.1*	7.4*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	3	< 0.1*	na	0.6*	0.8*
Pre-packaged RTE & RTH Doughnuts	5.6	64	0.3	na	5.9	9.9
Pre-packaged RTE & RTH Muffins	2.4	27	< 0.1*	na	2.1*	3.1*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	10.6	121	0.2	0.5	1.4	2.7

Table I-5 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	8.1	93	0.3	na	3.6	5.8
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	2.5	29	0.1*	na	5.1*	8.9*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	24	0.2*	na	6.9*	15.2*
Pre-packaged RTE & RTH Rolls	22.8	261	0.2	0.7	1.0	1.8
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.8	44	< 0.1	na	1.4	2.5
Pre-packaged RTE & RTH Waffles	6.0	69	0.1	na	1.7	3.0
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	10.4	119	0.1	0.3	1.3	2.7
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.7	8	< 0.1*	na	3.6*	16.2*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	17.6	202	0.2	0.8	1.4	2.7
Fats and Oils						
Pre-packaged RTE Mayonnaise	4.4	50	0.2	na	3.2	6.9
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.8	21	< 0.1*	na	0.8*	1.5*
Pre-packaged RTE Frozen Yogurt	1.1	13	< 0.1*	na	1.9*	2.2*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	5.7	65	< 0.1	na	1.4	2.4
Pre-packaged RTE & RTH Pizza Crust	8.0	92	0.1	na	1.7	3.4

Table I-5 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	17.5	200	0.4	1.5	2.7	4.4

na = not applicable
* 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 I-6 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.2	14	0.1*	na	3.6*	9.8*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.1	5	< 0.1*	na	4.9*	11.5*
Pre-packaged RTE Savory Snacks	6.6	29	0.1*	na	1.7*	3.5*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	7.9	35	< 0.1	na	0.4	0.7
Pre-packaged RTE & RTH Biscuits & English Muffins	3.9	17	< 0.1*	na	1.0*	1.9*
Pre-packaged RTE & RTH Bread	52.4	231	0.6	1.6	1.1	1.9
Pre-packaged RTE & RTH Bread Sticks (hard)	0.5	2	< 0.1*	na	0.1*	0.2*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	2	< 0.1*	na	0.8*	0.9*
Pre-packaged RTE & RTH Cakes	5.9	26	< 0.1*	na	1.8*	3.9*
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.9	57	0.1	0.4	0.8	1.7
Pre-packaged RTE & RTH Croissants	0.7	3	< 0.1*	na	3.0*	3.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Doughnuts	6.6	29	0.4*	na	5.1*	9.9*
Pre-packaged RTE & RTH Muffins	3.2	14	< 0.1*	na	1.2*	1.6*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	7.5	33	< 0.1	na	1.4	2.5

Table I-6 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	5.4	24	0.2*	na	3.1*	5.8*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	2.0	9	0.2*	na	8.5*	22.3*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.6	7	0.2*	na	10.3*	20.6*
Pre-packaged RTE & RTH Rolls	16.1	71	0.2	0.7	1.0	1.7
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.6	16	< 0.1*	na	2.1*	4.2*
Pre-packaged RTE & RTH Waffles	2.9	13	< 0.1*	na	1.7*	1.6*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	9.3	41	0.1	na	1.2	2.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.1	5	< 0.1*	na	1.5*	3.4*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.7	56	0.2	0.6	1.5	3.0
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.5	11	< 0.1*	na	2.3*	3.8*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.6	7	< 0.1*	na	1.6*	6.2*
Pre-packaged RTE Frozen Yogurt	0.9	4	< 0.1*	na	1.2*	2.1*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.9	17	< 0.1*	na	1.4*	2.8*
Pre-packaged RTE & RTH Pizza Crust	7.7	34	0.1	na	1.9	3.2

Table I-6 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	15.4	68	0.4	1.3	3.2	6.7

na = not applicable
*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 I-7 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.5	11	0.1*	na	5.9*	20.7*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.9	4	< 0.1*	na	2.9*	13.0*
Pre-packaged RTE Savory Snacks	7.4	33	0.3	na	3.1	8.4
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	3.8	17	< 0.1*	na	0.4*	0.7*
Pre-packaged RTE & RTH Biscuits & English Muffins	7.2	32	0.1	na	2.0	7.6
Pre-packaged RTE & RTH Bread	55.4	246	0.8	2.1	1.4	2.5
Pre-packaged RTE & RTH Bread Sticks (hard)	0.2	1	< 0.1*	na	0.1*	0.1*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	2	< 0.1*	na	2.1*	3.1*
Pre-packaged RTE & RTH Cakes	7.0	31	0.1*	na	2.3	5.2
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.5	60	0.1	0.3	1.7	3.7
Pre-packaged RTE & RTH Croissants	0.9	4	< 0.1*	na	3.4*	6.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	2	< 0.1*	na	0.7*	0.9*
Pre-packaged RTE & RTH Doughnuts	6.8	30	0.6	na	7.6	15.7
Pre-packaged RTE & RTH Muffins	2.3	10	< 0.1*	na	3.6*	6.4*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	7.4	33	0.1	na	2.1	4.5

Table I-7 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	6.3	28	0.2*	na	5.0*	10.9*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	5.2	23	0.4*	na	7.5*	12.8*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.5	11	0.3*	na	11.3*	15.4*
Pre-packaged RTE & RTH Rolls	22.3	99	0.3	1.4	1.3	2.3
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	6.5	29	0.2*	na	2.8*	5.6*
Pre-packaged RTE & RTH Waffles	5.0	22	0.1*	na	2.0*	3.0*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	12.8	57	0.3	0.7	2.2	5.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.2	1	< 0.1*	na	3.5*	3.5*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	14.2	63	0.2	0.6	1.4	2.7
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.7	12	0.2*	na	8.3*	38.3*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.0	9	< 0.1*	na	1.8*	2.0*
Pre-packaged RTE Frozen Yogurt	1.1	5	< 0.1*	na	3.9*	7.8*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	4.3	19	< 0.1*	na	1.6*	3.3*
Pre-packaged RTE & RTH Pizza Crust	10.8	48	0.3	0.8	3.2	6.3

Table I-7 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	16.0	71	0.4	1.6	2.2	4.2

na = not applicable
* 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 I-8 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.9	24	0.1*	na	3.7*	8.2*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.7	6	< 0.1*	na	2.1*	4.0*
Pre-packaged RTE Savory Snacks	7.6	62	0.2	na	2.4	9.3
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	8.2	67	< 0.1	na	0.4	0.6
Pre-packaged RTE & RTH Biscuits & English Muffins	2.8	23	< 0.1*	na	1.3*	3.8*
Pre-packaged RTE & RTH Bread	49.4	405	0.5	1.6	1.1	1.8
Pre-packaged RTE & RTH Bread Sticks (hard)	0.2	2	< 0.1*	na	0.2*	0.2*
Pre-packaged RTE & RTH Bread Sticks (soft)	1.2	10	< 0.1*	na	1.3*	2.9*
Pre-packaged RTE & RTH Cakes	5.0	41	0.1	na	2.7	6.1
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.5	111	0.1	0.2	1.0	2.8
Pre-packaged RTE & RTH Croissants	0.5	4	< 0.1*	na	2.7*	2.8*
Pre-packaged RTE & RTH Crackers (not snack type)	0.1	1	< 0.1*	na	0.7*	0.7*
Pre-packaged RTE & RTH Doughnuts	5.7	47	0.4	na	7.2	12.1
Pre-packaged RTE & RTH Muffins	3.5	29	< 0.1*	na	1.7*	3.2*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	3.7	30	< 0.1	na	1.2	2.3

Table I-8 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.5	37	0.2	na	4.4	7.6
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.8	15	0.1*	na	6.4*	12.9*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.6	21	0.2*	na	6.4*	9.8*
Pre-packaged RTE & RTH Rolls	16.5	135	0.1	0.7	0.9	1.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.0	25	< 0.1*	na	1.6*	2.7*
Pre-packaged RTE & RTH Waffles	2.2	18	< 0.1*	na	1.3*	1.8*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	7.7	63	0.1	na	1.7	3.2
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.2	10	< 0.1*	na	2.4*	7.0*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	10.1	83	0.2	na	1.9	4.8
Fats and Oils						
Pre-packaged RTE Mayonnaise	3.2	26	< 0.1*	na	2.5*	5.5*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.7	6	< 0.1*	na	0.6*	0.4*
Pre-packaged RTE Frozen Yogurt	1.8	15	< 0.1*	na	2.6*	4.2*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	4.5	37	< 0.1	na	1.4	2.4
Pre-packaged RTE & RTH Pizza Crust	5.9	48	0.1	na	2.4	4.3

Table I-8 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.3	101	0.4	1.0	2.9	5.6

na = not applicable
* 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 I-9 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.0	8	< 0.1*	na	5.6*	8.5*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.1	9	< 0.1*	na	6.8*	13.0*
Pre-packaged RTE Savory Snacks	5.9	50	0.2	na	2.5	7.6
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.7	48	< 0.1	na	0.5	1.1
Pre-packaged RTE & RTH Biscuits & English Muffins	3.3	28	< 0.1*	na	1.4*	3.9*
Pre-packaged RTE & RTH Bread	51.4	432	0.9	2.4	1.8	3.2
Pre-packaged RTE & RTH Bread Sticks (hard)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Bread Sticks (soft)	0.8	7	< 0.1*	na	1.6*	4.4*
Pre-packaged RTE & RTH Cakes	6.1	51	0.2	na	2.6	7.3
Pre-packaged RTH Cookies	0.0	na	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	14.0	118	0.2	0.4	1.5	3.7
Pre-packaged RTE & RTH Croissants	0.7	6	< 0.1*	na	4.8*	6.7*
Pre-packaged RTE & RTH Crackers (not snack type)	0.2	2	< 0.1*	na	0.2*	0.3*
Pre-packaged RTE & RTH Doughnuts	5.4	45	< 0.1	na	8.0	14.2
Pre-packaged RTE & RTH Muffins	1.5	13	< 0.1*	na	2.4*	5.1*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.3	36	< 0.1	na	2.0	3.3

Table I-9 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.9	41	0.2	na	4.8	7.8
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.9	16	0.2*	na	8.7*	14.4*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.7	14	0.1*	na	9.8*	21.6*
Pre-packaged RTE & RTH Rolls	19.4	163	0.3	1.2	1.5	2.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.8	32	< 0.1	na	2.2	5.1
Pre-packaged RTE & RTH Waffles	2.1	18	< 0.1*	na	2.1*	3.2*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	8.1	68	0.2	na	2.4	5.0
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.7	14	< 0.1*	na	3.4*	5.3*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	9.8	82	0.2	0.3	1.7	3.1
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.5	21	< 0.1*	na	3.5*	4.7*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.4	3	< 0.1*	na	1.6*	1.5*
Pre-packaged RTE Frozen Yogurt	1.1	9	< 0.1*	na	2.5*	3.3*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.7	31	< 0.1	na	1.8	3.6
Pre-packaged RTE & RTH Pizza Crust	6.4	54	0.2	na	3.0	6.1

Table I-9 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	13.9	117	0.4	1.4	2.9	6.1

na = not applicable
* 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 I-10 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.5	57	0.2	na	4.2	7.6
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	2.4	39	< 0.1	na	4.0	10.9
Pre-packaged RTE Savory Snacks	10.2	167	0.3	0.2	2.4	5.5
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	12.2	201	< 0.1	0.3	0.4	0.6
Pre-packaged RTE & RTH Biscuits & English Muffins	4.7	77	< 0.1	na	0.9	3.9
Pre-packaged RTE & RTH Bread	60.9	1,000	0.7	1.6	1.1	2.0
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	5	< 0.1*	na	0.9*	1.6*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	8	< 0.1*	na	1.5*	3.4*
Pre-packaged RTE & RTH Cakes	6.7	110	0.2	na	2.2	4.8
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	11.4	187	< 0.1	0.2	0.9	2.1
Pre-packaged RTE & RTH Croissants	0.9	14	< 0.1*	na	3.8*	5.9*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	8	< 0.1*	na	0.3*	1.2*
Pre-packaged RTE & RTH Doughnuts	5.3	87	0.3	na	5.7	11.2
Pre-packaged RTE & RTH Muffins	3.9	64	< 0.1	na	1.7	2.8
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	5.0	82	< 0.1	na	1.5	3.0

Table I-10 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.0	66	0.1	na	3.3	5.8
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	4.4	73	0.3	na	6.6	11.2
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.8	29	0.1*	na	7.2*	17.2*
Pre-packaged RTE & RTH Rolls	20.1	331	0.2	0.7	0.9	1.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	4.6	75	< 0.1	na	2.0	5.2
Pre-packaged RTE & RTH Waffles	2.9	48	< 0.1	na	1.5	3.0
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	6.7	110	0.1	na	1.5	3.1
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.9	15	< 0.1*	na	2.3*	4.4*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.4	204	0.1	0.6	1.1	2.3
Fats and Oils						
Pre-packaged RTE Mayonnaise	4.6	76	0.2	na	3.6	6.0
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.5	24	< 0.1*	na	0.7*	1.9*
Pre-packaged RTE Frozen Yogurt	2.7	44	< 0.1	na	2.2	3.4
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.7	61	< 0.1	na	1.3	2.4
Pre-packaged RTE & RTH Pizza Crust	4.8	79	< 0.1	na	1.8	3.2

Table I-10 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.4	204	0.3	0.7	2.9	6.1

na = not applicable
* 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 I-11 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.6	26	< 0.1*	na	4.7*	7.3*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.5	25	0.1*	na	6.0*	10.0*
Pre-packaged RTE Savory Snacks	6.5	109	0.2	na	3.0	7.7
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	8.1	136	< 0.1	na	0.5	0.7
Pre-packaged RTE & RTH Biscuits & English Muffins	4.4	73	< 0.1	na	1.2	3.9
Pre-packaged RTE & RTH Bread	60.8	1,020	1.0	2.4	1.6	3.1
Pre-packaged RTE & RTH Bread Sticks (hard)	0.1	2	< 0.1*	na	0.7*	1.2*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.4	7	< 0.1*	na	1.8*	3.2*
Pre-packaged RTE & RTH Cakes	7.6	127	0.2	na	2.4	4.8
Pre-packaged RTH Cookies	0.1	1	< 0.1*	na	1.5*	1.5*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.4	208	0.2	0.3	1.4	3.2
Pre-packaged RTE & RTH Croissants	0.4	6	< 0.1*	na	3.8*	5.7*
Pre-packaged RTE & RTH Crackers (not snack type)	0.2	4	< 0.1*	na	0.4*	0.5*
Pre-packaged RTE & RTH Doughnuts	6.3	106	0.5	na	8.0	14.2
Pre-packaged RTE & RTH Muffins	2.8	47	< 0.1	na	2.5	5.1
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	5.0	84	0.1	na	2.3	4.5

Table I-11 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.4	73	0.2	na	4.6	7.8
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	5.3	89	0.4	na	7.4	12.5
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	35	0.2	na	9.0	16.4
Pre-packaged RTE & RTH Rolls	23.6	395	0.3	1.4	1.3	2.1
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	4.6	77	< 0.1	na	2.1	3.3
Pre-packaged RTE & RTH Waffles	2.4	40	< 0.1	na	2.3	5.0
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	7.5	126	0.2	na	2.2	4.2
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.9	15	< 0.1*	na	5.2*	21.5*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.7	213	0.2	0.7	1.8	4.0
Fats and Oils						
Pre-packaged RTE Mayonnaise	4.1	68	0.2	na	3.7	8.3
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.8	31	< 0.1	na	1.5	3.3
Pre-packaged RTE Frozen Yogurt	1.9	32	< 0.1	na	3.0	4.5
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.2	54	< 0.1	na	2.0	3.8
Pre-packaged RTE & RTH Pizza Crust	5.5	92	0.2	na	3.0	6.3

Table I-11 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.2	204	0.4	0.8	3.2	7.9

na = not applicable
* 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 I-12 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.4	52	0.1	na	4.4	10.0
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	2.1	33	0.1	na	5.6	10.6
Pre-packaged RTE Savory Snacks	8.7	134	0.1	na	1.5	3.7
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	7.6	117	< 0.1	na	0.4	0.6
Pre-packaged RTE & RTH Biscuits & English Muffins	6.2	95	< 0.1	na	0.7	2.0
Pre-packaged RTE & RTH Bread	70.7	1,086	0.8	1.9	1.2	2.3
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	4	< 0.1*	na	0.3*	0.4*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.3	5	< 0.1*	na	1.1*	2.0*
Pre-packaged RTE & RTH Cakes	6.2	95	0.2	na	3.2	6.6
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	8.1	125	< 0.1	na	1.2	2.7
Pre-packaged RTE & RTH Croissants	0.5	8	< 0.1*	na	3.8*	6.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	8	< 0.1*	na	0.4*	0.7*
Pre-packaged RTE & RTH Doughnuts	4.0	61	0.2	na	5.4	9.5
Pre-packaged RTE & RTH Muffins	4.5	69	< 0.1	na	1.9	3.2
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.4	67	< 0.1	na	1.2	2.3

Table I-12 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	3.6	55	0.1	na	3.5	6.9
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	5.3	81	0.3	na	5.9	10.3
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.2	19	< 0.1*	na	7.4*	14.7*
Pre-packaged RTE & RTH Rolls	17.2	264	0.1	0.7	0.9	1.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.7	57	< 0.1	na	1.6	3.1
Pre-packaged RTE & RTH Waffles	2.3	36	< 0.1	na	1.3	2.8
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	3.8	58	< 0.1	na	1.5	3.2
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.4	6	< 0.1*	na	4.1*	11.7*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	9.9	152	0.1	na	1.4	3.1
Fats and Oils						
Pre-packaged RTE Mayonnaise	9.0	139	0.3	na	3.1	6.5
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.1	32	< 0.1*	na	1.3	2.5
Pre-packaged RTE Frozen Yogurt	2.7	42	< 0.1	na	1.8	3.3
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.8	27	< 0.1*	na	1.9*	4.2*
Pre-packaged RTE & RTH Pizza Crust	2.5	39	< 0.1	na	1.7	2.7

Table I-12 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	10.7	165	0.3	0.5	2.3	4.9

na = not applicable
* 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 I-13 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.0	48	0.2	na	5.6	8.0
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.3	21	< 0.1*	na	5.6*	13.0*
Pre-packaged RTE Savory Snacks	7.1	114	0.1	na	1.9	4.5
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.0	80	< 0.1	na	0.4	0.7
Pre-packaged RTE & RTH Biscuits & English Muffins	5.3	84	< 0.1	na	0.8	2.6
Pre-packaged RTE & RTH Bread	69.6	1,113	1.0	2.5	1.6	3.0
Pre-packaged RTE & RTH Bread Sticks (hard)	0.2	3	< 0.1*	na	0.4*	0.4*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.3	4	< 0.1*	na	1.7*	4.9*
Pre-packaged RTE & RTH Cakes	7.9	127	0.2	na	2.8	5.5
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	8.8	141	0.2	na	1.9	4.1
Pre-packaged RTE & RTH Croissants	0.3	5	< 0.1*	na	2.5*	3.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.4	7	< 0.1*	na	0.5*	1.2*
Pre-packaged RTE & RTH Doughnuts	4.7	75	0.3	na	5.7	9.5
Pre-packaged RTE & RTH Muffins	3.4	54	< 0.1	na	2.0	3.8
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.7	75	< 0.1	na	1.8	3.5

Table I-13 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.8	76	0.2	na	4.3	9.5
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	7.3	116	0.5	na	6.7	12.4
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.3	21	< 0.1*	na	6.7*	8.8*
Pre-packaged RTE & RTH Rolls	18.8	300	0.2	0.9	1.2	2.1
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	5.0	80	0.1	na	2.3	4.5
Pre-packaged RTE & RTH Waffles	3.0	48	< 0.1	na	2.3	3.2
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	4.4	71	0.1	na	2.6	4.3
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.8	12	< 0.1*	na	3.1*	7.1*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.0	191	0.2	0.6	1.7	3.3
Fats and Oils						
Pre-packaged RTE Mayonnaise	7.6	122	0.3	na	3.3	8.0
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.1	34	< 0.1*	na	1.7	4.0
Pre-packaged RTE Frozen Yogurt	2.7	43	< 0.1	na	2.1	3.3
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.7	27	< 0.1*	na	1.7*	3.1*
Pre-packaged RTE & RTH Pizza Crust	2.3	37	< 0.1	na	2.8	5.5

Table I-13 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.1	193	0.4	0.9	3.0	6.2

na = not applicable
* 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 I-14 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	4.5	28	0.1*	na	2.7*	6.1*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.0	6	< 0.1*	na	3.5*	8.2*
Pre-packaged RTE Savory Snacks	4.4	27	< 0.1*	na	1.2*	1.8*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	3.9	24	< 0.1*	na	0.3*	0.7*
Pre-packaged RTE & RTH Biscuits & English Muffins	6.9	43	< 0.1*	na	0.5*	1.0*
Pre-packaged RTE & RTH Bread	74.2	459	0.9	2.2	1.2	2.4
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	2	< 0.1*	na	0.3*	0.4*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.2	1	< 0.1*	na	0.4*	0.4*
Pre-packaged RTE & RTH Cakes	5.8	36	0.2	na	3.0	7.7
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	6.5	40	0.1	na	1.7	4.3
Pre-packaged RTE & RTH Croissants	0.2	1	< 0.1*	na	6.3*	6.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	3	< 0.1*	na	0.2*	0.5*
Pre-packaged RTE & RTH Doughnuts	4.2	26	0.2*	na	4.2*	6.0*
Pre-packaged RTE & RTH Muffins	3.2	20	< 0.1*	na	1.6*	2.6*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.7	29	< 0.1*	na	1.2*	2.4*

Table I-14 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.4	27	0.1*	na	2.9*	6.7*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	9.5	59	0.5	na	6.0	9.9
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.8	11	< 0.1*	na	4.0*	4.9*
Pre-packaged RTE & RTH Rolls	13.2	82	0.1	0.6	0.9	1.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	5.8	36	0.1	na	1.6	2.0
Pre-packaged RTE & RTH Waffles	2.6	16	< 0.1*	na	1.3*	1.6*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	2.6	16	< 0.1*	na	0.7*	1.8*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.6	4	< 0.1*	na	0.5*	1.2*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.1	75	0.2	0.6	1.1	1.9
Fats and Oils						
Pre-packaged RTE Mayonnaise	7.8	48	0.2	na	3.3	8.3
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.8	11	< 0.1*	na	1.1*	3.0*
Pre-packaged RTE Frozen Yogurt	4.2	26	< 0.1*	na	2.1*	4.2*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.3	8	< 0.1*	na	1.4*	2.7*
Pre-packaged RTE & RTH Pizza Crust	2.4	15	< 0.1*	na	1.0*	2.1*

Table I-14 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	7.6	47	0.2	na	2.1	4.4

na = not applicable
* 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 I-15 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.6	24	0.1*	na	3.5*	7.6*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.7	5	< 0.1*	na	5.0*	11.4*
Pre-packaged RTE Savory Snacks	5.1	34	< 0.1	na	1.7	3.8
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	3.4	23	< 0.1*	na	0.5*	0.9*
Pre-packaged RTE & RTH Biscuits & English Muffins	5.7	38	< 0.1	na	0.8	2.6
Pre-packaged RTE & RTH Bread	76.8	515	1.1	2611.4	1.5	2.8
Pre-packaged RTE & RTH Bread Sticks (hard)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Bread Sticks (soft)	0.3	2	< 0.1*	na	1.1*	2.2*
Pre-packaged RTE & RTH Cakes	8.0	54	< 0.1	na	2.7	7.2
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	4.8	32	< 0.1	na	2.1	4.0
Pre-packaged RTE & RTH Croissants	0.1	1	< 0.1*	na	2.8*	2.8*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	2	< 0.1*	na	0.9*	1.2*
Pre-packaged RTE & RTH Doughnuts	4.9	33	0.3	na	5.6	9.5
Pre-packaged RTE & RTH Muffins	2.4	16	< 0.1*	na	1.7*	3.8*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	6.9	46	< 0.1	na	1.4	2.3

Table I-15 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.5	30	0.2	na	3.7	7.7
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	12.4	83	0.9	3.5	7.1	11.3
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	14	0.2*	na	7.1*	13.7*
Pre-packaged RTE & RTH Rolls	16.2	109	0.2	0.7	1.0	1.8
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	4.9	33	< 0.1	na	1.5	3.3
Pre-packaged RTE & RTH Waffles	3.0	20	< 0.1*	na	1.8*	2.9*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	3.0	20	< 0.1*	na	2.5*	5.3*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.1	1	< 0.1*	na	0.6*	0.6*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	13.6	91	0.2	0.6	1.3	2.2
Fats and Oils						
Pre-packaged RTE Mayonnaise	7.3	49	0.2	na	2.7	5.5
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.4	16	< 0.1*	na	0.8*	2.0*
Pre-packaged RTE Frozen Yogurt	2.1	14	< 0.1*	na	1.4*	2.5*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	0.9	6	< 0.1*	na	2.6*	2.1*
Pre-packaged RTE & RTH Pizza Crust	2.5	17	< 0.1*	na	2.2*	3.9*

Table I-15 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	5.8	39	0.2	na	3.1	7.2

na = not applicable
* 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 I-16 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.3	465	0.1	na	4.2	8.0
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.4	287	< 0.1	na	4.5	10.9
Pre-packaged RTE Savory Snacks	7.6	1,556	0.2	na	2.2	5.4
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.9	1,211	< 0.1	na	0.4	0.6
Pre-packaged RTE & RTH Biscuits & English Muffins	3.6	732	< 0.1	na	1.0	3.5
Pre-packaged RTE & RTH Bread	60.8	12,397	0.8	2.0	1.3	2.4
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	71	< 0.1	na	0.3	0.8
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	97	< 0.1	na	1.3	3.1
Pre-packaged RTE & RTH Cakes	6.0	1,221	0.1	na	2.3	5.2
Pre-packaged RTH Cookies	< 0.1	5	< 0.1*	na	6.4*	12.1*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	11.3	2,299	0.1	0.1	1.2	2.7
Pre-packaged RTE & RTH Croissants	0.4	84	< 0.1	na	3.8	6.3
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	68	< 0.1	na	0.5	0.9
Pre-packaged RTE & RTH Doughnuts	5.3	1,088	0.3	na	6.3	11.9
Pre-packaged RTE & RTH Muffins	2.8	565	< 0.1	na	1.9	3.2
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	7.8	1,590	< 0.1	na	1.5	2.9

Table I-16 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	5.4	1,108	0.2	na	3.7	6.9
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	3.4	698	0.3	na	6.7	11.3
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.7	355	0.1	na	7.4	15.2
Pre-packaged RTE & RTH Rolls	16.9	3,456	0.2	0.7	1.1	2.0
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.9	792	< 0.1	na	1.9	3.9
Pre-packaged RTE & RTH Waffles	5.1	1,034	< 0.1	na	1.6	3.0
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	7.3	1,496	0.1	na	1.7	3.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.2	237	< 0.1	na	3.0	5.5
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.1	2,464	0.2	0.6	1.4	3.0
Fats and Oils						
Pre-packaged RTE Mayonnaise	3.8	781	0.2	na	3.3	7.6
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.5	304	< 0.1	na	1.2	2.5
Pre-packaged RTE Frozen Yogurt	1.5	313	< 0.1	na	2.2	4.2
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.6	739	< 0.1	na	1.5	2.4
Pre-packaged RTE & RTH Pizza Crust	5.7	1,155	0.1	na	2.2	4.5

Table I-16 Estimated Daily Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	11.3	2,296	0.3	0.8	2.7	5.6

na = not applicable
* 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).

ATTACHMENT II TO APPENDIX B

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 II-1 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	0.1	1	1.4*	na	996.7*	996.7*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.2	2	0.1*	na	50.4*	83.6*
Pre-packaged RTE Savory Snacks	1.2	11	0.4*	na	36.7*	104.4*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	0.5	5	0.1*	na	17.5*	23.0*
Pre-packaged RTE & RTH Biscuits & English Muffins	0.1	1	< 0.1*	na	16.0*	16.0*
Pre-packaged RTE & RTH Bread	9.5	88	4.3	na	44.0	87.1
Pre-packaged RTE & RTH Bread Sticks (hard)	0.1	1	< 0.1*	na	5.0*	5.0*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cakes	0.2	2	0.1*	na	37.7*	64.7*
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	2.4	22	0.4*	na	17.4*	51.6*
Pre-packaged RTE & RTH Croissants	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Crackers (not snack type)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Doughnuts	0.1	1	0.1*	na	216.3*	216.3*
Pre-packaged RTE & RTH Muffins	0.2	2	0.1*	na	47.9*	56.4*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	2.0	19	1.3*	na	52.8*	79.6*

Table II-1 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	0.3	3	0.8*	na	105.9*	197.6*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	0.1	1	0.3*	na	219.1*	219.1*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	0.3	3	1.6*	na	472.4*	903.6*
Pre-packaged RTE & RTH Rolls	1.2	11	0.6*	na	37.4*	82.0*
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	0.1	1	0.1*	na	59.4*	59.4*
Pre-packaged RTE & RTH Waffles	0.6	6	0.8*	na	101.6*	164.1*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.1	10	0.4*	na	28.7*	44.3*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.1	1	0.1*	na	71.6*	71.6*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	0.9	8	0.8*	na	91.6*	192.2*
Fats and Oils						
Pre-packaged RTE Mayonnaise	0.0	0	na	na	na	na
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.0	0	na	na	na	na
Pre-packaged RTE Frozen Yogurt	0.1	1	0.1*	na	76.6*	76.6*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	0.3	3	0.3*	na	63.4*	54.5*
Pre-packaged RTE & RTH Pizza Crust	1.1	10	0.5*	na	34.8*	51.5*

Table II-1 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 0 to 6 Months 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	0.3	3	0.2*	na	62.9*	77.8*

na = not applicable
* 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 II-2 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	0.3	1	0.1*	na	70.7*	70.7*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.0	0	na	na	na	na
Pre-packaged RTE Savory Snacks	2.0	7	0.4*	na	27.3*	46.7*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	2.0	7	0.4*	na	18.7*	33.6*
Pre-packaged RTE & RTH Biscuits & English Muffins	0.3	1	< 0.1*	na	11.3*	11.3*
Pre-packaged RTE & RTH Bread	17.5	62	7.4	24.2	50.7	103.5
Pre-packaged RTE & RTH Bread Sticks (hard)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Bread Sticks (soft)	0.8	3	0.5*	na	60.8*	153.3*
Pre-packaged RTE & RTH Cakes	0.3	1	0.4*	na	151.3*	151.3*
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	2.5	9	0.2*	na	9.8*	20.2*
Pre-packaged RTE & RTH Croissants	0.3	1	0.2*	na	63.0*	63.0*
Pre-packaged RTE & RTH Crackers (not snack type)	0.8	3	0.2*	na	15.2*	15.8*
Pre-packaged RTE & RTH Doughnuts	0.8	3	1.9*	na	298.8*	456.5*
Pre-packaged RTE & RTH Muffins	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	3.4	12	1.1*	na	40.0*	80.4*

Table II-2 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	1.1	4	0.7*	na	89.9*	119.2*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	0.3	1	0.1*	na	55.1*	55.1*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	0.3	1	0.3*	na	172.8*	172.8*
Pre-packaged RTE & RTH Rolls	2.0	7	0.5*	na	29.0*	35.4*
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	0.8	3	0.3*	na	41.3*	50.1*
Pre-packaged RTE & RTH Waffles	0.8	3	0.6*	na	106.7*	147.5*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.6	2	0.1*	na	33.1*	51.4*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.8	3	0.6*	na	121.4*	203.6*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	1.1	4	0.4*	na	36.4*	58.0*
Fats and Oils						
Pre-packaged RTE Mayonnaise	0.0	0	na	na	na	na
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.3	1	< 0.1*	na	18.6*	18.6*
Pre-packaged RTE Frozen Yogurt	0.0	0	na	na	na	na
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	0.6	2	1.1*	na	210.0*	222.2*
Pre-packaged RTE & RTH Pizza Crust	0.8	3	0.7*	na	119.0*	311.3*

Table II-2 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Infants Aged 7 to 11 Months 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	0.0	0	na	na	na	na

na = not applicable
* 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 II-3 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.1	78	3.4	na	155.1	277.3
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.5	55	1.4	na	85.2	156.5
Pre-packaged RTE Savory Snacks	10.5	383	8.4	5.8	79.5	175.2
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	4.7	170	0.7	na	14.1	27.9
Pre-packaged RTE & RTH Biscuits & English Muffins	2.2	79	1.1	na	55.1	155.8
Pre-packaged RTE & RTH Bread	65.0	2,368	37.0	95.5	57.5	111.6
Pre-packaged RTE & RTH Bread Sticks (hard)	0.6	22	0.1*	na	15.1*	30.5*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.6	22	0.3*	na	47.5*	96.3*
Pre-packaged RTE & RTH Cakes	5.1	185	4.0	na	86.9	179.1
Pre-packaged RTH Cookies	0.1	2	0.1*	na	136.3*	207.4*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.4	450	3.9	7.6	33.8	72.7
Pre-packaged RTE & RTH Croissants	0.3	12	0.3*	na	153.5*	330.0*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	11	0.1*	na	25.8*	35.8*
Pre-packaged RTE & RTH Doughnuts	5.8	210	15.8	na	310.7	602.8
Pre-packaged RTE & RTH Muffins	2.7	98	1.9	na	75.9	117.6
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	13.0	472	7.5	22.5	60.7	120.6

Table II-3 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	6.8	249	10.4	na	150.4	260.0
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.3	47	2.4	na	192.4	345.1
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	77	6.1	na	265.8	554.8
Pre-packaged RTE & RTH Rolls	13.7	500	5.7	26.0	43.7	75.4
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.3	120	2.9	na	93.1	167.7
Pre-packaged RTE & RTH Waffles	9.2	334	7.0	na	75.2	125.1
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	8.9	325	4.5	na	50.0	101.0
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	2.1	75	2.5	na	118.8	261.4
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.2	444	7.6	17.4	65.6	131.1
Fats and Oils						
Pre-packaged RTE Mayonnaise	1.8	65	1.8	na	103.1	252.8
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.1	40	0.4*	na	42.6	77.3
Pre-packaged RTE Frozen Yogurt	0.9	34	0.7	na	65.7	118.4
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	5.5	199	4.5	na	84.3	138.8
Pre-packaged RTE & RTH Pizza Crust	6.8	248	4.2	na	62.3	127.4

Table II-3 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Toddlers Aged 1 to 3 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	10.1	369	10.9	na	113.7	260.7

na = not applicable
* 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 II-4 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.8	64	2.5	na	139.9	280.2
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.5	54	1.3	na	87.6	152.1
Pre-packaged RTE Savory Snacks	8.7	306	6.7	na	77.0	172.1
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.5	192	0.8	na	12.7	21.9
Pre-packaged RTE & RTH Biscuits & English Muffins	2.8	98	1.8	na	58.5	192.5
Pre-packaged RTE & RTH Bread	68.5	2,402	33.5	83.4	49.0	95.6
Pre-packaged RTE & RTH Bread Sticks (hard)	0.6	21	0.1*	na	10.2*	18.7*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	16	0.3*	na	45.5*	84.3*
Pre-packaged RTE & RTH Cakes	6.6	231	4.2	na	58.0	108.0
Pre-packaged RTH Cookies	< 0.1	1	0.2*	na	354.0*	354.0*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.4	436	3.6	3.4	34.8	74.7
Pre-packaged RTE & RTH Croissants	0.3	11	1.1*	na	351.4*	612.4*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	11	0.1*	na	34.3*	52.0*
Pre-packaged RTE & RTH Doughnuts	7.1	249	18.0	na	263.8	487.9
Pre-packaged RTE & RTH Muffins	2.8	97	1.9	na	66.0	112.6
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	11.8	415	6.2	23.9	49.5	94.7

Table II-4 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	8.2	286	12.0	na	131.9	220.0
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.6	55	5.1	na	247.1	496.3
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.9	65	4.5	na	241.4	449.1
Pre-packaged RTE & RTH Rolls	18.9	664	7.2	31.2	36.9	64.9
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.7	129	2.4	na	63.1	118.3
Pre-packaged RTE & RTH Waffles	9.0	315	6.2	na	64.4	116.8
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	11.0	386	5.2	11.9	47.9	104.6
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.7	61	1.2	na	74.8	171.9
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	15.8	555	9.2	31.1	55.3	103.7
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.5	87	2.2	na	90.3	197.7
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.8	62	1.3	na	54.2	119.8
Pre-packaged RTE Frozen Yogurt	0.9	30	0.9	na	93.9	135.0
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	5.1	180	3.2	na	54.9	95.4
Pre-packaged RTE & RTH Pizza Crust	9.0	316	5.2	na	59.7	123.8

Table II-4 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 4 to 8 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	13.3	468	15.3	38.4	105.7	228.6

na = not applicable
* 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 II-5 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.8	20	2.2*	na	111.3*	246.6*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.9	21	2.2*	na	106.5*	363.7*
Pre-packaged RTE Savory Snacks	6.8	75	3.7	na	52.3	126.1
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	7.0	77	0.7	na	9.4	15.7
Pre-packaged RTE & RTH Biscuits & English Muffins	3.4	37	1.1	na	31.8	84.2
Pre-packaged RTE & RTH Bread	62.1	682	19.8	52.3	32.0	62.8
Pre-packaged RTE & RTH Bread Sticks (hard)	0.4	4	< 0.1*	na	5.0*	5.4*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	5	0.1*	na	13.8*	32.1*
Pre-packaged RTE & RTH Cakes	7.8	86	3.9	na	42.4	98.4
Pre-packaged RTH Cookies	0.1	1	0.6*	na	295.0*	295.0*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.5	137	2.5	3.4	23.2	55.9
Pre-packaged RTE & RTH Croissants	0.6	7	0.5*	na	66.0*	133.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	3	< 0.1*	na	17.8*	28.3*
Pre-packaged RTE & RTH Doughnuts	5.8	64	7.9	na	149.3	262.6
Pre-packaged RTE & RTH Muffins	2.5	27	1.6*	na	48.0*	75.2*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	10.2	112	3.9	10.5	35.7	62.8

Table II-5 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	8.4	92	7.8	na	92.5	162.3
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	2.6	29	2.8*	na	125.4*	200.4*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	23	5.2*	na	169.4*	343.0*
Pre-packaged RTE & RTH Rolls	22.9	251	5.6	20.8	23.8	44.5
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.8	42	1.5	na	37.6	73.8
Pre-packaged RTE & RTH Waffles	6.0	66	3.4	na	48.6	84.7
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	10.7	117	3.6	7.6	33.0	60.0
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.7	8	1.2*	na	105.4*	509.0*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	17.5	192	5.6	18.8	32.2	63.8
Fats and Oils						
Pre-packaged RTE Mayonnaise	4.5	49	4.0	na	78.2	210.7
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.9	21	0.5*	na	20.7*	49.3*
Pre-packaged RTE Frozen Yogurt	1.2	13	0.6*	na	49.9*	70.1*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	5.7	63	2.4	na	35.7	68.5
Pre-packaged RTE & RTH Pizza Crust	8.3	91	3.8	na	43.2	110.5

Table II-5 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Children Aged 9 to 13 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	17.8	195	11.1	33.0	65.2	121.2

na = not applicable
* 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 II-6 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.2	14	2.7*	na	62.4*	175.2*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.2	5	1.1*	na	95.4*	219.3*
Pre-packaged RTE Savory Snacks	6.7	29	2.2*	na	26.4*	53.3*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	8.1	35	0.5	na	6.4	11.4
Pre-packaged RTE & RTH Biscuits & English Muffins	3.9	17	0.7*	na	18.9	37.6
Pre-packaged RTE & RTH Bread	52.0	224	9.5	28.6	18.5	34.9
Pre-packaged RTE & RTH Bread Sticks (hard)	0.5	2	< 0.1*	na	2.8*	3.1*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	2	0.1*	na	15.3*	17.2*
Pre-packaged RTE & RTH Cakes	6.0	26	1.8*	na	30.6*	63.4*
Pre-packaged RTH Cookies	na	na	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.3	53	1.7	5.1	15.2	31.2
Pre-packaged RTE & RTH Croissants	0.7	3	0.5*	na	44.5*	52.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Doughnuts	6.3	27	6.4*	na	91.5*	186.5*
Pre-packaged RTE & RTH Muffins	3.2	14	0.8*	na	20.0*	30.0*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	7.4	32	1.7	na	25.2	38.7

Table II-6 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	5.6	24	3.9*	na	57.1*	99.0*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	2.1	9	2.8*	na	136.6*	358.5*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.6	7	3.0*	na	189.2*	432.6*
Pre-packaged RTE & RTH Rolls	16.5	71	3.1	13.9	16.5	31.0
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.7	16	1.7*	na	34.7*	56.6*
Pre-packaged RTE & RTH Waffles	3.0	13	0.8*	na	26.1*	36.6*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	9.5	41	2.3	4.4	23.0	38.3
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.2	5	0.3*	na	26.3*	62.3*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.8	55	3.4	9.6	26.1	59.9
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.6	11	1.1*	na	35.9*	40.0*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.6	7	0.4*	na	25.9*	97.2*
Pre-packaged RTE Frozen Yogurt	0.9	4	0.1*	na	17.8*	26.2*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.9	17	1.1*	na	25.0*	50.5*
Pre-packaged RTE & RTH Pizza Crust	7.9	34	2.8	na	35.1	55.6

Table II-6 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Teenagers Aged 14 to 18 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	15.5	67	7.8	21.2	56.0	110.8

na = not applicable
* 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 II-7 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.5	11	2.9*	na	110.0*	434.5*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.9	4	0.3*	na	44.9*	227.0*
Pre-packaged RTE Savory Snacks	7.5	33	3.9	na	46.3	105.4
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	3.9	17	0.3*	na	6.4*	11.0*
Pre-packaged RTE & RTH Biscuits & English Muffins	7.1	31	1.9	na	28.9	75.1
Pre-packaged RTE & RTH Bread	55.8	245	11.5	29.7	20.5	36.6
Pre-packaged RTE & RTH Bread Sticks (hard)	0.2	1	< 0.1*	na	2.3*	2.3*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	2	0.1*	na	25.6*	41.6*
Pre-packaged RTE & RTH Cakes	7.1	31	2.1*	na	35.7*	87.4*
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.0	57	2.5	3.3	23.9	40.3
Pre-packaged RTE & RTH Croissants	0.9	4	0.6*	na	51.1*	96.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	2	0.1*	na	12.5*	16.6*
Pre-packaged RTE & RTH Doughnuts	6.8	30	8.6	na	115.0	218.0
Pre-packaged RTE & RTH Muffins	2.3	10	1.3*	na	55.3*	107.5*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	7.1	31	2.4	na	36.4	73.6

Table II-7 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	6.4	28	4.0*	na	72.7*	131.3*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	5.2	23	5.6*	na	113.9*	234.1*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.5	11	4.2*	na	157.0*	222.9*
Pre-packaged RTE & RTH Rolls	22.3	98	4.0	17.1	18.9	34.6
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	6.4	28	2.6*	na	41.0*	84.3*
Pre-packaged RTE & RTH Waffles	5.0	22	2.2*	na	32.5*	55.3*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	13.0	57	3.9	11.6	30.7	74.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.2	1	0.1*	na	40.7*	40.7*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	14.4	63	2.9	11.7	21.7	45.4
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.7	12	3.9*	na	132.7*	628.8*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.1	9	0.5*	na	27.8*	30.9*
Pre-packaged RTE Frozen Yogurt	1.1	5	0.8*	na	62.8*	161.5*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	4.3	19	1.2*	na	26.1*	55.0*
Pre-packaged RTE & RTH Pizza Crust	10.9	48	4.7	11.4	44.5	91.9

Table II-7 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Teenagers Aged 14 to 18 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	15.9	70	5.5	23.0	33.4	60.2

na = not applicable
* 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 II-8 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.0	24	2.0*	na	61.2*	138.1*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.7	6	0.2*	na	31.4*	58.4*
Pre-packaged RTE Savory Snacks	7.7	62	3.4	na	39.5	158.1
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	8.3	67	0.5	na	6.1	10.5
Pre-packaged RTE & RTH Biscuits & English Muffins	2.9	23	0.5*	na	18.3*	71.3*
Pre-packaged RTE & RTH Bread	49.3	397	8.9	25.6	18.5	33.5
Pre-packaged RTE & RTH Bread Sticks (hard)	0.2	2	< 0.1*	na	3.0*	3.1*
Pre-packaged RTE & RTH Bread Sticks (soft)	1.2	10	0.2*	na	21.9*	55.5*
Pre-packaged RTE & RTH Cakes	5.0	40	2.2	na	43.4	80.5
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.3	107	1.9	3.7	16.0	41.0
Pre-packaged RTE & RTH Croissants	0.4	3	0.2*	na	45.0*	51.4*
Pre-packaged RTE & RTH Crackers (not snack type)	0.1	1	< 0.1*	na	13.6*	13.6*
Pre-packaged RTE & RTH Doughnuts	5.6	45	5.7	na	115.4	226.1
Pre-packaged RTE & RTH Muffins	3.6	29	0.9*	na	27.5*	48.4*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	3.5	28	0.7*	na	21.0*	38.9*

Table II-8 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.6	37	3.1	na	71.6	132.4
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.9	15	1.7*	na	101.9*	226.4*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.6	21	2.8*	na	102.8*	161.7*
Pre-packaged RTE & RTH Rolls	16.1	130	2.4	11.5	14.5	24.6
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.1	25	0.7*	na	25.8*	45.0*
Pre-packaged RTE & RTH Waffles	2.2	18	0.6*	na	22.8*	36.5*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	7.5	60	1.8	na	26.1	51.5
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.2	10	0.5*	na	38.5*	103.9*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	10.1	81	2.8	na	28.1	57.7
Fats and Oils						
Pre-packaged RTE Mayonnaise	3.1	25	1.0*	na	37.6*	78.2*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.7	6	< 0.1*	na	9.2*	6.5*
Pre-packaged RTE Frozen Yogurt	1.9	15	0.7*	na	44.2*	64.3*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.9	15	0.7*	na	44.2*	64.3*
Pre-packaged RTE & RTH Pizza Crust	4.6	37	1.1	na	23.4	43.3

Table II-8 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 19 to 30 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.3	99	6.5	16.3	49.1	103.3

na = not applicable
* 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 II-9 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.0	8	0.9*	na	76.7*	124.1*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.1	9	0.9*	na	80.7*	143.0*
Pre-packaged RTE Savory Snacks	6.0	50	2.3	na	32.0	79.5
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.7	48	0.4	na	6.6	13.8
Pre-packaged RTE & RTH Biscuits & English Muffins	3.2	27	0.5*	na	16.4*	49.5*
Pre-packaged RTE & RTH Bread	51.6	431	11.2	30.7	22.3	42.9
Pre-packaged RTE & RTH Bread Sticks (hard)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Bread Sticks (soft)	0.8	7	0.2*	na	23.6*	64.9*
Pre-packaged RTE & RTH Cakes	6.1	51	2.3	na	34.9	100.3
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	13.8	115	2.4	5.5	20.6	47.0
Pre-packaged RTE & RTH Croissants	0.7	6	0.5*	na	59.5*	86.3*
Pre-packaged RTE & RTH Crackers (not snack type)	0.2	2	< 0.1*	na	2.4*	2.6*
Pre-packaged RTE & RTH Doughnuts	5.4	45	6.0	na	108.9	185.3
Pre-packaged RTE & RTH Muffins	1.6	13	0.7*	na	32.8*	80.6*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.3	36	0.9	na	25.4	43.8

Table II-9 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.9	41	2.9	na	64.6	107.3
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	1.9	16	2.0*	na	113.2*	171.5*
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.7	14	2.1*	na	130.3*	351.5*
Pre-packaged RTE & RTH Rolls	19.5	163	3.6	13.6	18.3	31.2
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.8	32	1.0	na	27.0	63.6
Pre-packaged RTE & RTH Waffles	2.2	18	0.5*	na	25.4*	34.8*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	8.1	68	2.7	na	30.0	62.9
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.7	14	0.7*	na	42.5*	87.9*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	9.8	82	2.2	5.1	21.9	47.8
Fats and Oils						
Pre-packaged RTE Mayonnaise	2.5	21	1.2*	na	43.5*	60.9*
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	0.4	3	0.1*	na	20.2*	16.8*
Pre-packaged RTE Frozen Yogurt	1.1	9	0.4*	na	33.5*	47.5*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.7	31	0.9	na	21.3	42.0
Pre-packaged RTE & RTH Pizza Crust	6.5	54	2.9	na	38.3	75.4

Table II-9 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 19 to 30 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	13.9	116	5.1	15.7	37.6	76.7

na = not applicable
* 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 II-10 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.3	53	2.6	na	67.9	134.7
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	2.5	39	1.4	na	52.8	119.4
Pre-packaged RTE Savory Snacks	10.1	161	4.2	3.3	37.2	96.8
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	12.4	196	0.8	3.9	5.8	10.3
Pre-packaged RTE & RTH Biscuits & English Muffins	4.5	72	0.7	na	13.8	57.8
Pre-packaged RTE & RTH Bread	60.7	963	10.1	25.8	16.6	31.7
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	5	< 0.1*	na	14.7*	25.1*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	8	0.1*	na	21.2*	37.0*
Pre-packaged RTE & RTH Cakes	6.6	104	2.6	na	34.4	99.9
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	11.2	178	1.4	2.0	13.7	32.0
Pre-packaged RTE & RTH Croissants	0.9	14	0.5*	na	53.2*	117.8*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	8	< 0.1*	na	5.0*	13.0*
Pre-packaged RTE & RTH Doughnuts	5.2	82	4.4	na	85.0	166.0
Pre-packaged RTE & RTH Muffins	3.8	61	1.3	na	25.8	47.6
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	5.0	79	1.1	na	23.4	45.2

Table II-10 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	3.9	62	2.2	na	50.2	91.9
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	4.4	70	4.6	na	100.2	161.2
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.8	28	2.1*	na	127.1*	301.3*
Pre-packaged RTE & RTH Rolls	20.4	323	2.8	11.5	13.8	24.5
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	4.4	70	1.4	na	31.2	77.4
Pre-packaged RTE & RTH Waffles	2.9	46	0.6	na	21.7	36.9
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	6.8	108	1.6	na	22.2	45.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.9	15	0.4*	na	36.4*	73.8*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.0	191	2.2	7.0	17.4	33.3
Fats and Oils						
Pre-packaged RTE Mayonnaise	4.5	72	3.1	na	58.6	78.8
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.4	22	0.2*	na	12.5*	26.2*
Pre-packaged RTE Frozen Yogurt	2.6	42	1.1	na	36.1	57.4
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.8	60	0.8	na	20.3	36.6
Pre-packaged RTE & RTH Pizza Crust	4.9	77	1.4	na	27.7	47.4

Table II-10 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 31 to 50 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.4	197	5.2	11.4	42.7	82.8

na = not applicable
* 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 II-11 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	1.5	25	0.9*	na	53.6*	89.8*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.5	25	1.2*	na	65.9*	124.5*
Pre-packaged RTE Savory Snacks	6.5	109	2.5	na	34.7	91.3
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	8.2	136	0.5	na	5.6	10.2
Pre-packaged RTE & RTH Biscuits & English Muffins	4.4	73	0.7	na	14.1	48.1
Pre-packaged RTE & RTH Bread	60.9	1,016	11.9	29.3	19.5	37.3
Pre-packaged RTE & RTH Bread Sticks (hard)	0.1	2	< 0.1*	na	8.8*	14.1*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.4	7	0.1*	na	20.0*	31.2*
Pre-packaged RTE & RTH Cakes	7.6	126	2.0	na	29.0	57.1
Pre-packaged RTH Cookies	0.1	1	< 0.1*	na	19.8*	19.8*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	12.3	205	1.9	3.3	17.4	40.2
Pre-packaged RTE & RTH Croissants	0.4	6	0.2*	na	50.9*	92.9*
Pre-packaged RTE & RTH Crackers (not snack type)	0.2	4	< 0.1	na	4.9*	6.3*
Pre-packaged RTE & RTH Doughnuts	6.4	106	5.5	na	95.5	174.0
Pre-packaged RTE & RTH Muffins	2.8	47	0.9	na	30.4	55.1
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	5.0	83	1.5	na	27.6	54.3

Table II-11 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.4	73	3.0	na	56.7	95.3
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	5.3	89	4.7	na	89.9	152.9
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	35	2.4	na	104.7	200.8
Pre-packaged RTE & RTH Rolls	23.7	395	3.9	14.5	16.2	28.3
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	4.6	77	1.0	na	25.1	43.4
Pre-packaged RTE & RTH Waffles	2.4	40	0.7	na	26.9	53.6
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	7.5	125	2.0	na	26.2	45.3
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.9	15	0.7*	na	63.3*	258.1*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.7	212	2.6	8.2	21.8	46.0
Fats and Oils						
Pre-packaged RTE Mayonnaise	4.0	67	1.8	na	41.7	82.7
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.9	31	0.3	na	18.5	35.0
Pre-packaged RTE Frozen Yogurt	1.9	32	0.7	na	33.9	53.1
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.2	54	0.9	na	24.7	40.7
Pre-packaged RTE & RTH Pizza Crust	5.5	91	2.0	na	36.1	67.2

Table II-11 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 31 to 50 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.2	204	4.6	10.2	37.3	89.9

na = not applicable
* 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 II-12 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.4	50	2.2	na	66.3	135.8
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	2.2	32	2.0	na	84.4	156.1
Pre-packaged RTE Savory Snacks	8.7	129	2.2	na	23.2	67.1
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	7.5	111	0.4	na	5.3	9.4
Pre-packaged RTE & RTH Biscuits & English Muffins	6.2	92	0.6	na	9.6	31.2
Pre-packaged RTE & RTH Bread	70.7	1,050	12.2	28.6	17.5	33.3
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	4	< 0.1*	na	4.7*	7.2*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.3	4	< 0.1*	na	12.4*	22.8*
Pre-packaged RTE & RTH Cakes	6.3	93	2.6	na	46.6	104.0
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	8.1	120	1.4	na	17.9	36.7
Pre-packaged RTE & RTH Croissants	0.5	8	0.5*	na	62.7*	113.2*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	7	< 0.1*	na	7.1*	11.0*
Pre-packaged RTE & RTH Doughnuts	4.1	61	3.3	na	76.1	126.6
Pre-packaged RTE & RTH Muffins	4.4	66	1.3	na	28.1	46.6
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.4	66	0.8	na	17.9	32.2

Table II-12 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	3.4	51	1.6	na	49.6	115.6
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	5.3	79	5.1	na	87.8	151.5
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.2	18	1.2*	na	113.5*	239.5*
Pre-packaged RTE & RTH Rolls	17.3	257	2.3	9.9	13.0	23.1
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.8	56	0.9	na	24.5	42.9
Pre-packaged RTE & RTH Waffles	2.3	34	0.5	na	19.7	41.2
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	3.8	57	0.9	na	24.0	41.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.4	6	0.2*	na	76.8*	240.2*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	10.0	149	1.9	na	19.8	45.7
Fats and Oils						
Pre-packaged RTE Mayonnaise	8.9	132	4.1	na	45.9	95.8
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.2	32	0.5*	na	21.0	39.9
Pre-packaged RTE Frozen Yogurt	2.7	40	0.7	na	24.5	42.0
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.8	26	0.5*	na	28.8*	66.0*
Pre-packaged RTE & RTH Pizza Crust	2.6	39	0.6	na	25.0	39.5

Table II-12 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 51 to 70 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	11.0	163	3.9	8.1	34.2	77.4

na = not applicable
* 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 II-13 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.0	48	2.1	na	64.1	107.0
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.3	21	1.0*	na	68.8*	163.4*
Pre-packaged RTE Savory Snacks	7.0	111	1.8	na	23.4	57.0
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	5.0	80	0.3	na	5.0	8.6
Pre-packaged RTE & RTH Biscuits & English Muffins	5.3	84	0.5	na	9.6	32.9
Pre-packaged RTE & RTH Bread	69.6	1,106	12.7	31.3	18.8	37.2
Pre-packaged RTE & RTH Bread Sticks (hard)	0.2	3	< 0.1*	na	4.9*	6.2*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.3	4	0.1*	na	22.1*	72.1*
Pre-packaged RTE & RTH Cakes	8.0	127	2.8	na	35.1	65.0
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	8.9	141	1.9	na	22.3	46.7
Pre-packaged RTE & RTH Croissants	0.3	5	0.1*	na	34.2*	40.9*
Pre-packaged RTE & RTH Crackers (not snack type)	0.4	7	< 0.1*	na	5.6*	12.1*
Pre-packaged RTE & RTH Doughnuts	4.7	75	3.5	na	66.6	109.9
Pre-packaged RTE & RTH Muffins	3.4	54	1.0	na	23.8	44.1
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.7	75	1.0	na	22.3	39.8

Table II-13 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.8	76	2.3	na	51.6	105.0
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	7.2	114	5.9	na	78.9	153.6
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.3	21	0.8*	na	79.6*	128.0*
Pre-packaged RTE & RTH Rolls	18.7	297	2.6	10.4	14.3	26.2
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	5.0	80	1.3	na	28.6	52.7
Pre-packaged RTE & RTH Waffles	3.0	47	0.8	na	28.0	46.4
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	4.5	71	1.6	na	31.7	48.4
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.8	12	0.3*	na	37.1*	89.8*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.0	191	2.3	5.9	19.8	42.0
Fats and Oils						
Pre-packaged RTE Mayonnaise	7.6	121	3.3*	na	39.0	88.8
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.1	34	0.4	na	19.3	41.8
Pre-packaged RTE Frozen Yogurt	2.6	42	0.7	na	24.5	41.3
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.7	27	0.4*	na	20.0*	37.2*
Pre-packaged RTE & RTH Pizza Crust	2.3	37	0.8	na	32.5	63.5

Table II-13 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 51 to 70 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	12.1	193	4.3	10.0	35.7	80.7

na = not applicable
* 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 II-14 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	4.6	28	2.2*	na	43.7*	98.4*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.0	6	0.6*	na	49.0*	112.6*
Pre-packaged RTE Savory Snacks	4.3	26	0.9*	na	19.4*	25.8*
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	3.9	24	0.2*	na	5.3*	10.6*
Pre-packaged RTE & RTH Biscuits & English Muffins	6.7	41	0.7*	na	8.1*	14.9*
Pre-packaged RTE & RTH Bread	74.2	451	14.8	35.8	19.9	40.3
Pre-packaged RTE & RTH Bread Sticks (hard)	0.3	2	< 0.1*	na	4.6*	7.9*
Pre-packaged RTE & RTH Bread Sticks (soft)	0.2	1	< 0.1*	na	5.6*	5.6*
Pre-packaged RTE & RTH Cakes	5.9	36	2.6	na	43.5	100.6
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	6.4	39	1.8	na	27.4	57.8
Pre-packaged RTE & RTH Croissants	0.2	1	0.2*	na	83.0*	83.0*
Pre-packaged RTE & RTH Crackers (not snack type)	0.5	3	< 0.1*	na	2.6*	5.6*
Pre-packaged RTE & RTH Doughnuts	4.1	25	3.0*	na	66.4*	104.1*
Pre-packaged RTE & RTH Muffins	3.3	20	0.9*	na	24.4*	38.9*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	4.8	29	1.0*	na	18.8*	33.2*

Table II-14 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.4	27	2.0*	na	46.3*	101.5*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	9.5	58	8.1	na	91.0	167.5
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.8	11	1.5*	na	75.3*	93.3*
Pre-packaged RTE & RTH Rolls	13.2	80	1.7	8.5	13.5	25.1
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	5.9	36	1.5	na	24.1	35.7
Pre-packaged RTE & RTH Waffles	2.6	16	0.6*	na	22.8*	36.7*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	2.5	15	0.3*	na	12.8*	30.6*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.7	4	0.1*	na	9.1*	27.0*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.2	74	2.5	8.4	17.5	27.8
Fats and Oils						
Pre-packaged RTE Mayonnaise	7.7	47	3.9	na	51.6	146.3
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.6	10	0.3*	na	16.2*	38.6*
Pre-packaged RTE Frozen Yogurt	4.1	25	1.5*	na	33.3*	73.5*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	1.3	8	0.4*	na	20.9*	45.3*
Pre-packaged RTE & RTH Pizza Crust	2.3	14	0.4*	na	17.3*	37.4*

Table II-14 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Female Adults Aged 71 Years and Up 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	7.7	47	2.6	na	32.4	58.4

na = not applicable
* 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 II-15 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	3.6	24	1.8*	na	46.8*	101.9*
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	0.7	5	0.4*	na	53.2*	111.4*
Pre-packaged RTE Savory Snacks	5.1	34	1.2	na	22.0	53.7
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	3.4	23	0.3*	na	6.7*	12.4*
Pre-packaged RTE & RTH Biscuits & English Muffins	5.7	38	0.8	na	11.6	36.1
Pre-packaged RTE & RTH Bread	76.6	511	15.5	34.9	19.8	38.2
Pre-packaged RTE & RTH Bread Sticks (hard)	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Bread Sticks (soft)	0.3	2	< 0.1*	na	14.1*	28.6*
Pre-packaged RTE & RTH Cakes	8.1	54	2.8	na	39.0	119.8
Pre-packaged RTH Cookies	0.0	0	na	na	na	na
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	4.8	32	1.4	na	26.4	61.8
Pre-packaged RTE & RTH Croissants	0.1	1	0.1*	na	30.7*	30.7*
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	2	< 0.1*	na	9.4*	13.0*
Pre-packaged RTE & RTH Doughnuts	4.9	33	3.8	na	71.1	141.1
Pre-packaged RTE & RTH Muffins	2.4	16	0.6*	na	22.2*	42.5*
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	6.7	45	1.2	na	18.8	30.6

Table II-15 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	4.3	29	2.1*	na	46.0*	90.7*
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	12.4	83	11.2	44.3	89.4	139.8
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	2.1	14	2.6*	na	90.4*	170.7*
Pre-packaged RTE & RTH Rolls	16.3	109	2.1	8.0	13.2	24.5
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	4.9	33	1.1	na	20.0	47.6
Pre-packaged RTE & RTH Waffles	3.0	20	0.8*	na	24.5*	43.5*
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	3.0	20	1.1*	na	34.1*	74.7*
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	0.1	1	< 0.1*	na	8.8*	8.8*
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	13.6	91	2.5	9.0	17.0	28.2
Fats and Oils						
Pre-packaged RTE Mayonnaise	7.3	49	2.6	na	36.0	68.1
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	2.4	16	0.3*	na	9.4*	20.4*
Pre-packaged RTE Frozen Yogurt	2.1	14	0.4*	na	19.1*	35.3*
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	0.9	6	0.2*	na	31.7*	33.0*
Pre-packaged RTE & RTH Pizza Crust	2.5	17	0.8*	na	29.9*	58.6*

Table II-15 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by Male Adults Aged 71 Years and Up 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	5.8	39	3.1	na	41.9	93.8

na = not applicable
* 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 II-16 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population 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						
Baked Goods and Baking Mixes						
Pre-packaged RTE Cookies	2.3	449	2.0	na	73.4	150.7
Snack Foods						
Pre-packaged RTH Unpopped Popcorn	1.4	284	1.2	na	70.6	136.9
Pre-packaged RTE Savory Snacks	7.8	1,526	3.3	na	40.0	98.8
Proposed Uses						
Baked Goods and Baking Mixes						
Pre-packaged RTE & RTH Bagels	6.0	1,188	0.5	na	6.7	11.8
Pre-packaged RTE & RTH Biscuits & English Muffins	3.6	714	0.8	na	17.8	55.8
Pre-packaged RTE & RTH Bread	61.1	11,996	14.8	37.5	24.2	49.8
Pre-packaged RTE & RTH Bread Sticks (hard)	0.4	69	0.0	na	7.9	18.7
Pre-packaged RTE & RTH Bread Sticks (soft)	0.5	93	0.1	na	24.5	55.5
Pre-packaged RTE & RTH Cakes	6.1	1,193	2.7	na	39.9	88.9
Pre-packaged RTH Cookies	< 0.1	5	0.1*	na	219.6*	354.0*
Pre-packaged RTE & RTH Cornbread, Corn Muffins, Tortillas and Taco Shells (hard and soft)	10.7	2,101	2.1	0.7	20.6	44.5
Pre-packaged RTE & RTH Croissants	0.4	82	0.4	na	67.4	113.2
Pre-packaged RTE & RTH Crackers (not snack type)	0.3	64	0.0	na	8.7	16.6
Pre-packaged RTE & RTH Doughnuts	5.4	1,056	6.5	na	121.0	223.7
Pre-packaged RTE & RTH Muffins	2.8	554	1.2	na	33.1	59.4
Pre-packaged RTE & RTH Pancakes, Crepes, and French Toast	7.8	1,534	2.0	na	32.8	66.3

Table II-16 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population 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)
Pre-packaged RTE & RTH Pastries, Sweet (pastry portion)	5.5	1,082	4.0	na	76.1	147.9
Pre-packaged RTE & RTH Pies, Sweet (pastry portion)	3.5	689	4.4	na	101.0	179.5
Pre-packaged RTE & RTH Pies and Pastries, Meat and Vegetable (pastry portion)	1.8	349	2.7	na	138.0	252.6
Pre-packaged RTE & RTH Rolls	17.1	3,356	3.6	13.6	18.5	35.0
Pre-packaged RTE & RTH Sweet Rolls & Quick Breads	3.8	748	1.4	na	33.4	69.4
Pre-packaged RTE & RTH Waffles	5.1	998	1.6	na	41.1	84.7
Cheeses						
Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	7.4	1,462	2.3	na	30.7	60.6
Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods	1.2	231	0.6	na	59.7	129.0
Confections and Frostings						
Pre-packaged RTE Frosting and Icing	12.2	2,392	3.4	8.3	27.3	55.9
Fats and Oils						
Pre-packaged RTE Mayonnaise	3.9	758	2.5	na	52.8	101.9
Frozen Dairy Desserts and Mixes						
Pre-packaged RTE Ice Cream	1.5	294	0.4	na	22.7	47.3
Pre-packaged RTE Frozen Yogurt	1.6	306	0.7	na	36.1	67.6
Grain Products and Pastas						
Pre-packaged RTE Breakfast, Granola, and Nutritional Bars	3.7	732	1.2	na	32.2	66.0
Pre-packaged RTE & RTH Pizza Crust	5.7	1,124	2.2	na	39.9	78.9

Table II-16 Estimated Daily Per Kilogram Body Weight Intake of Olestra from Individual Permitted and Proposed Food-Uses by the Total Population 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)
Soft Candy						
Pre-packaged RTE Chocolate Confections (chocolate portion)	11.3	2,230	6.3	13.6	50.6	103.3

na = not applicable
* 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).

ATTACHMENT III TO APPENDIX B

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

PERMITTED USES

Baked Goods and Baking Mixes

Pre-packaged Ready-to-Eat Cookies
(Reduced-fat, low-fat, and fat-free cookie codes were used as products containing Olestra will be marketed as such)

100% of total fat may be replaced with Olestra
[Olestra] = 7.3 to 30.6%

53204840	Cookie, brownie, low-fat, without 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

Mixtures containing pre-packaged ready-to-eat cookies
(Adjusted for cookie content of 80%)
[Olestra] = 11.0 to 13.0%

53204800	Cookie, brownie, diet, NS as to icing
53204830	Cookie, brownie, low-fat, with icing
53204850	Cookie, brownie, fat-free, cholesterol free, with icing

Snack Foods

Pre-packaged Ready-to-Heat Unpopped Popcorn
100% of total fat may be replaced with Olestra
[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

Pre-packaged Ready-to-Eat Savory Snacks
(Reduced-fat, low-fat, and fat-free savory snack codes were used as products containing Olestra will be marketed as such)

100% of total fat may be replaced with Olestra
[Olestra] = 1.3 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	Crispbread, 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, all flavors
71202100	White potato, chips, unsalted, reduced-fat

PROPOSED USES

Baked Goods and Baking Mixes

Pre-packaged Ready-to-Eat and Ready-to-Heat Bagels
75% of shortening is replaced with Olestra; shortening content of 1.5%
[Olestra] = 1.13%

51180010	Bagel
51180020	Bagel, toasted
51208000	Bagel, whole wheat, 100%
51208010	Bagel, whole wheat, 100%, toasted
51301700	Bagel, wheat
51301710	Bagel, wheat, toasted
51301750	Bagel, whole wheat, other than 100% or NS as to 100%
51301760	Bagel, whole wheat, other than 100% or NS as to 100%, toasted
51301900	Bagel, wheat bran
51301910	Bagel, wheat bran, toasted
51404500	Bagel, pumpernickel
51404510	Bagel, pumpernickel, toasted
51501080	Bagel, oat bran
51501090	Bagel, oat bran, toasted
51630000	Bagel, multigrain
51630010	Bagel, multigrain, toasted

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bagels
75% of shortening is replaced with Olestra; shortening content of 1.5%
(Adjusted for bagel content of 88.0%)
[Olestra] = 0.99%

51180030	Bagel, with raisins
51180040	Bagel, with raisins, toasted
51208100	Bagel, whole wheat, 100%, with raisins
51208110	Bagel, whole wheat, 100%, with raisins, toasted
51301800	Bagel, wheat, with raisins
51301810	Bagel, wheat, with raisins, toasted
51301820	Bagel, wheat, with fruit and nuts
51301830	Bagel, wheat, with fruit and nuts, toasted
51630100	Bagel, multigrain, with raisins
51630110	Bagel, multigrain, with raisins, toasted

Pre-packaged Ready-to-Eat and Ready-to-Heat Biscuits & English Muffins
75% of shortening is replaced with Olestra; shortening content of 1.1 to 14.1%
[Olestra] = 0.80 to 10.6%

51186010	Muffin, English
51186020	Muffin, English, toasted
51186100	Muffin, English, with raisins
51186120	Muffin, English, with raisins, toasted
51186140	Muffin, English, cheese, toasted
51186180	Muffin, English, with fruit other than raisins, toasted
51202000	Muffin, English, whole wheat, 100%
51202020	Muffin, English, whole wheat, 100%, toasted
51202050	Muffin, English, whole wheat, 100%, with raisins
51202060	Muffin, English, whole wheat, 100%, with raisins, toasted
51302500	Muffin, English, wheat bran
51302510	Muffin, English, wheat bran, toasted
51302520	Muffin, English, wheat bran, with raisins
51302530	Muffin, English, wheat bran, with raisins, toasted
51303010	Muffin, English, wheat or cracked wheat
51303020	Muffin, English, wheat or cracked wheat, toasted
51303030	Muffin, English, whole wheat, other than 100% or NS as to 100%
51303040	Muffin, English, whole wheat, other than 100% or NS as to 100%, toasted
51303050	Muffin, English, wheat or cracked wheat, with raisins
51303060	Muffin, English, wheat or cracked wheat, with raisins, toasted
51303070	Muffin, English, whole wheat, other than 100% or NS as to 100%, with raisins
51303080	Muffin, English, whole wheat, other than 100% or NS as to 100%, with raisins, toasted
51401200	Muffin, English, rye
51401210	Muffin, English, rye, toasted
51404550	Muffin, English, pumpernickel
51404560	Muffin, English, pumpernickel, toasted
51503000	Muffin, English, oat bran
51503010	Muffin, English, oat bran, toasted
51503040	Muffin, English, oat bran, with raisins
51503050	Muffin, English, oat bran with raisins, toasted
51630200	Muffin, English, multigrain
51630210	Muffin, English, multigrain, toasted
52101020	Biscuit dough, raw
52101030	Biscuit dough, fried
52101040	Crumpet

52101050	Crumpet, toasted
52103000	Biscuit, baking powder or buttermilk type, commercially baked
52104040	Biscuit, whole wheat
52104100	Biscuit, cheese
52104200	Biscuit, cinnamon-raisin
52105100	Scone
52105110	Scone, whole wheat
52105200	Scone, with fruit

Mixtures containing pre-packaged ready-to-eat and ready-to-heat biscuits & English muffins
75% of shortening in the biscuit or English muffin portion is replaced with Olestra; shortening content of 1.2 to 10.0%
(Adjusted for biscuit & English muffin content of 68.0 to 95.0%)
[Olestra] = 5.10 to 6.69%

27515080	Steak sandwich, plain, on biscuit
27520170	Bacon on biscuit
27520250	Ham on biscuit
27540180	Chicken patty sandwich or biscuit
27560650	Sausage on biscuit
27560700	Sausage on biscuit, diet
32202020	Egg, cheese, and ham on biscuit
32202060	Egg and sausage on biscuit
32202090	Egg and bacon on biscuit
32202110	Egg and ham on biscuit
51186130	Muffin, English, cheese
51186160	Muffin, English, with fruit other than raisins

Mixtures containing pre-packaged ready-to-eat and ready-to-heat biscuits & English muffins
75% of shortening in the biscuit or English muffin portion is replaced with Olestra; shortening content of 1.2 to 10.0%
(Adjusted for biscuit & English muffin content of 16.7 to 57.0%)
[Olestra] = 0.14 to 4.28%

27520380	Ham and cheese on English muffin
27560670	Sausage and cheese on English muffin
32101500	Egg, Benedict
32202010	Egg, cheese, and ham on English muffin
32202030	Egg, cheese, and sausage on English muffin
32202040	Egg, cheese, and beef on English Muffin
32202050	Egg, cheese, and sausage on biscuit
32202070	Egg, cheese, and bacon on biscuit
32202080	Egg, cheese, and bacon on English muffin
32202130	Egg and steak on biscuit
32202200	Egg and cheese on biscuit
58128000	Biscuit with gravy

Pre-packaged Ready-to-Eat and Ready-to-Heat Bread
75% of shortening is replaced with Olestra; shortening content of 0.8 to 4.4%
[Olestra] = 0.60 to 3.27%

51000100	Bread, NS as to major flour
51000110	Toast, NS as to major flour
51101000	Bread, white
51101010	Bread, white, toasted
51102010	Bread, white with whole wheat swirl

51102020	Bread, white with whole wheat swirl, toasted
51105010	Bread, Cuban
51105040	Bread, Cuban, toasted
51106010	Bread, Native, Puerto Rican style (Pan Criollo)
51106020	Bread, Native, Puerto Rican style, toasted (Pan Criollo)
51106100	Bread, Native water, Puerto Rican style (Pan de agua)
51106200	Bread, lard, Puerto Rican style (Pan de manteca)
51106210	Bread, lard, Puerto Rican style, toasted (Pan de manteca)
51106300	Bread, caressed, Puerto Rican style (Pan sobao)
51106310	Bread, caressed, Puerto Rican style, toasted (Pan sobao)
51107010	Bread, French or Vienna
51107040	Bread, French or Vienna, toasted
51109010	Bread, Italian, Grecian, Armenian
51109040	Bread, Italian, Grecian, Armenian, toasted
51109100	Bread, pita
51109110	Bread, pita, toasted
51113010	Bread, cinnamon
51113100	Bread, cinnamon, toasted
51115010	Bread, cornmeal and molasses
51115020	Bread, cornmeal and molasses, toasted
51119010	Bread, egg, Challah
51119040	Bread, egg, Challah, toasted
51119100	Bread, low-fat, 98% fat-free
51119110	Bread, low-fat, 98% fat-free, toasted
51121500	Bread, gluten
51121510	Bread, gluten, toasted
51122000	Bread, reduced calorie and/or high fiber, white or NFS
51122010	Bread, reduced calorie and/or high fiber, white or NFS, toasted
51122050	Bread, reduced calorie and/or high fiber, Italian
51122060	Bread, reduced calorie and/or high fiber, Italian, toasted
51122300	Bread, white, special formula, added fiber
51122310	Bread, white, special formula, added fiber, toasted
51122400	Bread, white, special formula, high calcium
51123010	Bread, high protein
51123020	Bread, high protein, toasted
51126010	Bread, milk and honey
51126020	Bread, milk and honey, toasted
51127010	Bread, potato
51127020	Bread, potato, toasted
51129010	Bread, raisin
51129020	Bread, raisin, toasted
51130510	Bread, white, low sodium or no salt
51130520	Bread, white, low sodium or no salt, toasted
51131010	Bread, salt-rising
51131040	Bread, salt-rising, toasted
51133010	Bread, sour dough
51133020	Bread, sour dough, toasted
51134000	Bread, sweet potato
51201010	Bread, whole wheat, 100%
51201020	Bread, whole wheat, 100%, toasted
51201150	Bread, pita, whole wheat, 100%
51201160	Bread, pita, whole wheat, 100%, toasted
51204010	Bread, wheat germ
51204020	Bread, wheat germ, toasted
51207010	Bread, sprouted wheat
51207020	Bread, sprouted wheat, toasted

51300110	Bread, whole wheat, other than 100% or NS as to 100%
51300120	Bread, whole wheat, other than 100% or NS as to 100%, toasted
51300610	Bread, whole wheat, NS as to 100%, low sodium or no salt
51300620	Bread, whole wheat, NS as to 100%, low sodium or no salt, toasted
51301010	Bread, wheat or cracked wheat
51301020	Bread, wheat or cracked wheat, toasted
51301510	Bread, wheat or cracked wheat, reduced calorie and/or high fiber
51301520	Bread, wheat or cracked wheat, reduced calorie and/or high fiber, toasted
51301600	Bread, pita, whole wheat, other than 100% or NS as to 100%
51301620	Bread, pita, wheat or cracked wheat
51301610	Bread, pita, whole wheat, other than 100% or NS as to 100%, toasted
51301630	Bread, pita, wheat or cracked wheat, toasted
51302010	Bread, wheat bran
51302020	Bread, wheat bran, toasted
51401010	Bread, rye
51401020	Bread, rye, toasted
51401030	Bread, marble rye and pumpernickel
51401040	Bread, marble rye and pumpernickel, toasted
51401060	Bread, rye, reduced calorie and/or high fiber
51401070	Bread, rye, reduced calorie and/or high fiber, toasted
51404010	Bread, pumpernickel
51404020	Bread, pumpernickel, toasted
51407010	Bread, black
51407020	Bread, black, toasted
51501010	Bread, oatmeal
51501020	Bread, oatmeal, toasted
51501040	Bread, oat bran
51501050	Bread, oat bran, toasted
51501060	Bread, oat bran, reduced calorie and/or high fiber
51501070	Bread, oat bran, reduced calorie and/or high fiber, toasted
51601010	Bread, multigrain, toasted
51601020	Bread, multigrain
51601210	Bread, multigrain, with raisins
51601220	Bread, multigrain, with raisins, toasted
51602010	Bread, multigrain, reduced calorie and/or high fiber
51602020	Bread, multigrain, reduced calorie and/or high fiber, toasted
51701010	Bread, cottonseed, toasted
51801010	Bread, barley
51802010	Bread, triticale
51802020	Bread, triticale, toasted
51803010	Bread, buckwheat
51803020	Bread, buckwheat, toasted
51804010	Bread, soy
51804020	Bread, soy, toasted
51805010	Bread, sunflower meal
51805020	Bread, sunflower meal, toasted
51806010	Bread, rice
51806020	Bread, rice, toasted
51807000	Injera (American-style Ethiopian bread)
51808000	Bread, low gluten
51808010	Bread, low gluten, toasted

Pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening is replaced with Olestra; shortening content of 4.5 to 14.3%
(Adjusted for bread content of 71.9 to 98.4%)
[Olestra] = 3.23 to 9.27%

51109150	Bread, pita with fruit
51109200	Bread, pita with fruit, toasted
51111010	Bread, cheese
51111040	Bread, cheese, toasted
51121010	Bread, garlic
51121040	Bread, garlic, toasted
51121110	Bread, onion
51122100	Bread, reduced calorie and/or high fiber, white or NFS, with fruit and/or nuts
51122110	Bread, reduced calorie and/or high fiber, white or NFS, with fruit and/or nuts, toasted
51135000	Bread, vegetable
51135010	Bread, vegetable, toasted
51201110	Bread, whole wheat, 100%, with raisins
51201120	Bread, whole wheat, 100%, with raisins, toasted
51300210	Bread, whole wheat, NS as to 100%, with raisins
51300220	Bread, whole wheat, NS as to 100%, with raisins, toasted
51301120	Bread, wheat or cracked wheat, with raisins
51301130	Bread, wheat or cracked wheat, with raisins, toasted
51302050	Bread, wheat bran, with raisins
51302060	Bread, wheat bran, with raisins, toasted
71930200	Casabe, cassava bread

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 45.2 to 68.4%)
[Olestra] = 1.36 to 2.05%

14640000	Cheese sandwich
14640100	Cheese sandwich, grilled
14640300	Cheese spread sandwich
27500050	Sandwich, NFS
27500100	Meat sandwich, NFS
27520110	Bacon sandwich, with spread
27520520	Pork sandwich
27540110	Chicken sandwich, with spread
27540170	Chicken patty sandwich, miniature, with spread
27560000	Luncheon meat sandwich, NFS, with spread
27560110	Bologna sandwich, with spread
27560120	Bologna and cheese sandwich, with spread
27560510	Salami sandwich, with spread
27560710	Sausage sandwich
27563010	Meat spread or potted meat sandwich
27570310	Hors d'oeuvres, with spread
32201000	Fried egg sandwich
32204010	Scrambled egg sandwich
42301010	Peanut butter sandwich
42302010	Peanut butter and jelly sandwich
55301000	French toast, plain

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 30.1 to 44.8%)
[Olestra] = 0.90 to 1.34%

27250450	Shrimp toast, fried
27347230	Chicken or turkey, stuffing, and vegetables (excluding carrots, broccoli, and dark-green leafy), gravy
27510000	Beef sandwich, NFS
27510910	Corned beef sandwich
27511010	Pastrami sandwich
27513010	Roast beef sandwich
27513050	Roast beef sandwich with cheese
27520120	Bacon and cheese sandwich, with spread
27520130	Bacon, chicken, and tomato club sandwich, with lettuce and spread
27520150	Bacon, lettuce, and tomato sandwich with spread
27520300	Ham sandwich, with spread
27520310	Ham sandwich with lettuce and spread
27520320	Ham and cheese sandwich, with lettuce and spread
27520330	Ham and egg sandwich
27520340	Ham salad sandwich
27520350	Ham and cheese sandwich, with spread, grilled
27540120	Chicken salad or chicken spread sandwich
27540130	Chicken barbecue sandwich
27540140	Chicken fillet (breaded, fried) sandwich
27540310	Turkey sandwich, with spread
27540320	Turkey salad or turkey spread sandwich
27550710	Tuna salad sandwich, with lettuce
27550720	Tuna salad sandwich
32203010	Egg salad sandwich
42303010	Peanut butter and banana sandwich
58128220	Dressing with chicken or turkey and vegetables
58128250	Dressing with meat and vegetables
74701000	Tomato sandwich
77230510	Cassava pie stuffed with crab meat, Puerto Rican style (Empanada de jueyes)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 12.3 to 29.7%)
[Olestra] = 0.37 to 0.89%

13210110	Pudding, bread
13210150	Puerto Rican bread pudding made with evaporated milk and rum (Budin de pan)
13210180	Pudding, Mexican bread (Capirotada)
13210190	Pudding, Mexican bread (Capirotada), lower fat
27214600	Creamed dried beef on toast
27250150	Tuna loaf
27510950	Reuben sandwich (corned beef sandwich with sauerkraut and cheese), with spread
27513020	Roast beef sandwich, with gravy
27513030	Roast beef sandwich dipped in egg, fried, with gravy and spread
27515050	Fajita-style beef sandwich with cheese, on pita bread, with lettuce and tomato
27516010	Gyro sandwich (pita bread, beef, lamb, onion, condiments), with tomato and spread
27520140	Bacon and egg sandwich
27520530	Pork sandwich, with gravy
27520540	Ham and tomato club sandwich, with lettuce and spread
27540200	Fajita-style chicken sandwich with cheese, on pita bread, with lettuce and tomato

27540330	Turkey sandwich, with gravy
27550510	Sardine sandwich, with lettuce and spread
28110380	Salisbury steak with gravy, macaroni and cheese (frozen meal)
28141630	Chicken cordon bleu with vegetable, rice (frozen meal)
32105190	Egg casserole with bread, cheese, milk and meat
53415100	Crisp, apple, apple dessert
55310100	Bread fritters, Puerto Rican style (Torrejas, Galician fritters)
58128210	Dressing with oysters
58310110	Frozen breakfast, NFS (frozen meal)
58310210	Sausage and French toast (frozen meal)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 0.19 to 10.7%)
[Olestra] = 0.006 to 0.32%

23203020	Veal chop, fried, lean and fat eaten
23205010	Veal cutlet or steak, fried, NS as to fat eaten
23205020	Veal cutlet or steak, fried, lean and fat eaten
27118110	Meatballs, Puerto Rican style (Albondigas)
27150020	Crab, deviled
27214100	Meat loaf made with beef
27214110	Meat loaf made with beef, with tomato-based sauce
27230010	Lamb or mutton loaf
27235000	Meat loaf made with venison / deer
27246500	Meat loaf made with chicken or turkey
27250080	Salmon loaf
27250250	Flounder with crab stuffing
27260010	Meat loaf, NS as to type of meat
27260080	Meat loaf made with beef and pork
27260090	Meat loaf made with beef, veal and pork
27260100	Meat loaf made with beef and pork, with tomato-based sauce
27260510	Liver dumpling
27351020	Codfish salad, Puerto Rican style (Gazpacho de bacalao)
28110110	Beef with potatoes (frozen meal)
28145100	Turkey with dressing, gravy, vegetable and fruit (diet frozen meal)
28145120	Turkey and vegetables, in sauce (diet frozen meal)
28160310	Meat loaf in tomato sauce with potatoes, vegetable (frozen meal)
32301100	Garlic egg soup, Puerto Rican style (Sopa de ajo)
58131100	Ravioli, NS as to filling, no sauce
58131110	Ravioli, NS as to filling, with tomato sauce
58131310	Ravioli, meat-filled, no sauce
58131320	Ravioli, meat-filled, with tomato sauce or meat sauce
58162090	Stuffed pepper, with meat
58162120	Stuffed pepper, with rice, meatless
58305010	Mosticolli with meatballs, sauce, bread (frozen meal)
72116140	Caesar salad (with romaine)
72125260	Spinach and cheese casserole
74203010	Tomatoes, NS as to form, scalloped
74203011	Tomatoes, from fresh, scalloped

Pre-packaged Ready-to-Eat and Ready-to-Heat Bread Sticks (Hard)
75% of shortening is replaced with Olestra; shortening content of 3.0%
[Olestra] = 2.25%

51184000	Bread sticks, hard
51184100	Bread stick, hard, low sodium
51306000	Bread stick, hard, whole wheat, NS as to 100%

Pre-packaged Ready-to-Eat and Ready-to-Heat Bread Sticks (Soft)
75% of shortening is replaced with Olestra; shortening content of 5.0 to 8.7%
[Olestra] = 3.75 to 6.52%

51184010	Bread stick, soft
51184020	Bread stick, NS as to hard or soft
51184030	Bread stick, soft, prepared with garlic and parmesan cheese

Pre-packaged Ready-to-Eat and Ready-to-Heat Cakes
75% of shortening is replaced with Olestra; shortening content of 0.4 to 24.0%
[Olestra] = 0.29 to 17.98%

53100100	Cake, NS as to type, with or without icing
53102100	Cake, applesauce, without icing
53102300	Cake, applesauce, diet, without icing
53102600	Cake, banana, without icing
53103000	Cake, Boston cream pie
53104100	Cake, carrot, without icing
53104300	Cake, carrot, diet
53104500	Cheesecake
53104520	Cheesecake, diet
53104550	Cheesecake with fruit
53104570	Cheesecake, diet, with fruit
53104580	Cheesecake -type dessert, made with yogurt, with fruit
53104600	Cheesecake, chocolate
53104650	Cheesecake, chocolate, reduced-fat
53104920	Cake, chocolate, made with mayonnaise or salad dressing, without icing or filling
53106100	Cake, Poor Man's (spice-type), without icing
53106500	Cake, cream, without icing or topping
53107000	Cake, cupcake, NS as to type or icing
53107100	Cake, cupcake, NS as to type, without icing
53107200	Cake, cupcake, NS as to type, with icing
53108000	Cake, cupcake, chocolate, NS as to icing
53108100	Cake, cupcake, chocolate, without icing or filling
53109270	Cake, cupcake, chocolate, with or without icing, fruit filling or cream filling, low-fat, cholesterol free
53110000	Cake, fruit cake, light or dark, holiday type cake
53110100	Cake, plum pudding
53111500	Cake, graham cracker, without icing
53112000	Cake, ice cream and cake roll, chocolate
53112100	Cake, ice cream and cake roll, not chocolate
53112150	Cake, frozen yogurt and cake layer, not chocolate, with icing
53112160	Cake, frozen yogurt and cake layer, chocolate, with icing
53112500	Cake, ice box with fruit and whipped cream
53113000	Cake, jelly roll
53115400	Cake, oatmeal, without icing
53115410	Cake, oatmeal, with icing
53115500	Cake, pineapple, fat-free, cholesterol free, without icing

53115600	Cake, poppy seed, without icing
53116000	Cake, pound, without icing
53116270	Cake, pound, chocolate
53116280	Cake, pound, chocolate, fat-free, cholesterol free
53116350	Cake, pound, Puerto Rican style (Ponque)
53116380	Cake, pound, fat-free, cholesterol free
53116390	Cake, pound, reduced-fat, cholesterol free
53116500	Cake, pumpkin, without icing
53116570	Cake, Ravani (made with farina)
53116600	Cake, rice flour, without icing
53116650	Cake, Quezadilla, El Salvadorian style
53116750	Cake, soy flour, without icing
53118100	Cake, sponge, without icing
53118300	Cake, sponge, chocolate, without icing
53118310	Cake, sponge, chocolate, with icing
53118410	Cake, rum flavored, without icing (Sopa Borracha)
53118500	Cake, torte
53118600	Cake, chiffon, NS as to icing
53118700	Cake, chiffon, without icing
53118800	Cake, chiffon, with icing
53118900	Cake, chiffon, chocolate, without icing
53118950	Cake, chiffon, chocolate, with icing
53119000	Cake, upside down (all fruits)
53120400	Cake, white, eggless, low-fat
53120500	Cake, whole wheat, with fruit and nuts, without icing
53122070	Cake, shortcake, biscuit type, with whipped cream and fruit
53122080	Cake, shortcake, biscuit type, with fruit
53123070	Cake, shortcake, sponge type, with whipped cream and fruit
53123080	Cake, shortcake, sponge type, with fruit
53123500	Cake, shortcake, with whipped topping and fruit, diet
53124110	Cake, zucchini, without icing

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cakes
75% of shortening in the cake portion is replaced with Olestra; shortening content of 7.0 to 11.0%
(Adjusted for cake content of 71.1 to 80.0%)
[Olestra] = 3.73 to 6.60%

53115450	Cake, peanut butter, with icing
53116020	Cake, pound, with icing

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cakes
75% of shortening in the cake portion is replaced with Olestra; shortening content of 1.0 to 16.0%
(Adjusted for cake content of 63.0 to 70.0%)
[Olestra] = 0.006 to 0.32%

53102000	Cake, applesauce, NS as to icing
53102200	Cake, applesauce, with icing
53102500	Cake, banana, NS as to icing
53102700	Cake, banana, with icing
53102800	Cake, black forest (chocolate-cherry)
53104000	Cake, carrot, NS as to icing
53104260	Cake, carrot, with icing
53104400	Cake, coconut, with icing
53104900	Cake, chocolate, made with mayonnaise or salad dressing, NS as to icing
53104950	Cake, chocolate, made with mayonnaise or salad dressing, with icing, coating, or filling
53105500	Cake, chocolate, with icing, diet

53108200	Cake, cupcake, chocolate, with icing or filling
53109200	Cake, cupcake, not chocolate, with icing or filling
53109210	Cake, cupcake, not chocolate, with icing or filling, low-fat, cholesterol free
53109300	Cake, Dobos Torte (non-chocolate layer cake with chocolate filling and icing)
53114150	Cake, lemon, low-fat, NS as to icing
53114250	Cake, lemon, low-fat, with icing
53116490	Cake, pumpkin, NS as to icing
53116510	Cake, pumpkin, with icing
53118000	Cake, sponge, NS as to icing
53118200	Cake, sponge, with icing
53118350	Cake, sweet potato, with icing
53124100	Cake, zucchini, NS as to icing
53124120	Cake, zucchini, with icing

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cakes
75% of shortening in the cake portion is replaced with Olestra; shortening content of 11.0%
(Adjusted for cake content of 19.0%)
[Olestra] = 1.56%

13210160	Diplomat pudding, Puerto Rican style (Budin Diplomatico)

Pre-packaged Ready-to-Heat Cookies
75% of shortening is replaced with Olestra; shortening content of 25.7%
[Olestra] = 19.31%

53200100	Cookie, batter or dough, raw, not chocolate

Pre-packaged Ready-to-Eat and Ready-to-Heat Cornbread, Corn Muffins, Tortillas and Taco Shells (Hard and Soft)
75% of shortening is replaced with Olestra; shortening content of 2.1 to 6.4%
[Olestra] = 1.7 to 4.8%

52201000	Cornbread, prepared from mix
52204000	Cornbread stuffing
52206010	Cornbread muffin, stick, round
52206020	Cornbread muffin, stick, round, toasted
52207010	Corn flour patty or tart, fried
52208010	Corn pone, baked
52208020	Corn pone, fried
52208750	Gordita/sope shell, plain, no filling, grilled, no fat added
52208760	Gordita/sope shell, plain, no filling, fried in oil
52209010	Hush puppy
52211010	Johnnycake
52213010	Spoonbread
52215000	Tortilla, NFS
52215100	Tortilla, corn
52215200	Tortilla, flour (wheat)
52215260	Tortilla, whole wheat
52215300	Taco shell, corn
52215350	Taco shell, flour
52220110	Cornmeal bread, Dominican style (Arepa Dominicana)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 40.6 to 80.1%)
[Olestra] = 0.76 to 1.50%

53452500	Pastry, mainly flour and water, fried
58100100	Burrito with beef, no beans
58100300	Burrito with beans and rice, meatless
58101400	Soft taco with beef, cheese, and lettuce
58104710	Quesadilla with cheese, meatless
58104730	Quesadilla with meat and cheese

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 26.2 to 39.2%)
[Olestra] = 0.49 to 0.73%

58100110	Burrito with beef and beans
58100130	Burrito with beef and cheese, no beans
58100150	Burrito with beef and potato, no beans
58100180	Burrito with pork and beans
58100200	Burrito with chicken, no beans
58100210	Burrito with chicken and beans
58100240	Burrito with chicken, NFS
58100310	Burrito with beans, meatless
58100320	Burrito with beans and cheese, meatless
58100340	Burrito with eggs, sausage, cheese and vegetables
58100400	Enchilada with beef, no beans
58100560	Enchilada with ham and cheese, no beans
58100600	Enchilada with chicken, tomato-based sauce
58100900	Enchilada with seafood, tomato-based sauce
58101200	Flauta, NFS
58101300	Taco or tostada with beef, cheese and lettuce
58101350	Soft taco with beef, cheese, lettuce, tomato and sour cream
58101450	Soft taco with chicken, cheese, and lettuce
58104450	Chimichanga with beef and tomato
58104530	Chimichanga with chicken and cheese
58104810	Taquitoes
58306500	Chicken burritos (diet frozen meal)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 16.3 to 25.8%)
[Olestra] = 0.30 to 1.11%

27560380	Pochito (frankfurter or hot dog and beef chili wrapped in tortilla)
58100120	Burrito with beef, beans, and cheese
58100140	Burrito with beef, beans, cheese, and sour cream
58100220	Burrito with chicken, beans, and cheese
58100230	Burrito with chicken and cheese

58100330	Burrito with rice, beans, cheese, sour cream, lettuce, tomato and guacamole, meatless
58100350	Burrito with eggs and cheese, no beans
58100510	Enchilada with beef and beans
58100520	Enchilada with beef, beans, and cheese
58100530	Enchilada with beef and cheese, no beans
58100610	Enchilada with chicken and beans, tomato-based sauce
58100620	Enchilada with chicken, beans, and cheese, tomato- based sauce
58100630	Enchilada with chicken and cheese, no beans, tomato- based sauce
58100710	Enchilada with beans, meatless
58100720	Enchilada with beans and cheese, meatless
58100800	Enchilada with cheese, meatless, no beans
58101230	Flauta with beef
58101240	Flauta with chicken
58101310	Taco or tostada with beef, lettuce, tomato and salsa
58101320	Taco or tostada with beef, cheese, lettuce, tomato and salsa
58101510	Taco or tostada with chicken or turkey, lettuce, tomato and salsa
58101520	Taco or tostada with chicken, cheese, lettuce, tomato and salsa
58101540	Taco or tostada with fish, lettuce, tomato, salsa
58101800	Ground beef with tomato sauce and taco seasonings on a cornbread crust
58104500	Chimichanga with beef, beans, lettuce and tomato
58104510	Chimichanga with beef, cheese, lettuce and tomato
58104520	Chimichanga with beans and cheese, meatless, with lettuce and tomato
58104550	Chimichanga with chicken, sour cream, lettuce and tomato, no cheese
58104600	Chimichanga with beef and rice
58105000	Fajita with chicken and vegetables
58105050	Fajita with beef and vegetables
58306070	Cheese enchilada (frozen meal)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 1.2 to 15.2%)
[Olestra] = 0.02 to 0.29%

28110280	Sirloin enchilada with tomatoes, zucchini and chilies (diet frozen entree)
28140910	Chicken, fried, with potatoes, vegetable, cornbread, dessert (frozen meal)
32105100	Egg omelet or scrambled egg, with potatoes and/or onions (Tortilla Espanola, traditional style Spanish
32105180	Huevos rancheros
32105310	Ripe plantain omelet, Puerto Rican style (Tortilla de amarillo)
58100360	Chilaquiles, tortilla casserole with salsa, cheese, and egg
58100370	Chilaquiles, tortilla casserole with salsa and cheese, no egg
58101710	Taco or tostada with beans, meatless, with lettuce, tomato and salsa
58101720	Taco or tostada with beans and cheese, meatless, with lettuce, tomato and salsa
58101730	Taco or tostada with beans, cheese, meat, lettuce, tomato and salsa
58101930	Taco or tostada salad with beef and cheese, fried flour tortilla
58101940	Taco or tostada salad, meatless, with cheese, fried flour tortilla
58104260	Chalupa with beans, cheese, lettuce and tomato
58104310	Chalupa with beans, chicken, cheese, lettuce and tomato
58306100	Chicken enchilada (diet frozen meal)
58421080	Sopa de tortilla, Mexican style tortilla soup

Pre-packaged Ready-to-Eat and Ready-to-Heat Croissants
75% of shortening is replaced with Olestra; shortening content of 13.3%
[Olestra] = 10.0%

51166000 Croissant

Mixtures containing pre-packaged ready-to-eat and ready-to-heat croissants
75% of shortening in the croissant portion is replaced with Olestra; shortening content of 13.0 to 13.9%
(Adjusted for croissant content of 90.0 to 100%)
[Olestra] = 9.00 to 10.40%

51166100 Croissant, cheese
51166200 Croissant, chocolate
51166500 Croissant, fruit
51166700 Croissant, nut
58127200 Croissant sandwich, filled with broccoli and cheese
58127210 Croissant sandwich, filled with ham and cheese
58127220 Croissant sandwich, filled with chicken, broccoli, and cheese sauce

Mixtures containing pre-packaged ready-to-eat and ready-to-heat croissants
75% of shortening in the croissant portion is replaced with Olestra; shortening content of 13.3 to 15.8%
(Adjusted for croissant content of 31.5 to 55.8%)
[Olestra] = 3.14 to 11.90%

58127250 Croissant sandwich with vegetables and cheese
58127270 Croissant sandwich with sausage and egg
58127290 Croissant sandwich with bacon and egg
58127310 Croissant sandwich with ham, egg, and cheese
58127330 Croissant sandwich with sausage, egg, and cheese
58127350 Croissant sandwich with bacon, egg, and cheese

Pre-packaged Ready-to-Eat and Ready-to-Heat Crackers (not snack type)
75% of shortening is replaced with Olestra; shortening content of 3.2 to 10.5%
[Olestra] = 2.40 to 7.88%

51187000 Melba toast
51187010 Melba toast with wheat germ
54001000 Crackers, NS as to sweet or nonsweet

Pre-packaged Ready-to-Eat and Ready-to-Heat Doughnuts
100% of frying oil is replaced with Olestra; frying oil content of 12.0 to 21.6%
[Olestra] = 12.0 to 21.62%

53520000 Doughnut, NS as to cake or yeast
53520110 Doughnut, cake type
53520120 Doughnut, cake type, chocolate
53520500 Doughnut, oriental
53520600 Cruller, NFS
53520700 French cruller
53521110 Doughnut, raised or yeast
53521140 Doughnut, jelly
53521210 Doughnut, custard-filled
53521250 Doughnut, wheat
53521300 Doughnut, wheat, chocolate covered
53521400 Doughnut, eggless, carocovered, raised or yeast

Mixtures containing pre-packaged ready-to-eat and ready-to-heat doughnuts
100% of frying oil is replaced with Olestra; frying oil content of 5.5 to 17.6%
(Adjusted for doughnut content of 59.3 to 95.2%)
[Olestra] = 5.48 to 17.58%

53520140	Doughnut, cake type, chocolate covered
53520150	Doughnut, cake type, chocolate covered, dipped in peanuts
53520160	Doughnut, cake type, chocolate, with chocolate icing
53521100	Doughnut, raised or yeast, chocolate, with chocolate icing
53521120	Doughnut, raised or yeast, chocolate
53521130	Doughnut, raised or yeast, chocolate covered
53521220	Doughnut, chocolate cream-filled
53521230	Doughnut, custard-filled, with icing

Pre-packaged Ready-to-Eat and Ready-to-Heat Muffins
75% of shortening is replaced with Olestra; shortening content of 1.8 to 8.6%
[Olestra] = 1.34 to 6.43%

52301000	Muffin, NFS
52302010	Muffin, fruit and/or nuts
52302100	Muffin, fruit, fat-free, cholesterol free
52302500	Muffin, chocolate chip
52302600	Muffin, chocolate
52303010	Muffin, whole wheat
52303500	Muffin, wheat
52303550	Muffin, buckwheat
52304010	Muffin, wheat bran
52304020	Muffin, wheat bran, toasted
52304040	Muffin, bran with fruit, low-fat
52304060	Muffin, bran with fruit, no fat, no cholesterol
52304100	Muffin, oatmeal
52304150	Muffin, oat bran
52304200	Muffin, oat bran with fruit and/or nuts
52306010	Muffin, plain
52306100	Muffin, plain, no wheat, sugar free
52306300	Muffin, cheese
52306500	Muffin, pumpkin
52306550	Muffin, zucchini
52306700	Muffin, carrot
52307020	Muffin, multigrain, with nuts
52307120	Muffin, multigrain, with fruit
52308010	Matzo, fritters
52311010	Popover
52320100	Toaster muffin, fruit, untoasted
52320110	Toaster muffin, fruit, toasted

Pre-packaged Ready-to-Eat and Ready-to-Heat Pancakes, Crepes, and French Toast
75% of shortening is replaced with Olestra; shortening content of 0.08 to 7.3%
[Olestra] = 0.06 to 5.48%

55101000	Pancakes, plain
55101010	Pancakes, reduced calorie, high fiber
55103000	Pancakes, with fruit
55103100	Pancakes, with chocolate chips
55105000	Pancakes, buckwheat
55105100	Pancakes, cornmeal

55105200	Pancakes, whole wheat
55105300	Pancakes, sour dough
55105400	Pancakes, rye
55301000	French toast, plain
55301050	French toast sticks, plain
55401000	Crepe, plain
58310210	Sausage and French toast (frozen meal)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat pancakes, crepes or French toast
75% of shortening in the pancakes, crepes or French toast portion is replaced with Olestra; shortening content of 3.9 to 4.9%
(Adjusted for pancake, crepe or French toast content of 29.0 to 58.1%)
[Olestra] = 0.99 to 1.70%

35003000	Scrambled eggs, sausage, pancakes (frozen meal)
58120110	Crepes, filled with meat, fish, or poultry, with sauce
58120120	Crepe, filled with beef, pork, fish and/or poultry, no sauce on top
58310310	Pancakes and sausage (frozen meal)
58310410	Sausage rice links and whole wheat pancakes (frozen meal)

Pre-packaged Ready-to-Eat and Ready-to-Heat Pastries, Sweet (pastry portion)
75% of shortening is replaced with Olestra; shortening content of 1.3 to 19.2%
[Olestra] = 0.95 to 14.42%

53400200	Blintz, cheese-filled
53400300	Blintz, fruit-filled
53410100	Cobbler, apple
53410200	Cobbler, apricot
53410300	Cobbler, berry
53410500	Cobbler, cherry
53410800	Cobbler, peach
53410850	Cobbler, pear
53410860	Cobbler, pineapple
53410880	Cobbler, plum
53410900	Cobbler, rhubarb
53415100	Crisp, apple, apple dessert
53415120	Fritter, apple
53415200	Fritter, banana
53415220	Fritter, berry
53415300	Crisp, blueberry
53415400	Crisp, cherry
53415500	Crisp, peach
53415600	Crisp, rhubarb
53420000	Cream puff, eclair, custard or cream filled, NS as to icing
53420100	Cream puff, eclair, custard or cream filled, not iced
53420200	Cream puff, eclair, custard or cream filled, iced
53420210	Cream puff, eclair, custard or cream filled, iced, reduced-fat
53420250	Cream puff, no filling or icing
53420300	Air filled fritter or fried puff, without syrup, Puerto Rican style (Bunuelos de viento)
53420310	Wheat flour fritter, without syrup
53420400	Sopaipilla, without syrup or honey
53420410	Sopaipilla with syrup or honey
53430000	Crepe, dessert type, NS as to filling
53430100	Crepe, dessert type, chocolate-filled
53430200	Crepe, dessert type, fruit-filled
53430250	Crepe suzette

53430300	Crepe, dessert type, ice cream-filled
53430700	Tamale, sweet
53430750	Tamale, sweet, with fruit
53440000	Strudel, apple
53440300	Strudel, berry
53440500	Strudel, cherry
53440600	Strudel, cheese
53440700	Strudel, peach
53440750	Strudel, pineapple
53440800	Strudel, cheese and fruit
53441110	Baklava
53441210	Basbousa (semolina dessert dish)
53450000	Turnover or dumpling, apple
53450300	Turnover or dumpling, berry
53450500	Turnover or dumpling, cherry
53450800	Turnover or dumpling, lemon
53451000	Turnover or dumpling, peach
53451500	Turnover, guava
53451750	Turnover, pumpkin
53452100	Pastry, fruit-filled
53452120	Pastry, Oriental, made with bean or lotus seed paste filling (baked)
53452130	Pastry, Oriental, made with bean paste and salted egg yolk filling (baked)
53452150	Pastry, Chinese, made with rice flour
53452170	Pastry, cookie type, fried
53452200	Pastry, Italian, with cheese
53452400	Pastry, puff
53452420	Pastry, puff, custard or cream filled, iced or not iced
53452450	Cheese pastry puffs
53452500	Pastry, mainly flour and water, fried
53453150	Empanada, Mexican turnover, fruit-filled
53453170	Empanada, Mexican turnover, pumpkin
53500100	Breakfast pastry, NFS
53510000	Danish pastry, plain or spice
53510100	Danish pastry, with fruit
53510200	Danish pastry, with nuts
53511000	Danish pastry, with cheese
53511500	Danish pastry, with cheese, fat-free, cholesterol free
53530000	Breakfast tart
53530010	Breakfast tart, low-fat
58124210	Pastry, cheese-filled

Pre-packaged Ready-to-Eat and Ready-to-Heat Pies, Sweet (pastry portion)
75% of shortening is replaced with Olestra; shortening content of 1.3 to 22.8%
[Olestra] = 0.96 to 17.13%

53300100	Pie, NFS
53300170	Pie, individual size or tart, NFS
53300180	Pie, fried, NFS
53301000	Pie, apple, two crusts
53301070	Pie, apple, individual size or tart
53301080	Pie, apple, fried pie
53301500	Pie, apple, one crust
53301750	Pie, apple, diet
53302000	Pie, apricot, two crusts
53302070	Pie, apricot, individual size or tart
53302080	Pie, apricot, fried pie

53303000	Pie, blackberry, two crusts
53303070	Pie, blackberry, individual size or tart
53303500	Pie, berry, not blackberry, blueberry, boysenberry, huckleberry, raspberry, or strawberry; two crust
53303510	Pie, berry, not blackberry, blueberry, boysenberry, huckleberry, raspberry, or strawberry; one crust
53303570	Pie, berry, not blackberry, blueberry, boysenberry, huckleberry, raspberry, or strawberry, individual
53304000	Pie, blueberry, two crusts
53304050	Pie, blueberry, one crust
53304070	Pie, blueberry, individual size or tart
53305000	Pie, cherry, two crust
53305010	Pie, cherry, one crust
53305070	Pie, cherry, individual size or tart
53305080	Pie, cherry, fried pie
53305700	Pie, lemon (not cream or meringue)
53305720	Pie, lemon (not cream or meringue), individual size or tart
53305750	Pie, lemon, fried pie
53306000	Pie, mince, two crusts
53306070	Pie, mince, individual size or tart
53307000	Pie, peach, two crust
53307050	Pie, peach, one crust
53307070	Pie, peach, individual size or tart
53307080	Pie, peach, fried pie
53307500	Pie, pear, two crusts
53307570	Pie, pear, individual size or tart
53308000	Pie, pineapple, two crusts
53308070	Pie, pineapple, individual size or tart
53308300	Pie, plum, two crust
53308500	Pie, prune, one crust
53309000	Pie, raisin, two crusts
53309070	Pie, raisin, individual size or tart
53310000	Pie, raspberry, one crust
53310050	Pie, raspberry, two crusts
53311000	Pie, rhubarb, two crusts
53311050	Pie, rhubarb, one crust
53311070	Pie, rhubarb, individual size or tart
53312000	Pie, strawberry, one crust
53313000	Pie, strawberry-rhubarb, two crusts
53314000	Pie, strawberry, individual size or tart
53340000	Pie, apple-sour cream
53340500	Pie, cherry, made with cream cheese and sour cream
53341000	Pie, banana cream
53341070	Pie, banana cream, individual size or tart
53341500	Pie, buttermilk
53341750	Pie, chess
53342000	Pie, chocolate cream
53342070	Pie, chocolate cream, individual size or tart
53343000	Pie, coconut cream
53343070	Pie, coconut cream, individual size or tart
53344000	Pie, custard
53344070	Pie, custard, individual size or tart
53345000	Pie, lemon cream
53345070	Pie, lemon cream, individual size or tart
53346000	Pie, peanut butter cream
53346500	Pie, pineapple cream

53347000	Pie, pumpkin
53347070	Pie, pumpkin, individual size or tart
53347100	Pie, raspberry cream
53347500	Pie, sour cream, raisin
53347600	Pie, squash
53348000	Pie, strawberry cream
53348070	Pie, strawberry cream, individual size or tart
53360000	Pie, sweet potato
53365000	Pie, vanilla cream
53366000	Pie, yogurt, frozen
53370000	Pie, chiffon, not chocolate
53371000	Pie, chiffon, chocolate
53371100	Pie, chiffon, with liqueur
53373000	Pie, black bottom
53381000	Pie, lemon meringue
53381070	Pie, lemon meringue, individual size or tart
53382000	Pie, chocolate-marshmallow
53385000	Pie, pecan
53385070	Pie, pecan, individual size or tart
53385500	Pie, oatmeal
53385600	Pie, praline mousse, with nuts
53386000	Pie, pudding, flavors other than chocolate
53386050	Pie, pudding, flavors other than chocolate, individual size or tart
53386250	Pie, pudding, chocolate, with chocolate coating, individual size
53386500	Pie, pudding, flavors other than chocolate, with chocolate coating, individual size
53387000	Pie, Toll house chocolate chip
53390000	Pie, shoo-fly
53390100	Pie, tofu with fruit
53391000	Pie shell
53391100	Pie shell, graham cracker
53391150	Pie shell, chocolate wafer

Pre-packaged Ready-to-Eat and Ready-to-Heat Pies and Pastries, Meat and Vegetable (pastry portion)
75% of shortening is replaced with Olestra; shortening content of 0.31 to 16.4%
[Olestra] = 0.23 to 12.32%

27211250	Beef and potatoes with gravy in pie crust (mixture)
27311510	Shepherd's pie with beef
27317010	Beef pot pie
27320020	Ham pot pie
27330010	Shepherd's pie with lamb
27347100	Chicken or turkey pot pie
27350070	Tuna pot pie
27350200	Oyster pie
27360050	Meat pie, NFS
28143220	Chicken in barbecue sauce, with rice, vegetable and dessert, reduced-fat and sodium (diet frozen meal)
41812400	Vegetarian pot pie
58109010	Italian pie with meat
58116110	Meat turnover, Puerto Rican style (Pastelillo de carne; Empanadilla)
58116120	Empanada, Mexican turnover, filled with meat and vegetables
58116210	Meat pie, Puerto Rican style (Pastelon de carne)
58121510	Dumpling, meat-filled
58124500	Pastry, filled with potatoes and peas, fried
58125110	Quiche with meat, poultry or fish

58125120	Spinach quiche, meatless
58125180	Cheese quiche, meatless
58126000	Bierock (turnover filled with ground beef and cabbage mixture)
58126110	Turnover, meat-filled, no gravy
58126120	Turnover, meat-filled, with gravy
58126130	Turnover, meat- and cheese-filled, no gravy
58126140	Turnover, meat- and bean-filled, no gravy
58126150	Turnover, meat- and cheese-filled, tomato-based sauce
58126170	Turnover, meat-and vegetable- filled (no potatoes, no gravy)
58126180	Turnover, meat-, potato-, and vegetable-filled, no gravy
58126270	Turnover, chicken- or turkey-, and cheese-filled, no gravy
58126280	Turnover, chicken- or turkey-, and vegetable-filled
58126310	Turnover, chicken, with gravy
58127110	Vegetables in pastry
58127150	Vegetables and cheese in pastry
77141010	Potato chicken pie, Puerto Rican style (Pastelon de pollo)
77205610	Ripe plantain meat pie, Puerto Rican style (Pinon)
77230510	Cassava pie stuffed with crab meat, Puerto Rican style (Empanada de jueyes)

Pre-packaged Ready-to-Eat and Ready-to-Heat Rolls
75% of shortening is replaced with Olestra; shortening content of 0.4 to 5.1%
[Olestra] = 0.27 to 3.86%

51000200	Roll, NS as to major flour
51000230	Roll, NS as to major flour, toasted
51000300	Roll, hard, NS as to major flour
51000400	Roll, bran, NS as to type of bran
51000410	Roll, bran, NS as to type of bran, toasted
51150000	Roll, white, soft
51150100	Roll, white, soft, toasted
51152000	Roll, white, soft, reduced calorie and/or high fiber
51152100	Roll, white, soft, reduced calorie and/or high fiber, toasted
51153000	Roll, white, hard
51153010	Roll, white, hard, toasted
51154510	Roll, diet
51154550	Roll, egg bread
51154560	Roll, egg bread, toasted
51155000	Roll, French or Vienna
51155010	Roll, French or Vienna, toasted
51157000	Roll, hoagie, submarine
51157010	Roll, hoagie, submarine, toasted
51158100	Roll, Mexican, bolillo
51159000	Roll, sour dough
51220000	Roll, whole wheat, 100%
51220010	Roll, whole wheat, 100%, toasted
51320010	Roll, wheat or cracked wheat
51320020	Rolls, wheat or cracked wheat, toasted
51320500	Roll, whole wheat, NS as to 100%
51320510	Roll, whole wheat, NS as to 100%, toasted
51420000	Roll, rye
51421000	Roll, pumpernickel
51421100	Roll, pumpernickel, toasted
51502010	Roll, oatmeal
51502020	Roll, oatmeal, toasted
51502100	Roll, oat bran
51502110	Roll, oat bran, toasted

51620000	Roll, multigrain
51620010	Roll, multigrain, toasted

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 95.0 to 99.5%)
[Olestra] = 2.85 to 2.99%

51154600	Roll, cheese
51156500	Roll, garlic

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 40.6 to 59.3%)
[Olestra] = 1.22 to 1.78%

27510130	Beef barbecue submarine sandwich, on bun
27510270	Double cheeseburger (2 patties), plain, on bun
27510210	Cheeseburger, plain, on bun
27510220	Cheeseburger, with mayonnaise or salad dressing, on bun
27510290	Double cheeseburger (2 patties), plain, on double-decker bun
27510311	Cheeseburger, 1 oz meat, plain, on miniature bun
27510420	Taco burger, on bun
27510500	Hamburger, plain, on bun
27510510	Hamburger, with tomato and/or catsup, on bun
27510530	Hamburger, 1/4 lb meat, plain, on bun
27510590	Hamburger, with mayonnaise or salad dressing, on bun
27510600	Hamburger, 1 oz meat, plain, on miniature bun
27510650	Double hamburger (2 patties), plain, on bun
27515150	Steak patty (breaded, fried) sandwich, with mayonnaise or salad dressing, lettuce, and tomato, on bun
27520410	Cuban sandwich, (Sandwich cubano), with spread
27540190	Chicken patty sandwich, with lettuce and spread
27550000	Fish sandwich, on bun, with spread
27550100	Fish sandwich, on bun, with cheese and spread
27550750	Tuna salad submarine sandwich, on roll, with lettuce
27560320	Frankfurter or hot dog, plain, on bun
27560400	Chicken frankfurter or hot dog, plain, on bun
27560410	Puerto Rican sandwich (Sandwich criollo)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 30.0 to 39.6%)
[Olestra] = 0.90 to 1.19%

14640200	Cheese sandwich, hoagie
27510230	Cheeseburger, with mayonnaise or salad dressing and tomatoes, on bun
27510240	Cheeseburger, 1/4 lb meat, plain, on bun
27510250	Cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing, on bun
27510280	Double cheeseburger (2 patties), with mayonnaise or salad dressing, on bun
27510300	Double cheeseburger (2 patties), with mayonnaise or salad dressing, on double-decker bun
27510310	Cheeseburger with tomato and/or catsup, on bun
27510340	Double cheeseburger (2 patties), with mayonnaise or salad dressing and tomatoes, on bun
27510360	Cheeseburger with mayonnaise or salad dressing, tomato and bacon, on bun

27510410	Chiliburger, on bun
27510440	Bacon cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun
27510450	Cheeseburger, 1/4 lb meat, with ham, on bun
27510520	Hamburger, with mayonnaise or salad dressing and tomatoes, on bun
27510540	Double hamburger (2 patties), with tomato and/or catsup, on bun
27510550	Double hamburger (2 patties), with mayonnaise or salad dressing and tomatoes, on double-decker bun
27510560	Hamburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun
27510570	Hamburger, 2-1/2 oz meat, with mayonnaise or salad dressing and tomatoes, on bun
27510610	Hamburger, 1 oz meat, with tomato and/or catsup, on miniature bun
27510620	Hamburger, 1/4 lb meat, with tomato and/or catsup, on bun
27510630	Hamburger, 1/4 lb meat, with mayonnaise or salad dressing, on bun
27510660	Double hamburger (2 patties), with mayonnaise or salad dressing, on bun
27510700	Meatball and spaghetti sauce submarine sandwich, on roll
27510720	Pizzaburger (hamburger, cheese, sauce) on whole bun
27513040	Roast beef submarine sandwich, on roll, with lettuce, tomato and spread
27513070	Roast beef submarine sandwich, on roll, au jus
27515000	Steak submarine sandwich, on roll, with lettuce and tomato
27515010	Steak sandwich, plain, on roll
27515030	Steak and cheese sandwich, plain, on roll
27515070	Steak and cheese submarine sandwich, with fried peppers and onions, on roll
27520420	Midnight sandwich, (Media noche), with spread
27520500	Pork, barbecue sauce, onions and dill pickles on white roll
27540150	Chicken fillet (breaded, fried) sandwich with lettuce, tomato and spread
27540240	Chicken fillet, (broiled), sandwich, on whole wheat roll, with lettuce, tomato and spread
27540250	Chicken fillet, broiled, sandwich with cheese, on whole wheat roll, with lettuce, tomato and non-mayonnaise type spread
27540260	Chicken fillet, broiled, sandwich, on oat bran bun, with lettuce, tomato, spread
27540270	Chicken fillet, broiled, sandwich, with lettuce, tomato, and non-mayonnaise type spread
27540280	Chicken fillet, broiled, sandwich with cheese, on bun, with lettuce, tomato and spread
27540350	Turkey submarine sandwich, on roll, with cheese, lettuce, tomato and spread
27550110	Crab cake sandwich, on bun
27560330	Frankfurter or hot dog, with cheese, plain, on bun
27560340	Frankfurter or hot dog, with catsup and/or mustard, on bun
27560720	Sausage and spaghetti sauce sandwich
41901020	Soyburger, meatless, with cheese on bun

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 21.7 to 28.9%)
[Olestra] = 0.65 to 0.86%

27510110	Beef barbecue or Sloppy Joe, on bun
27510260	Cheeseburger, 1/4 lb meat, with mushrooms in sauce, on bun
27510320	Cheeseburger, 1/4 lb meat, with tomato and/or catsup, on bun
27510330	Double cheeseburger (2 patties), with tomato and/or catsup, on bun
27510350	Cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun
27510370	Double cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, on bun
27510390	Double bacon cheeseburger (2 patties, 1/4 lb meat each), on bun
27510490	Cheeseburger, 1/4 lb meat (beef modified in fat content), with tomato and/or catsup, on bun
27510640	Hamburger, 1/4 lb meat (beef modified in fat content), with tomato and/or catsup, on bun
27510670	Double hamburger (2 patties), with mayonnaise or salad dressing and tomatoes, on bun
27510680	Double hamburger (2 patties, 1/4 lb meat each), with tomato and/or catsup, on bun

27510690	Double hamburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing and tomatoes and/or catsup, on double-decker bun
27510710	Pizzaburger (hamburger, cheese, sauce) on 1/2 bun
27515020	Steak and cheese submarine sandwich, on roll, with lettuce and tomato
27515040	Steak and cheese submarine sandwich, plain, on roll
27520160	Bacon, chicken, and tomato club sandwich, on multigrain roll with lettuce and spread
27520360	Ham and cheese sandwich, on bun, with lettuce and spread
27520370	Hot ham and cheese sandwich, on bun
27520510	Pork barbecue or Sloppy Joe, on bun
27560310	Corny dog, with chili, on bun
27560360	Frankfurter or hot dog, with chili, on bun
27560370	Frankfurter or hot dog with chili and cheese, on bun
27560910	Submarine, cold cut sandwich, on bun, with lettuce

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 14.9 to 19.6%)
[Olestra] = 0.43 to 0.59%

27510380	Triple cheeseburger (3 patties, 1/4 lb meat each), with mayonnaise or salad dressing and tomatoes
27510430	Double bacon cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing and tomato
27520390	Ham and cheese submarine sandwich, on multigrain roll, with lettuce, tomato and spread

Pre-packaged Ready-to-Eat and Ready-to-Heat Sweet Rolls and Quick Breads
75% of shortening is replaced with Olestra; shortening content of 3.4 to 15.2%
[Olestra] = 2.13 to 11.37%

51160000	Roll, sweet
51160010	Roll, sweet, toasted
51160100	Roll, sweet, cinnamon bun, no frosting
51161000	Roll, sweet, with fruit, no frosting
51161100	Roll, sweet, with fruit and nuts, no frosting
51161250	Roll, sweet, no topping, Mexican (Pan Dulce)
51161260	Roll, sweet, crumb topping, Mexican (Pan Dulce)
51161270	Roll, sweet, sugar topping, Mexican (Pan Dulce)
51161280	Roll, sweet, with raisins and icing, Mexican (Pan Dulce)
51167000	Brioche
51168000	Bread, Spanish coffee
51188100	Pannetone (Italian-style sweetbread)
52401000	Bread, Boston Brown
52403000	Bread, nut
52404060	Bread, pumpkin
52405010	Bread, fruit, without nuts
52405100	Bread, fruit and nut
52406010	Bread, whole wheat, with nuts
52407000	Bread, zucchini
52408000	Bread, Irish soda

Mixtures containing pre-packaged ready-to-eat and ready-to-heat sweet rolls & quick breads
75% of shortening in the sweet roll portion is replaced with Olestra; shortening content of 1.2 to 7.4%
(Adjusted sweet rolls and quick bread content of 44.6 to 94.7%)
[Olestra] = 0.64 to 3.41%

51160110	Roll, sweet, cinnamon bun, frosted
51161020	Roll, sweet, with fruit, frosted
51161030	Roll, sweet, with fruit, frosted, diet
51161050	Roll, sweet, with nuts, frosted
51161070	Roll, sweet, with fruit, frosted, fat-free
51161150	Roll, sweet, with fruit and nuts, frosted
51161200	Roll, sweet, with nuts, no frosting

Pre-packaged Ready-to-Eat and Ready-to-Heat Waffles
75% of shortening is replaced with Olestra; shortening content of 2.7 to 9.4%
[Olestra] = 1.99 to 7.08%

55201000	Waffle, plain
55202000	Waffle, wheat, bran, or multigrain
55203500	Waffle, nut and honey
55204000	Waffle, cornmeal
55205000	Waffle, 100% whole wheat or 100% whole grain
55206000	Waffle, oat bran
55207000	Waffle, multi-bran
55211000	Waffle, plain, fat-free
55211050	Waffle, plain, low-fat

Mixtures containing pre-packaged ready-to-eat and ready-to-heat waffles
75% of shortening in the waffle portion is replaced with Olestra; shortening content of 5.4%
(Adjusted for waffle content of 80.5%)
[Olestra] = 3.27%

55203000	Waffle, fruit

<u>Cheeses</u>

Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods
(Pre-packaged RTE & RTH prepared foods containing reduced-fat, low-fat, and fat-free natural cheese codes were used as products containing olestra will be marketed as such)

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat is replaced with Olestra; butter fat content of 3.4 to 10.5%
(Adjusted for natural cheese content of 50.0 to 64.3%)
[Olestra] = 1.46 to 3.48%

14204020	Cheese, cottage, low-fat, with fruit

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 10.5 to 34.9%
(Adjusted for natural cheese content of 24.4 to 37.0%)
[Olestra] = 0.66 to 8.60%

53104520	Cheesecake, diet
53104570	Cheesecake, diet, with fruit
53104650	Cheesecake, chocolate, reduced-fat
58106900	Pizza with seafood, NS as to type of crust

58106910	Pizza with seafood, thin crust
58108010	Calzone, with meat and cheese
58122210	Gnocchi, cheese

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 10.4 to 47.2%
(Adjusted for natural cheese content of 11.3 to 17.9%)
[Olestra] = 0.31 to 5.62%

53511500	Danish pastry, with cheese, fat-free, cholesterol free
58106210	Pizza, cheese, NS as to type of crust
58106220	Pizza, cheese, thin crust
58106310	Pizza, cheese, with vegetables, NS as to type of crust
58106320	Pizza, cheese, with vegetables, thin crust
58106510	Pizza with meat, NS as to type of crust
58106520	Pizza with meat, thin crust
58106780	Pizza with meat and vegetables, low-fat, thin crust
58106810	Pizza with beans and vegetables, NS as to type of crust
58106820	Pizza with beans and vegetables, thin crust
58106920	Pizza with seafood, thick crust
58108000	Calzone, with cheese, meatless
58108030	Panzerotti, with meat, vegetables, and cheese
58108040	Panzerotti, with vegetables and cheese
58108050	Pizza rolls
58109000	Italian pie, meatless
58124250	Spanakopitta

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 21.6%
(Adjusted for natural cheese content of 6.2 to 10.6%)
[Olestra] = 0.89 to 1.52%

58106230	Pizza, cheese, thick crust
58106330	Pizza, cheese, with vegetables, thick crust
58106360	Pizza, cheese, with fruit, thick crust
58106530	Pizza with meat, thick crust
58106710	Pizza with meat and vegetables, NS as to type of crust
58106720	Pizza with meat and vegetables, thin crust
58106730	Pizza with meat and vegetables, thick crust
58106740	Pizza with meat and fruit, NS as to type of crust
58106750	Pizza with meat and fruit, thin crust
58106760	Pizza with meat and fruit, thick crust
58106830	Pizza with beans and vegetables, thick crust
58107210	White pizza, NS as to type of crust
58107220	White pizza, thin crust
58130010	Lasagna with meat and/or poultry
58130020	Lasagna with meat and spinach
58130150	Lasagna, with chicken or turkey, and spinach
58130310	Lasagna, meatless
58130320	Lasagna, meatless, with spinach
58130610	Lasagna with meat, whole wheat noodles
58130810	Lasagna, meatless, whole wheat noodles
58130910	Lasagna with meat, spinach noodles
58130950	Lasagna, meatless, spinach noodles

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 10.4 to 21.6%
(Adjusted for natural cheese content of 1.4 to 5.4%)
[Olestra] = 0.098 to 0.77%

53105500	Cake, chocolate, with icing, diet
58107230	White pizza, thick crust
58109010	Italian pie with meat
58134623	Tortellini, cheese-filled, meatless, with tomato sauce, canned
58134630	Tortellini, cheese-filled, meatless, with vegetables and vinaigrette dressing

Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods
(Pre-packaged RTE & RTH prepared foods containing reduced-fat, low-fat, and fat-free processed cheese codes were used as products containing olestra will be marketed as such)

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 21.6%
(Adjusted for processed cheese content of 75.1%)
[Olestra] = 10.82%

14660200	Cheese, nuggets or pieces, breaded, baked, or fried

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 3.5 to 32.0%
(Adjusted for processed cheese content of 21.3 to 32.3%)
[Olestra] = 0.50 to 6.89%

14650150	Cheese sauce made with low-fat cheese
58301050	Lasagna with cheese and meat sauce (diet frozen meal)
58301080	Lasagna with cheese and meat sauce, reduced-fat and sodium (diet frozen meal)
58304200	Ravioli, cheese-filled, with tomato sauce (diet frozen meal)
58304250	Manicotti, cheese-filled, with tomato sauce (diet frozen meal)

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 3.5 to 32.0%
(Adjusted for processed cheese content of 9.2 to 19.1%)
[Olestra] = 0.36 to 2.07%

27550100	Fish sandwich, on bun, with cheese and spread
28110660	Meatballs, Swedish, in gravy, with noodles (diet frozen meal)
28141050	Chicken patty parmigiana, breaded, with vegetable (diet frozen meal)
58145115	Macaroni or noodles with cheese, from boxed mix with already prepared cheese sauce
58301020	Lasagna with cheese and sauce (diet frozen meal)
58301150	Zucchini lasagna (diet frozen meal)
58302030	Macaroni with veal, cheese, and sauce (diet frozen meal)
58302050	Beef and noodles with meat sauce and cheese (diet frozen meal)
58304300	Cannelloni, cheese-filled, with tomato sauce (diet frozen meal)
75412070	Eggplant with cheese and tomato sauce

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 21.6%
(Adjusted for processed cheese content of 2.5 to 6.9%)
[Olestra] = 0.36 to 0.99%

14610520	Cheese with nuts
28113050	Salisbury steak with vegetables in tomato-based sauce, noodles (diet frozen meal)

28113110	Salisbury steak, baked, with tomato sauce, vegetable (diet frozen meal)
28133210	Veal parmigiana with vegetable (diet frozen meal)
28133340	Veal parmigiana with vegetable, fettuccine alfredo, dessert (frozen meal)
58301030	Veal lasagna (diet frozen meal)
58301130	Tuna lasagna (diet frozen meal)
58304220	Rigatoni with meat sauce and cheese (diet frozen meal)

Confections and Frostings

Pre-packaged Ready-to-Eat Frosting and Icing
100% of shortening is replaced with Olestra; shortening content of 10.81%
[Olestra] = 10.81%

91305010	Icing, chocolate
91305020	Icing, white

Mixtures containing pre-packaged ready-to-eat frosting and icing
100% of shortening in the frosting or icing portion is replaced with Olestra; shortening content of 10.81%
(Adjusted for frosting and icing content of 30.5 to 44.0%)
[Olestra] = 3.29 to 4.76%

53105300	Cake, German chocolate, with icing and filling
53105750	Cake, chocolate, devil's food, or fudge, pudding type mix, made by "cholesterol free" recipe (water, oil and egg whites added to dry mix), with “light” icing, coating or filling
53105900	Cake, chocolate, devil's food, or fudge, pudding-type mix (oil, eggs, and water added to dry mix), NS as to icing
53106050	Cake, chocolate, devil's food, or fudge, pudding-type mix (oil, eggs, and water added to dry mix), with icing, coating, or filling
53114150	Cake, lemon, low-fat, NS as to icing
53116490	Cake, pumpkin, NS as to icing
53116510	Cake, pumpkin, with icing
53118200	Cake, sponge, with icing
53120300	Cake, white, pudding-type mix (oil, egg whites, and water added to dry mix), NS as to icing
53120350	Cake, white, pudding-type mix (oil, egg whites, and water added to dry mix), with icing
53121280	Cake, yellow, pudding-type mix (oil, eggs, and water added to dry mix), NS as to icing
53121330	Cake, yellow, pudding-type mix (oil, eggs, and water added to dry mix), with icing
53452420	Pastry, puff, custard or cream filled, iced or not iced
53521230	Doughnut, custard-filled, with icing

Mixtures containing pre-packaged ready-to-eat frosting and icing
100% of shortening in the frosting or icing portion is replaced with Olestra; shortening content of 10.81%
(Adjusted for frosting and icing content of 30.0%)
[Olestra] = 3.24%

53100100	Cake, NS as to type, with or without icing
53101000	Cake, angel food, NS as to icing
53101200	Cake, angel food, with icing
53101250	Cake, angel food, with fruit and icing or filling
53102000	Cake, applesauce, NS as to icing
53102200	Cake, applesauce, with icing
53102500	Cake, banana, NS as to icing
53102700	Cake, banana, with icing
53102800	Cake, black forest (chocolate-cherry)
53103500	Cake, butter, NS as to icing
53103600	Cake, butter, with icing

53104000	Cake, carrot, NS as to icing
53104260	Cake, carrot, with icing
53104400	Cake, coconut, with icing
53104900	Cake, chocolate, made with mayonnaise or salad dressing, NS as to icing
53104950	Cake, chocolate, made with mayonnaise or salad dressing, with icing, coating, or filling
53105000	Cake, chocolate, devil's food, or fudge, standard-type mix (eggs and water added to dry mix), NS as to icing
53105050	Cake, chocolate, devil's food, or fudge, made from home recipe or purchased ready-to-eat, NS as to icing
53105200	Cake, chocolate, devil's food, or fudge, standard-type mix (eggs and water added to dry mix), with icing
53105260	Cake, chocolate, devil's food, or fudge, with icing, coating, or filling, made from home recipe or purchased ready-to-eat
53105500	Cake, chocolate, with icing, diet
53105600	Cake, chocolate, devil's food, or fudge, pudding-type mix, made by "Lite" recipe (eggs and water added
53105650	Cake, chocolate, devil's food, or fudge, pudding type mix, made by "cholesterol free" recipe (water, oil and egg whites added to dry mix), NS as to icing or filling
53107000	Cake, cupcake, NS as to type or icing
53107200	Cake, cupcake, NS as to type, with icing
53108000	Cake, cupcake, chocolate, NS as to icing
53108200	Cake, cupcake, chocolate, with icing or filling
53109000	Cake, cupcake, not chocolate, NS as to icing
53109200	Cake, cupcake, not chocolate, with icing or filling
53109210	Cake, cupcake, not chocolate, with icing or filling, low-fat, cholesterol free
53109270	Cake, cupcake, chocolate, with or without icing, fruit filling or cream filling, low-fat, cholesterol
53109300	Cake, Dobos Torte (non-chocolate layer cake with chocolate filling and icing)
53113950	Cake, lemon, NS as to icing
53114100	Cake, lemon, with icing
53114250	Cake, lemon, low-fat, with icing
53115000	Cake, marble, NS as to icing
53115200	Cake, marble, with icing
53115300	Cake, nut, NS as to icing
53115320	Cake, nut, with icing
53115410	Cake, oatmeal, with icing
53116560	Cake, raisin-nut, with icing
53117000	Cake, spice, NS as to icing
53117200	Cake, spice, with icing
53118310	Cake, sponge, chocolate, with icing
53118350	Cake, sweet potato, with icing
53118600	Cake, chiffon, NS as to icing
53118800	Cake, chiffon, with icing
53118950	Cake, chiffon, chocolate, with icing
53120000	Cake, white, standard-type mix (egg whites and water added), NS as to icing
53120060	Cake, white, made from home recipe or purchased ready-to-eat, NS as to icing
53120200	Cake, white, standard-type mix (egg whites and water added to mix), with icing
53120260	Cake, white, with icing, made from home recipe or purchased ready-to-eat
53121000	Cake, yellow, standard-type mix (eggs and water added to dry mix), NS as to icing
53121060	Cake, yellow, made from home recipe or purchased ready-to- eat, NS as to icing
53121200	Cake, yellow, standard-type mix (eggs and water added to dry mix), with icing
53121260	Cake, yellow, with icing, made from home recipe or purchased ready-to-eat
53124100	Cake, zucchini, NS as to icing
53124120	Cake, zucchini, with icing
54102200	Crackers, graham, sandwich-type, with filling

Mixtures containing pre-packaged ready-to-eat frosting and icing
100% of shortening in the frosting or icing portion is replaced with Olestra; shortening content of 10.81%
(Adjusted for frosting and icing content of 20.0 to 28.9%)
[Olestra] = 2.16 to 3.13%

51161020	Roll, sweet, with fruit, frosted
51161030	Roll, sweet, with fruit, frosted, diet
51161050	Roll, sweet, with nuts, frosted
51161070	Roll, sweet, with fruit, frosted, fat-free
51161150	Roll, sweet, with fruit and nuts, frosted
53115450	Cake, peanut butter, with icing
53116020	Cake, pound, with icing
53204000	Cookie, brownie, NS as to icing
53204100	Cookie, brownie, with icing
53204600	Cookie, brownie, with peanut butter fudge icing
53204800	Cookie, brownie, diet, NS as to icing
53204830	Cookie, brownie, low-fat, with icing
53204850	Cookie, brownie, fat-free, cholesterol free, with icing
53244010	Cookie, butter or sugar, with chocolate icing or filling
53244020	Cookie, butter or sugar, iced, with icing other than chocolate
53420000	Cream puff, eclair, custard or cream filled, NS as to icing
53520140	Doughnut, cake type, chocolate covered
53520160	Doughnut, cake type, chocolate, with chocolate icing
53521100	Doughnut, raised or yeast, chocolate, with chocolate icing

Mixtures containing pre-packaged ready-to-eat frosting and icing
100% of shortening in the frosting or icing portion is replaced with Olestra; shortening content of 10.81%
(Adjusted for frosting and icing content of 9.1 to 19.9%)
[Olestra] = 0.98 to 2.16%

51160110	Roll, sweet, cinnamon bun, frosted
53112150	Cake, frozen yogurt and cake layer, not chocolate, with icing
53112160	Cake, frozen yogurt and cake layer, chocolate, with icing
53209010	Cookie, chocolate-covered, sugar wafer, creme- or caramel-filled
53610150	Coffee cake, crumb or quick-bread type, with icing

Fats and Oils

Pre-packaged Ready-to-Eat Mayonnaise
(Reduced-fat, low-fat, and fat-free mayonnaise codes were used as products containing olestra will be marketed as such)

67% of soybean oil is replaced with Olestra; soybean oil content of 5.1 to 79.4%
[Olestra] = 3.40 to 52.90%

83107100	Mayonnaise, made with yogurt
83107200	Mayonnaise, made with tofu
83108000	Mayonnaise, imitation
83108100	Mayonnaise, imitation, cholesterol free
83203250	Mayonnaise-type salad dressing, fat-free
83204000	Mayonnaise, low-calorie or diet
83204010	Mayonnaise, low-calorie or diet, low sodium
83204020	Mayonnaise, reduced calorie or diet, cholesterol-free
83204050	Mayonnaise-type salad dressing, low-calorie or diet
83204060	Mayonnaise-type salad dressing, low-calorie or diet, cholesterol-free

Mixtures containing pre-packaged ready-to-eat mayonnaise
67% of soybean oil in the mayonnaise portion is replaced with Olestra; soybean oil content of 0.2 to 16.3%
(Adjusted for mayonnaise content of 4.2 to 90.8%)
[Olestra] = 0.16 to 10.87%

27540250	Chicken fillet, broiled, sandwich with cheese, on whole wheat roll, with lettuce, tomato and non-mayonnaise
27540270	Chicken fillet, broiled, sandwich, with lettuce, tomato, and non-mayonnaise type spread
81312000	Tartar sauce, low-calorie

Frozen Dairy Desserts and Mixes

Pre-packaged Ready-to-Eat Ice Cream
(Reduced-fat, low-fat, and fat-free ice cream codes were used as products containing olestra will be marketed as such)

67% of butter fat is replaced with Olestra; butter fat content of 1.7 to 9.1%
[Olestra] = 1.13 to 6.07%

13130350	Light ice cream, premium, flavors other than chocolate (formerly ice milk)
13130300	Light ice cream, flavors other than chocolate (formerly ice milk)
13130310	Light ice cream, chocolate (formerly ice milk)
13130360	Light ice cream, premium, chocolate (formerly ice milk)
13130370	Light ice cream, premium, NS as to flavor (formerly ice milk)
13130590	Light ice cream, soft serve, NS as to flavor (formerly ice milk)
13130600	Light ice cream, soft serve, flavors other than chocolate (formerly ice milk)
13130610	Light ice cream, soft serve, chocolate (formerly ice milk)
13130640	Light ice cream, soft serve cone, NS as to flavor (formerly ice milk)
13161630	Light ice cream, bar or stick, with low-calorie sweetener, chocolate-coated (formerly ice milk)

Mixtures containing pre-packaged ready-to-eat ice cream
67% of butter fat in the ice cream portion is replaced with Olestra; butter fat content of 0.6 to 13.5%
(Adjusted for ice cream content of 75.2 to 96.0%)
[Olestra] = 0.30 to 7.83%

13130100	Light ice cream, NFS (formerly ice milk)
13130620	Light ice cream, soft serve cone, flavors other than chocolate (formerly ice milk)
13130630	Light ice cream, soft serve cone, chocolate (formerly ice milk)
13135000	Light ice cream, sandwich (formerly ice milk)
13140100	Light ice cream, bar or stick, chocolate-coated (formerly ice milk)
13140110	Light ice cream, bar or stick, chocolate covered, with nuts (formerly ice milk)
13140500	Light ice cream, cone, flavors other than chocolate (formerly ice milk)
13140550	Light ice cream, cone, chocolate (formerly ice milk)
13140660	Light ice cream, sundae, soft serve, chocolate or fudge topping (without whipped cream) (formerly ice milk)
13140670	Light ice cream, sundae, soft serve, fruit topping (without whipped cream) (formerly ice milk)
13140680	Light ice cream, sundae, soft serve, not fruit or chocolate topping (without whipped cream) (formerly ice milk)
13140900	Light ice cream, fudgesicle (formerly ice milk)

Mixtures containing pre-packaged ready-to-eat ice cream
67% of butter fat in the ice cream portion is replaced with Olestra; butter fat content of 1.7%
(Adjusted for ice cream content of 44.8 to 50.2%)
[Olestra] = 0.51 to 0.57%

13140450	Light ice cream, cone, NFS (formerly ice milk)
13140600	Light ice cream, sundae, soft serve, chocolate or fudge topping, with whipped cream (formerly ice milk)
13140630	Light ice cream, sundae, soft serve, fruit topping, with whipped cream (formerly ice milk)
13140650	Light ice cream, sundae, soft serve, not fruit or chocolate topping, with whipped cream (formerly ice milk)
13140700	Light ice cream, creamsicle or dreamsicle (formerly ice milk)
13141100	Light ice cream, with sherbet or ice cream (formerly ice milk)

Pre-packaged Ready-to-Eat Frozen Yogurt
(Reduced-fat, low-fat, and fat-free yogurt codes were used as products containing olestra will be marketed as such)

67% of butter fat is replaced with Olestra; butter fat content of 3.6%
[Olestra] = 2.40%

11459990	Yogurt, frozen, NS as to flavor, NS as to type of milk
11460190	Yogurt, frozen, NS as to flavor, nonfat milk
11460400	Yogurt, frozen, chocolate, nonfat milk, with low-calorie sweetener

Mixtures containing pre-packaged ready-to-eat frozen yogurt
67% of butter fat in the frozen yogurt portion is replaced with Olestra; butter fat content of 3.6%
(Adjusted for frozen yogurt content of 81.8 to 94.1%)
[Olestra] = 1.96 to 2.26%

11460000	Yogurt, frozen, flavors other than chocolate, NS as to type of milk
11460100	Yogurt, frozen, chocolate, NS as to type of milk
11460160	Yogurt, frozen, chocolate, low-fat milk
11460170	Yogurt, frozen, flavors other than chocolate, low-fat milk
11460200	Yogurt, frozen, chocolate, nonfat milk
11460300	Yogurt, frozen, flavors other than chocolate, nonfat milk
11461270	Yogurt, frozen, cone, flavors other than chocolate, low-fat milk
11461280	Yogurt, frozen, cone, chocolate, low-fat milk

Mixtures containing pre-packaged ready-to-eat frozen yogurt
67% of butter fat in the frozen yogurt portion is replaced with Olestra; butter fat content of 3.6%
(Adjusted for frozen yogurt content of 20.0 to 68.2%)
[Olestra] = 0.48 to 1.64%

11460150	Yogurt, frozen, NS as to flavor, low-fat milk
11460250	Yogurt, frozen, flavors other than chocolate, with sorbet or sorbet-coated
11460410	Yogurt, frozen, flavors other than chocolate, nonfat milk, with low-calorie sweetener

<u>Grain Products and Pastas</u>

Pre-packaged Ready-to-Eat Breakfast, Granola, and Nutritional Bars
75% of shortening is replaced with Olestra; shortening content of 2.7 to 16.0%
[Olestra] = 2.03 to 12.0%

41435010	High protein bar, soy base
41435110	High protein bar, candy-like, soy and milk base

41435200	High protein bar, cookie type, soy and milk base
53540000	Breakfast bar, NFS
53540100	Breakfast bar, cake-like
53540200	Breakfast bar, cereal crust with fruit filling, low-fat
53540250	Breakfast bar, cereal crust with fruit filling, fat-free
53540500	Breakfast bar, date, with yogurt coating
53541100	Breakfast bar, diet meal type
53541200	Meal replacement bar
53542100	Granola bar, oats, sugar, raisins, coconut
53542200	Granola bar, oats, fruit and nuts, low-fat
53542210	Granola bar, nonfat
53543100	Granola bar, peanuts, oats, sugar, wheat germ
53544100	Granola bar, with nougat
53544200	Granola bar, chocolate-coated
53544210	Granola bar, with coconut, chocolate-coated
53544220	Granola bar with nuts, chocolate-coated
53544250	Granola bar, coated with non-chocolate coating
53544300	Granola bar, high fiber, coated with non-chocolate yogurt coating
53544400	Granola bar, with rice cereal
53544450	PowerBar (fortified high energy bar)

Pre-packaged Ready-to-Eat and Ready-to-Heat Pizza Crust
75% of shortening is replaced with Olestra; shortening content of 2.1 to 4.9%
[Olestra] = 1.54 to 3.64%

58106210	Pizza, cheese, NS as to type of crust
58106220	Pizza, cheese, thin crust
58106230	Pizza, cheese, thick crust
58106310	Pizza, cheese, with vegetables, NS as to type of crust
58106320	Pizza, cheese, with vegetables, thin crust
58106330	Pizza, cheese, with vegetables, thick crust
58106360	Pizza, cheese, with fruit, thick crust
58106510	Pizza with meat, NS as to type of crust
58106520	Pizza with meat, thin crust
58106530	Pizza with meat, thick crust
58106710	Pizza with meat and vegetables, NS as to type of crust
58106720	Pizza with meat and vegetables, thin crust
58106730	Pizza with meat and vegetables, thick crust
58106740	Pizza with meat and fruit, NS as to type of crust
58106750	Pizza with meat and fruit, thin crust
58106760	Pizza with meat and fruit, thick crust
58106780	Pizza with meat and vegetables, low-fat, thin crust
58106810	Pizza with beans and vegetables, NS as to type of crust
58106820	Pizza with beans and vegetables, thin crust
58106830	Pizza with beans and vegetables, thick crust
58106900	Pizza with seafood, NS as to type of crust
58106910	Pizza with seafood, thin crust
58106920	Pizza with seafood, thick crust
58107000	Ground beef with tomato sauce on a pizza crust
58107030	Pizza, no cheese, NS as to type of crust
58107050	Pizza, no cheese, thin crust
58107100	Pizza, no cheese, thick crust
58107210	White pizza, NS as to type of crust
58107220	White pizza, thin crust
58107230	White pizza, thick crust

Soft Candy

Pre-packaged Ready-to-Eat Chocolate Confections (chocolate portion)
100% of cocoa butter is replaced with Olestra; cocoa butter content of 10.0 to 21.5%
[Olestra] = 10.0 to 21.5%

91703010	Caramel, chocolate-flavored roll
91705010	Chocolate, milk, plain
91705200	Chocolate, semi-sweet morsel
91705210	Special Dark
91705300	Chocolate, sweet or dark
91705400	Chocolate, white
91705500	Mexican chocolate (tablet)
91713030	Fudge, chocolate

Mixtures containing pre-packaged ready-to-eat chocolate confections
100% of cocoa butter is replaced with Olestra; cocoa butter content of 10.0 to 21.5%
(Adjusted for chocolate content of 70.0 to 85.0%)
[Olestra] = 7.0 to 18.28%

91703150	Toblerone, milk chocolate with honey and almond nougat
91705020	Chocolate, milk, with cereal
91705040	Chocolate, milk, with nuts, not almond or peanuts
91705050	Chocolate, milk, with fruit and nuts
91705060	Chocolate, milk, with almonds
91705070	Chocolate, milk, with peanuts
91705410	Chocolate, white, with almonds
91705420	Chocolate, white, with cereal
91713040	Fudge, chocolate, with nuts
91734200	Reese's Pieces
91746010	Sugar-coated chocolate discs
91746100	M & M's Plain Chocolate Candies
91746120	Sixlets
91746150	Easter egg, candy coated chocolate
91760500	Truffles

Mixtures containing pre-packaged ready-to-eat chocolate confections
100% of cocoa butter is replaced with Olestra; cocoa butter content of 21.5%
(Adjusted for chocolate content of 30.0 to 64.0%)
[Olestra] = 6.45 to 13.75%

91701010	Almonds, chocolate covered
91705090	Chocolate with fondant and caramel
91715000	Fudge, caramel and nut, chocolate-coated
91723010	Marshmallow, chocolate covered
91727010	Nuts, chocolate covered, not almonds or peanuts
91733200	Peanut Bar, chocolate covered
91734000	Peanut butter, chocolate covered
91734050	P.B. Max Peanut Butter Snack

Mixtures containing pre-packaged ready-to-eat chocolate confections
100% of cocoa butter is replaced with Olestra; cocoa butter content of 21.5%
(Adjusted for chocolate content of 29.0%)
[Olestra] = 6.24%

91700500	M & M's Almond Chocolate Candies
91703050	Caramel with nuts and cereal, chocolate covered
91703060	Caramel with nuts, chocolate covered
91703070	Rolo
91703200	TWIX Cookie Bars
91703250	TWIX Chocolate Fudge Cookie Bars
91703300	TWIX Peanut Butter Cookie Bars
91703350	Bar None
91703400	Whatchamacallit
91705030	Kit Kat
91706000	Coconut candy, chocolate covered
91707010	Fondant, chocolate covered
91715100	SNICKERS Bar
91715110	Snickers Peanut Butter Bar
91715200	Baby Ruth
91715300	100 GRAND Bar
91718050	Honey-combed hard candy with peanut butter, chocolate covered
91718100	Butterfinger
91726110	Nougat, with caramel, chocolate covered
91726120	Milky Way II
91726130	MILKY WAY Bar
91726140	MILKY WAY DARK Bar
91726150	MARS Bar
91726420	3 MUSKETEER Bar
91731000	Peanuts, chocolate covered
91731010	M & M's Peanut Chocolate Candies
91731060	M & M's Peanut Butter Chocolate Candies
91734100	Reese's Peanut Butter Cup
91739010	Raisins, chocolate covered
91770030	Dietetic or low-calorie candy, chocolate covered

Mixtures containing pre-packaged ready-to-eat chocolate confections
100% of cocoa butter is replaced with Olestra; cocoa butter content of 21.5%
(Adjusted for chocolate content of 10.0 to 28.0%)
[Olestra] = 2.15 to 6.02%

91703040	Caramel, chocolate covered
91703600	Espresso coffee beans, chocolate-covered
91709000	Gumdrops, chocolate covered
91716110	Halvah, chocolate covered
91726410	Nougat, chocolate covered
91760100	Toffee, chocolate covered
91760200	Toffee, chocolate-coated, with nuts

ATTACHMENT IV TO APPENDIX B

Representative CSFII 1994-1996, 1998 Food Codes for All Fat Modified Products

Representative CSFII 1994-1996, 1998 Food Codes for All Fat Modified Products

Note: Food codes representative of fat modified milks, yogurt, and cheese that were excluded from the analyses for scenario (2) have been highlighted (see Section 7.0).

11111160	Milk, calcium fortified, cow's, fluid, 1% fat
11111170	Milk, calcium fortified, cow's, fluid, skim or nonfat
11112000	Milk, cow's, fluid, other than whole, NS as to 2%, 1%, or skim (formerly milk, cow's, fluid, "low-fat", NS as to percent fat)
11112120	Milk, cow's, fluid, acidophilus, 1% fat
11112210	Milk, cow's, fluid, 1% fat
11113000	Milk, cow's, fluid, skim or nonfat, 0.5% or less butterfat
11114200	Milk, cow's, fluid, filled with vegetable oil, low-fat
11114300	Milk, cow's, fluid, lactose reduced, 1% fat
11114310	Milk, cow's, fluid, lactose reduced, 1% fat, fortified with calcium
11114320	Milk, cow's, fluid, lactose reduced, nonfat
11114321	Milk, cow's, fluid, lactose reduced, nonfat, fortified with calcium
11115000	Buttermilk, fluid, nonfat
11121210	Milk, dry, reconstituted, low-fat
11411200	Yogurt, plain, low-fat milk
11422000	Yogurt, vanilla, lemon, maple, or coffee flavor, low-fat milk
11424000	Yogurt, vanilla, lemon, maple, or coffee flavor, nonfat milk, sweetened with low-calorie sweetener
11432000	Yogurt, fruit variety, low-fat milk
11433500	Yogurt, fruit variety, nonfat milk, sweetened with low-calorie sweetener
11445000	Yogurt, fruit and nuts, low-fat milk
11460150	Yogurt, frozen, NS as to flavor, low-fat milk
11460160	Yogurt, frozen, chocolate, low-fat milk
11460170	Yogurt, frozen, flavors other than chocolate, low-fat milk
11460400	Yogurt, frozen, chocolate, nonfat milk, with low-calorie sweetener
11460410	Yogurt, frozen, flavors other than chocolate, nonfat milk, with low-calorie sweetener
11461270	Yogurt, frozen, cone, flavors other than chocolate, low-fat milk
11461280	Yogurt, frozen, cone, chocolate, low-fat milk
11511200	Milk, chocolate, reduced-fat milk-based (formerly "low-fat")
11511300	Milk, chocolate, skim milk-based
11513150	Cocoa and sugar mixture, reduced-fat milk added
11513200	Cocoa and sugar mixture, low-fat milk added
11513300	Cocoa and sugar mixture, skim milk added
11513550	Chocolate syrup, reduced-fat milk added
11513600	Chocolate syrup, low-fat milk added
11513700	Chocolate syrup, skim milk added
11514300	Cocoa with nonfat dry milk and low-calorie sweetener, mixture, water added
11515400	Cocoa with nonfat dry milk and low-calorie sweetener, high calcium, water added
11516000	Cocoa, whey, and low-calorie sweetener mixture, low-fat milk added
11518000	Milk beverage with nonfat dry milk and low-calorie sweetener, water added, chocolate
11518050	Milk beverage with nonfat dry milk and low-calorie sweetener, water added, flavors other than chocolate
11518100	Milk beverage with nonfat dry milk and low-calorie sweetener, high calcium, water added, chocolate
11521010	Milk, malted, unfortified, chocolate, made with skim milk
11531500	Eggnog, made with 2% reduced-fat milk (formerly eggnog, made with "2% lowfat" milk)
11621000	Diet beverage, liquid, canned
11622000	Diet beverage, powder, milk added
11622010	Diet beverage, powder, reconstituted with skim milk
11651010	Meal replacement formula, Cambridge diet, reconstituted, all flavors

11812000	Milk, dry, lowfat, not reconstituted
11830110	Cocoa powder with nonfat dry milk and low-calorie sweetener, dry mix, not reconstituted
11830500	Milk beverage, powder, with nonfat dry milk and low-calorie sweetener, dry mix, not reconstituted, chocolate
11830550	Milk beverage, powder, with nonfat dry milk and low-calorie sweetener, dry mix, not reconstituted, flavors other than chocolate
11835000	Meal replacement or nutritional supplement, Cambridge diet formula, powdered, nonfat milk solids base, dry, not reconstituted
12110100	Cream, light, fluid
12110300	Cream, light, whipped, unsweetened
12210250	Cream substitute, light, liquid
12210410	Cream substitute, light, powdered
12220250	Whipped topping, nondairy, frozen, low-fat
12220400	Whipped cream substitute, nondairy, low-fat, low sugar, made from powdered mix
12310300	Sour cream, reduced-fat
12310350	Sour cream, light
12310370	Sour cream, fat-free
12350020	Dip, sour cream base, reduced calorie
13130100	Light ice cream, NFS (formerly ice milk)
13130300	Light ice cream, flavors other than chocolate (formerly ice milk)
13130310	Light ice cream, chocolate (formerly ice milk)
13130350	Light ice cream, premium, flavors other than chocolate (formerly ice milk)
13130360	Light ice cream, premium, chocolate (formerly ice milk)
13130370	Light ice cream, premium, NS as to flavor (formerly ice milk)
13130590	Light ice cream, soft serve, NS as to flavor (formerly ice milk)
13130600	Light ice cream, soft serve, flavors other than chocolate (formerly ice milk)
13130610	Light ice cream, soft serve, chocolate (formerly ice milk)
13130620	Light ice cream, soft serve cone, flavors other than chocolate (formerly ice milk)
13130630	Light ice cream, soft serve cone, chocolate (formerly ice milk)
13130640	Light ice cream, soft serve cone, NS as to flavor (formerly ice milk)
13135000	Light ice cream, sandwich (formerly ice milk)
13140100	Light ice cream, bar or stick, chocolate-coated (formerly ice milk)
13140110	Light ice cream, bar or stick, chocolate covered, with nuts (formerly ice milk)
13140450	Light ice cream, cone, NFS (formerly ice milk)
13140500	Light ice cream, cone, flavors other than chocolate (formerly ice milk)
13140550	Light ice cream, cone, chocolate (formerly ice milk)
13140600	Light ice cream, sundae, soft serve, chocolate or fudge topping, with whipped cream (formerly ice milk)
13140630	Light ice cream, sundae, soft serve, fruit topping, with whipped cream (formerly ice milk)
13140650	Light ice cream, sundae, soft serve, not fruit or chocolate topping, with whipped cream (formerly ice milk)
13140660	Light ice cream, sundae, soft serve, chocolate or fudge topping (without whipped cream) (formerly ice milk)
13140670	Light ice cream, sundae, soft serve, fruit topping (without whipped cream) (formerly ice milk)
13140680	Light ice cream, sundae, soft serve, not fruit or chocolate topping (without whipped cream) (formerly ice milk)
13140700	Light ice cream, creamsicle or dreamsicle (formerly ice milk)
13140900	Light ice cream, fudgesicle (formerly ice milk)
13141100	Light ice cream, with sherbet or ice cream (formerly ice milk)
13160000	Milk dessert, frozen, made from low-fat milk
13160100	Milk dessert, frozen, low-fat, made with low-calorie sweetener, flavors other than chocolate
13160150	Milk dessert, frozen, nonfat, made with low-calorie sweetener, chocolate
13160160	Milk dessert, frozen, nonfat, made with low-calorie sweetener, flavors other than chocolate
13160200	Milk dessert, frozen, low-fat, flavors other than chocolate
13160210	Milk dessert, frozen, low-fat, chocolate
13160400	Milk dessert, frozen, milk-fat-free, flavors other than chocolate

13160410	Milk dessert, frozen, milk-fat-free, chocolate
13160550	Milk dessert, frozen, milk-fat-free, made with Simplesse, flavors other than chocolate
13160560	Milk dessert, frozen, milk-fat-free, made with Simplesse, chocolate
13161000	Milk dessert bar, frozen, made from low-fat milk
13161500	Milk dessert sandwich bar, frozen, made from low-fat milk
13161520	Milk dessert sandwich bar, frozen, with low-calorie sweetener, made from low-fat milk
13161600	Milk dessert bar, frozen, made from low-fat milk and low-calorie sweetener
13161630	Light ice cream, bar or stick, with low-calorie sweetener, chocolate-coated (formerly ice milk)
13210190	Pudding, Mexican bread (Capirotada), lower fat
13210250	Pudding, chocolate, ready-to-eat, low-calorie, containing artificial sweetener, NS as to from dry mix or canned
13210290	Pudding, flavors other than chocolate, ready-to-eat, low-calorie, containing artificial sweetener, NS as to from dry mix or canned
13220210	Pudding, flavors other than chocolate, prepared from dry mix, low-calorie, containing artificial sweetener, milk added
13220220	Pudding, chocolate, prepared from dry mix, low-calorie, containing artificial sweetener, milk added
13220230	Pudding, canned, chocolate, reduced-fat
13220235	Pudding, canned, chocolate, fat-free
13220245	Pudding, canned, flavors other than chocolate, fat-free
13230120	Pudding, canned, low-calorie, containing artificial sweetener, flavors other than chocolate
13230140	Pudding, canned, low-calorie, containing artificial sweetener, chocolate
13230510	Pudding, canned, tapioca, fat-free
13250200	Mousse, chocolate, low-fat, reduced calorie, prepared from dry mix, water added
14106500	Cheese, Monterey, low-fat
14107030	Cheese, Mozzarella, part skim
14107060	Cheese, Mozzarella, nonfat or fat-free
14107250	Cheese, Muenster, low-fat
14108060	Parmesan cheese topping, fat-free
14108410	Cheese, Provolone, reduced-fat, reduced sodium
14109030	Cheese, Swiss, low-fat
14110020	Cheese, Cheddar or Colby, low sodium, low-fat
14110030	Cheese, Cheddar or Colby, low-fat
14204010	Cheese, cottage, low-fat (1-2% fat)
14204020	Cheese, cottage, low-fat, with fruit
14204030	Cheese, cottage, low-fat, with vegetables
14206010	Cheese, cottage, low-fat, low sodium
14207010	Cheese, cottage, low-fat, lactose reduced
14303010	Cheese, cream, low-fat
14410300	Cheese, processed, American or Cheddar type, low-fat
14410310	Cheese, processed, American, Cheddar, or Colby, low-fat, low sodium
14410330	Cheese, processed cheese product, American or Cheddar type, reduced-fat
14410340	Cheese, processed cheese product, American or Cheddar type, reduced-fat, reduced sodium
14410350	Cheese, processed, American or Cheddar type, nonfat or fat-free
14410380	Cheese, processed cream cheese product, nonfat or fat-free
14410420	Cheese, processed, Swiss, low-fat
14410440	Cheese, processed, Swiss, low-fat, low sodium
14410450	Cheese, processed cheese product, Swiss, reduced-fat
14410830	Cheese, processed, Muenster, low-fat, low sodium
14420140	Cheese spread, American or Cheddar cheese base, low-fat, low sodium
14650150	Cheese sauce made with low-fat cheese
24198770	Chicken nuggets, low-fat
25210230	Frankfurter or hot dog, beef and pork, low-fat
25210250	Frankfurter or hot dog, meat and poultry, fat-free
25210610	Frankfurter or hot dog, beef, low-fat

25210700	Frankfurter or hot dog, meat & poultry, low-fat
25220390	Bologna, beef, low-fat
25220500	Bologna, beef and pork, low-fat
25221860	Turkey sausage, reduced-fat, brown and serve, cooked
25221880	Turkey, pork, and beef sausage, reduced-fat, smoked
25221890	Turkey, pork, and beef sausage, low-fat, smoked
25230520	Ham, luncheon meat, chopped, minced, pressed, spiced, low-fat, not canned
27440150	Chicken or turkey pate with vegetables, diet
27560700	Sausage on biscuit, diet
28110150	Beef with vegetable (diet frozen meal)
28110260	Sirloin tips, potato, vegetable, fruit (diet frozen meal)
28110280	Sirloin enchilada with tomatoes, zucchini and chilies (diet frozen entree)
28110290	Sirloin tips and mushrooms in wine sauce with rotini (diet frozen entree)
28110390	Salisbury steak, potatoes, vegetable, dessert (diet frozen meal)
28110500	Beef, sliced, with gravy, barley and wild rice, vegetables (diet frozen meal)
28110660	Meatballs, Swedish, in gravy, with noodles (diet frozen meal)
28113010	Beef, oriental style, with vegetable, rice (diet frozen meal)
28113040	Beef, oriental style, with vegetable, rice, and fruit dessert (diet frozen meal)
28113050	Salisbury steak with vegetables in tomato-based sauce, noodles (diet frozen meal)
28113110	Salisbury steak, baked, with tomato sauce, vegetable (diet frozen meal)
28113150	Beef steak with rice, vegetable (diet frozen meal)
28113160	Beef steak, with noodles and vegetables in soy-based sauce (diet frozen meal)
28120310	Pork with rice, vegetable, in soy-based sauce (diet frozen meal)
28133210	Veal parmigiana with vegetable (diet frozen meal)
28133220	Veal with peppers in sauce, rice (diet frozen meal)
28133240	Veal with vegetable, potato wedges (diet frozen meal)
28141050	Chicken patty parmigiana, breaded, with vegetable (diet frozen meal)
28141060	Chicken patty with vegetable (diet frozen meal)
28141250	Chicken with rice-vegetable mixture (diet frozen meal)
28141300	Chicken with rice and vegetable, reduced-fat and sodium (diet frozen meal)
28141610	Chicken and vegetables in cream or white sauce (diet frozen meal)
28141620	Chicken cordon bleu with vegetables (diet frozen meal)
28141650	Chicken and vegetables au gratin with rice-vegetable mixture (diet frozen entree)
28142000	Chicken in cream sauce, with brown and wild rice, vegetable, and fruit dessert (diet frozen meal)
28143020	Chicken and vegetable entree with rice, Oriental (diet frozen meal)
28143030	Chicken and vegetable entree, oriental (diet frozen meal)
28143040	Chicken chow mein with rice (diet frozen meal)
28143050	Chicken chow mein with rice, reduced-fat and sodium (diet frozen meal)
28143080	Chicken with noodles and cheese sauce (diet frozen meal)
28143110	Chicken cacciatore with noodles (diet frozen meal)
28143150	Chicken and vegetable entree with noodles (diet frozen meal)
28143180	Chicken in butter sauce with potatoes and vegetable (diet frozen meal)
28143210	Chicken in orange sauce with almond rice (diet frozen meal)
28143220	Chicken in barbecue sauce, with rice, vegetable and dessert, reduced-fat and sodium (diet frozen meal)
28145100	Turkey with dressing, gravy, vegetable and fruit (diet frozen meal)
28145110	Turkey with vegetable, stuffing (diet frozen meal)
28145120	Turkey and vegetables, in sauce (diet frozen meal)
28150210	Haddock with chopped spinach (diet frozen meal)
28150220	Flounder with chopped broccoli (diet frozen meal)
28150230	Turbot with vegetable (diet frozen meal)
28150240	Sole with vegetable (diet frozen meal)
28150350	Cod with vegetable (diet frozen meal)
28150360	Cod in cheese sauce with vegetable (diet frozen meal)
28150370	Flounder in cream sauce with potatoes, carrots (diet frozen meal)

28151030	Shrimp creole with rice, peppers (diet frozen meal)
28153050	Shrimp and noodles in tomato-based sauce, with vegetable and fruit dessert (diet frozen meal)
28154010	Shrimp and vegetables in sauce with noodles (diet frozen meal)
28160660	Stuffed green pepper (diet frozen meal)
28160710	Stuffed cabbage, with meat and tomato sauce (diet frozen meal)
28160810	Livers, chicken, with vegetable (diet frozen meal)
28160910	Vegetable and beef in soy-based sauce, reduced-fat and sodium (diet frozen meal)
28501010	Gravy, beef or meat, fat-free
28501110	Gravy, poultry, fat-free
41430100	Formulated diet meal, powdered, soy protein isolate, with herbs
41430310	Protein diet powder with soy and casein
42202150	Peanut butter, reduced-fat
51119100	Bread, low-fat, 98% fat-free
51119110	Bread, low-fat, 98% fat-free, toasted
51154510	Roll, diet
51161030	Roll, sweet, with fruit, frosted, diet
51161070	Roll, sweet, with fruit, frosted, fat-free
51165100	Coffee cake, yeast type, fat-free, cholesterol free, with fruit
52101150	Biscuit, baking powder or buttermilk type, made from refrigerated dough, low-fat
52302100	Muffin, fruit, fat-free, cholesterol free
52304040	Muffin, bran with fruit, low-fat
52304060	Muffin, bran with fruit, no fat, no cholesterol
53102300	Cake, applesauce, diet, without icing
53104300	Cake, carrot, diet
53104520	Cheesecake, diet
53104570	Cheesecake, diet, with fruit
53104650	Cheesecake, chocolate, reduced-fat
53105500	Cake, chocolate, with icing, diet
53109210	Cake, cupcake, not chocolate, with icing or filling, low-fat, cholesterol free
53109270	Cake, cupcake, chocolate, with or without icing, fruit filling or cream filling, low-fat, cholesterol free
53114150	Cake, lemon, low-fat, NS as to icing
53114200	Cake, lemon, low-fat, without icing
53114250	Cake, lemon, low-fat, with icing
53115500	Cake, pineapple, fat-free, cholesterol free, without icing
53116280	Cake, pound, chocolate, fat-free, cholesterol free
53116380	Cake, pound, fat-free, cholesterol free
53116390	Cake, pound, reduced-fat, cholesterol free
53120400	Cake, white, eggless, low-fat
53123500	Cake, shortcake, with whipped topping and fruit, diet
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
53301750	Pie, apple, diet
53420210	Cream puff, eclair, custard or cream filled, iced, reduced-fat
53511500	Danish pastry, with cheese, fat-free, cholesterol free
53530010	Breakfast tart, low-fat
53540200	Breakfast bar, cereal crust with fruit filling, low-fat
53540250	Breakfast bar, cereal crust with fruit filling, fat-free
53541100	Breakfast bar, diet meal type
53542200	Granola bar, oats, fruit and nuts, low-fat
53610120	Coffee cake, crumb or quick-bread type, reduced-fat, cholesterol free
54102100	Crackers, graham, low-fat
54102110	Crackers, graham, fat-free
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
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
54403060	Popcorn, popped in oil, low-fat, low sodium
54403070	Popcorn, popped in oil, low-fat
54403150	Popcorn, sugar syrup or caramel-coated, fat-free
55211000	Waffle, plain, fat-free
55211050	Waffle, plain, low-fat
57229500	Granola with Raisins, low-fat, Kellogg's
57321500	100 % Natural Wholegrain Cereal with raisins, low-fat, Quaker
58106780	Pizza with meat and vegetables, low-fat, thin crust
58301020	Lasagna with cheese and sauce (diet frozen meal)
58301030	Veal lasagna (diet frozen meal)
58301050	Lasagna with cheese and meat sauce (diet frozen meal)
58301080	Lasagna with cheese and meat sauce, reduced-fat and sodium (diet frozen meal)
58301130	Tuna lasagna (diet frozen meal)
58301150	Zucchini lasagna (diet frozen meal)
58302000	Macaroni and cheese (diet frozen meal)
58302030	Macaroni with veal, cheese, and sauce (diet frozen meal)
58302050	Beef and noodles with meat sauce and cheese (diet frozen meal)
58302060	Spaghetti or noodles with beef in tomato-based sauce, low-fat, reduced sodium (diet frozen meal)
58302080	Noodles with vegetables in tomato-based sauce (diet frozen meal)
58304050	Spaghetti with meat and mushroom sauce (diet frozen meal)
58304060	Spaghetti with meat sauce (diet frozen meal)
58304200	Ravioli, cheese-filled, with tomato sauce (diet frozen meal)
58304220	Rigatoni with meat sauce and cheese (diet frozen meal)

58304250	Manicotti, cheese-filled, with tomato sauce (diet frozen meal)
58304300	Cannelloni, cheese-filled, with tomato sauce (diet frozen meal)
58304350	Linguini with clam sauce (diet frozen meal)
58304400	Linguini with vegetables and seafood in white wine sauce (diet frozen meal)
58305100	Macaroni or noodles, spinach, with chicken and cheese sauce (diet frozen meal)
58305200	Pasta, spinach, with vegetables and cheese sauce (diet frozen meal)
58305250	Pasta with vegetable and cheese sauce (diet frozen meal)
58306100	Chicken enchilada (diet frozen meal)
58306150	Chicken enchilada with salsa, rice, vegetable, and dessert (diet frozen meal)
58306200	Chicken fajitas (diet frozen meal)
58306500	Chicken burritos (diet frozen meal)
58307010	Beef and pork cannelloni (diet frozen meal)
67250050	Apple juice with low-fat yogurt, baby food
67250100	Banana juice with low-fat yogurt, baby food
67250150	Mixed fruit juice with low-fat yogurt, baby food
67250200	Pear-peach juice with low-fat yogurt, baby food
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, all flavors
71202100	White potato, chips, unsalted, reduced-fat
74404060	Spaghetti sauce, fat-free
81101500	Light butter, stick, salted
81101510	Light butter, stick, unsalted
81101520	Light butter, whipped, tub, salted
81104010	Margarine-like spread, reduced calorie, about 40% fat, tub, salted
81104011	Margarine-like spread, reduced calorie, about 40% fat, made with yogurt, tub, salted
81104020	Margarine-like spread, reduced calorie, about 40% fat, stick, salted
81104050	Margarine-like spread, reduced calorie, about 20% fat, tub, salted
81104070	Margarine-like spread, reduced calorie, about 20% fat, tub, unsalted
81104100	Margarine-like spread, fat-free, tub, salted
81104110	Margarine-like spread, fat-free, liquid, salted
81106010	Butter replacement, fat-free powder
83200100	Salad dressing, low-calorie, NFS
83201200	Blue or roquefort cheese dressing, reduced calorie, fat-free, cholesterol-free
83202000	French dressing, low-calorie
83202010	French dressing, reduced calorie, fat-free, cholesterol-free
83203250	Mayonnaise-type salad dressing, fat-free
83204000	Mayonnaise, low-calorie or diet
83204010	Mayonnaise, low-calorie or diet, low sodium
83204020	Mayonnaise, reduced calorie or diet, cholesterol-free
83204050	Mayonnaise-type salad dressing, low-calorie or diet
83204060	Mayonnaise-type salad dressing, low-calorie or diet, cholesterol-free
83205000	Italian dressing, low-calorie
83205500	Italian dressing, reduced calorie, fat-free
83207000	Thousand Island dressing, low-calorie
83207100	Thousand Island dressing, reduced calorie, fat-free, cholesterol-free
83210000	Creamy dressing, made with sour cream and/or buttermilk and oil, diet, NS as to low or reduced calorie
83210050	Creamy dressing made with sour cream and/or buttermilk and oil, low-calorie
83210200	Creamy dressing, made with sour cream and/or buttermilk and oil, reduced calorie, fat-free, cholesterol-free
91304350	Topping, chocolate flavor, fat-free
91351010	Syrup, dietetic

91351020	Topping, dietetic
91405000	Jelly, dietetic, all flavors, sweetened with artificial sweetener
91406000	Jams, preserves, marmalades, dietetic, all flavors, sweetened with artificial sweetener
91510100	Gelatin powder, dietetic, sweetened with low-calorie sweetener, dry
91511010	Gelatin dessert, dietetic, sweetened with low-calorie sweetener
91511020	Gelatin dessert, dietetic, with fruit, sweetened with low-calorie sweetener
91511030	Gelatin dessert, dietetic, with whipped topping, sweetened with low-calorie sweetener
91511050	Gelatin dessert, dietetic, with cream cheese, sweetened with low-calorie sweetener
91511060	Gelatin dessert, dietetic, with sour cream, sweetened with low-calorie sweetener
91511070	Gelatin dessert, dietetic, with fruit and sour cream, sweetened with low-calorie sweetener
91511080	Gelatin dessert, dietetic, with fruit and cream cheese, sweetened with low-calorie sweetener
91511090	Gelatin dessert, dietetic, with fruit and vegetable(s), sweetened with low-calorie sweetener
91511100	Gelatin salad, dietetic, with vegetables, sweetened with low-calorie sweetener
91511110	Gelatin dessert, dietetic, with fruit and whipped topping, sweetened with low-calorie sweetener
91770000	Dietetic or low-calorie candy, NFS
91770010	Dietetic or low-calorie gumdrops
91770020	Dietetic or low-calorie hard candy
91770030	Dietetic or low-calorie candy, chocolate covered
91770050	Dietetic or low-calorie mints
92520910	Lemonade, low-calorie
92741000	Fruit-flavored drink, non-carbonated, made from low-calorie powdered mix
92802000	Wine, light, nonalcoholic
92900200	Fruit-flavored beverage, dry concentrate, low-calorie, not reconstituted
93102000	Beer, lite
93403000	Wine, light

ATTACHMENT V TO APPENDIX B

ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM ALL PERMITTED AND PROPOSED FOOD-USES (NHANES 2003-2004, 2005-2006)

ESTIMATED DAILY INTAKE OF OLESTRA BY THE U.S. POPULATION FROM ALL PERMITTED AND PROPOSED FOOD-USES (NHANES 2003-2004, 2005-2006)

The CSFII survey data was employed to assess the intake of Olestra from all proposed food uses. Since the original undertaking of this intake assessment, two cycles of the National Health and Nutrition Examination Survey (NHANES) have been released. An update to the original intake assessment was conducted with this data set to ensure that changing patterns of consumption would not have significantly altered the estimated intakes derived with the CSFII data. The same proposed food uses were employed for the NHANES assessment as with the CSFII assessment. A complete list of the food codes employed in this assessment is presented in the Addendum to this report.

As previously described, the manner in which age was described in the CSFII dataset required the infant population group to be divide into infants 0 to 6 months of age and 7 to 11 months of age. While the NHANES data provides the age in months for all individuals in the survey, to ensure that the population groups remained consistent the same age limitations were employed in the NHANES assessment as were established for the CSFII assessment. This same philosophy applies to the limitation of the food source and the selection of the food codes. To ensure that the estimates for the intake of Olestra were as conservative as possible, in any instance in which uncertainty existed as to whether a food code or food source should be included in the assessment, it was included. For example, all food codes with an unknown food source were included in the assessment.

1.0 FOOD CONSUMPTION SURVEY DATA

1.1 NHANES Survey Description

National Health and Nutrition Examination Surveys (NHANES) for the years 2003-2004 and 2005-2006 are available for public use. NHANES are conducted as a continuous, annual survey, and are released in 2-year cycles. Each year about 7,000 people from 15 different locations across the U.S. are interviewed, and approximately 5,000 complete the health examination component of the survey. Any combination of consecutive years of data collection is a nationally representative sample of the U.S. population. 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 NHANES 2003-2004, 2005-2006 survey, these data were used to generate estimates for the current intake analysis.

NHANES 2003-2004, 2005-2006 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. Day 1 data were collected in-person, and Day 2 data were collected by telephone in the following 3 to 10 days, on different days of the week, to achieve the desired degree of statistical independence. The data were collected by first selecting Primary Sampling Units (PSUs), which were counties throughout the U.S, of which 15 PSUs are visited per year. Small counties were combined to attain a minimum population size. These PSUs were segmented and households were chosen within each segment. One or more participants within a household were interviewed. For NHANES 2003-2004 12,761 individuals were selected for the sample, 10,122 were interviewed (79.3%), and 9,643 were sampled (75.6%). For NHANES 2005-2006 12,862 individuals were selected for the sample, 10,348 were interviewed (80.4%), and 9,950 were sampled (77.4%).

In addition to collecting information on the types and quantities of foods being consumed, NHANES 2003-2004 and 2005-2006 collected socioeconomic, physiological and demographic information from individual participants in the survey, such as sex, age, 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. Sample weights were incorporated with NHANES 2003-2004 and 2005-2006 data 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 (CDC, 2006; USDA, 2009).

1.2 Statistical Methods

Consumption data from individual dietary records, detailing food items ingested by each survey participant, 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 NHANES 2005-2006 data; these average amounts comprised the distribution from which mean and percentile intake estimates were produced. Mean and percentile estimates were generated incorporating 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 potentially consumed food products containing Olestra, and therefore includes “zero” consumers (those who reported no intake of food products containing Olestra during the 2 survey days). All-user intake refers to the estimated intake of Olestra by those individuals potentially 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.

1.3 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% or the sample size is less than 30 respondents. These values were not considered when assessing the relative contribution of specific food-uses to total Olestra consumption and are marked with an asterisk.

2.0 DAILY INTAKE OF OLESTRA FROM ALL PERMITTED AND PROPOSED FOOD-USES (NHANES 2003-2004, 2005-2006 DATA)

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 2-1 and 2-2 on an absolute (g/day) and a per kilogram body weight (mg/kg body weight/day) basis, respectively. Approximately 87.5% of the total U.S. population was identified as potential consumers of Olestra from the proposed food-uses (14,596 actual users identified). Consumption of these types of foods by the total U.S. population resulted in estimated mean all-person and all-user intakes of Olestra of 4.6 g/person/day (79 mg/kg body weight/day) and 11.3 g/person/day (187 mg/kg body weight/day), respectively. The 90th percentile all-person and all-user intakes of Olestra from all proposed food-uses by the total population were 5.2 g/person/day (87 mg/kg body weight/day) and 11.9 g/person/day (200 mg/kg body weight/day), respectively.

Table 2-1 Estimated Daily Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (NHANES 2003-2004, 2005-2006 Data)

Population Group	% Users	Actual # of Total Users	All-Person Consumption (g)		All-Users Consumption (g)	
			Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 Months	15.6	112	0.1	0.2	0.8	1.8
7 to 11 Months	60.5	89	0.5	1.4	0.8	1.8
Toddlers and Children						
1 to 3 Years	89.7	1,214	2.3	5.2	2.5	5.4
4 to 8 Years	93.4	1,429	3.9	9.4	4.2	9.4
9 to 13 Years	92.1	1,757	5.2	12.0	5.5	12.3
Female Teenagers and Adults						
14 to 18 Years	88.0	1,097	4.7	11.2	5.2	11.5
19 to 30 Years	89.5	1,087	4.2	10.1	4.7	11.0
31 to 50 Years	90.6	1,285	4.4	10.0	4.8	10.9
51 to 70 Years	92.7	1,098	4.2	10.5	4.6	10.9
71 and older	93.8	656	3.8	9.4	4.1	9.5
Male Teenagers and Adults						
14 to 18 Years	87.9	1,064	6.2	15.4	7.0	16.2
19 to 30 Years	85.9	794	5.1	14.3	6.0	16.0
31 to 50 Years	91.0	1,178	5.4	13.0	5.9	13.7
51 to 70 Years	93.9	1,045	5.9	14.0	6.4	14.5
71 and older	95.6	691	5.3	12.1	5.7	12.5
Total Population						
Total Population	87.5	14,596	4.6	11.3	5.2	11.9

Within the individual population groups, the largest percentage of identified users was observed to occur in male adults aged 71 years and older with 95.6% of this population group identified as potential consumers of Olestra. As expected, the lowest percentage of identified users was observed to occur in infants at 15.6%. On an individual population basis, the greatest mean all-person and all-user intakes of Olestra on an absolute basis were observed to occur in male teenagers aged 14 to 18 years at 6.2 g/person/day (91 mg/kg body weight/day) and 7.0 g/person/day (102 mg/kg body weight/day), respectively. Infants aged 0 to 6 months and 7 to 11 months were observed to consume the least Olestra on an absolute basis with mean all-person intakes of 0.1 g/person/day and mean all-user intakes of 0.8 g/person/day, respectively. On a body weight basis, the mean all-person intake of Olestra was highest in toddlers and children aged 1 to 3 years and 4 to 8 years, both with values of 167 mg/kg body weight/day. The mean all-user intake of Olestra was observed to be greatest in toddlers and children aged 1 to 3 years at 181 mg/kg body weight/day. The lowest all-person mean intake on a per kilogram body weight basis was observed to occur in infants aged 0 to 6 months, with a value of 11 mg/kg

body weight/day, while the lowest all-user mean intake was observed to occur in female adults aged 71 and older, with a value of 62 mg/kg body weight/day.

Table 2-2 Estimated Daily per Kilogram Body Weight Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (NHANES 2003-2004, 2005-2006 Data)

Population Group	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)		All-Users Consumption (mg/kg)	
			Mean	90th Percentile	Mean	90th Percentile
Infants						
0 to 6 Months	15.6	112	11	15	91	169
7 to 11 Months	60.5	89	56	143	88	193
Toddlers and Children						
1 to 3 Years	89.7	1,214	167	384	181	395
4 to 8 Years	93.4	1,429	167	393	179	396
9 to 13 Years	92.1	1,757	122	285	130	290
Female Teenagers and Adults						
14 to 18 Years	88.0	1,097	78	196	86	204
19 to 30 Years	89.5	1,087	61	149	69	153
31 to 50 Years	90.6	1,285	61	132	67	136
51 to 70 Years	92.7	1,098	58	136	64	141
71 and older	93.8	656	58	138	62	141
Male Teenagers and Adults						
14 to 18 Years	87.9	1,064	91	228	102	245
19 to 30 Years	85.9	794	62	172	73	179
31 to 50 Years	91.0	1,178	62	149	68	158
51 to 70 Years	93.9	1,045	68	154	73	160
71 and older	95.6	691	67	149	71	154
Total Population						
Total Population	87.5	14,596	79	187	87	200

When heavy consumers (90th percentile) were assessed, the all-person and all-user intakes of Olestra from all proposed food-uses also were determined to be greatest in male teenagers aged 14 to 18 years at 15.4 and 16.2 g/person/day, respectively. The lowest 90th percentile all-person and all-user intakes were observed to occur in infants aged 0 to 6 months at 0.2 and 1.8 g/person/day, respectively, on an absolute basis. On a body weight basis, children aged 4 to 8 years were determined to have the greatest all-person and all-user 90th percentile intakes of Olestra with values of 393 and 396 mg/kg body weight/day, respectively. The lowest estimate for the 90th percentile all-person intake of Olestra on a body weight basis was observed to occur in infants aged 0 to 6 months with an intake of 15 mg/kg body weight/day. The lowest 90th percentile all-user intake was observed to occur in female adults at 136 mg/kg body weight/day.

3.0 COMPARISON OF CSFII AND NHANES RESULTS

Direct comparisons of the results for the estimated number of consumers and their intakes in each population group are presented in Table 3-1 and 3-2 on an absolute and per kilogram body weight basis, respectively. As previously mentioned, the same set of conditions was applied to the NHANES intake assessment as to the previously conducted CSFII assessment to ensure that the result encompassed a worst case scenario. After comparing the intake estimates derived from the NHANES data to those derived from the CSFII it was concluded that the rates of consumption are similar between the two surveys while levels of intake increased. Within the infant population groups, the intake of Olestra remained relatively constant between the two surveys which would be expected as the Olestra is not intended for use in infant foods or formula.

Table 3-1 Comparison of the Estimated Daily Intake of Olestra from All Proposed Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII *vs.* 2003-2004, 2005-2006 NHANES Data)

age	% Users		All-User Consumption (g/day)			
			Mean		90th Percentile	
	CSFII	NHANES	CSFII	NHANES	CSFII	NHANES
Infants						
0 to 6 Months	14.2	15.6	1.0	0.84	2.1	1.75
7 to 11 Months	28.6	60.5	0.7	0.82	1.6	1.76
Toddlers and Children						
1 to 3 Years	89.2	89.7	2.5	2.46	5.7	5.44
4 to 8 Years	93.2	93.4	3.9	4.22	8.5	9.38
9 to 13 Years	92.1	92.1	4.7	5.53	10.0	12.26
Female Teenagers and Adults						
14 to 18 Years	85.7	88.0	4.3	5.16	9.6	11.45
19 to 30 Years	83.5	89.5	4.1	4.68	10.0	10.99
31 to 50 Years	89.5	90.6	4.4	4.81	10.4	10.87
51 to 70 Years	90.2	92.7	4.1	4.59	9.3	10.85
71 and older	90.6	93.8	3.9	4.10	8.8	9.45
Male Teenagers and Adults						
14 to 18 Years	89.4	87.9	6.2	6.97	13.4	16.15
19 to 30 Years	83.9	85.9	5.3	5.95	12.2	15.95
31 to 50 Years	89.2	91.0	5.7	5.90	13.7	13.67
51 to 70 Years	90.4	93.9	5.2	6.38	11.6	14.53
71 and older	91.2	95.6	5.0	5.67	11.3	12.54
Total Population						
Total Population	85.2	87.5	4.6	5.15	10.6	11.87

This increase in the estimate of the intake of Olestra resulting from the NHANES survey data was most notable in male teenagers and adults, where the 90th percentile all-user intakes increased by 1.2 to 3.8 g/person/day. Within the total population the mean and 90th percentile all-user estimates for the intake of Olestra increased from 4.6 and 10.6 g/person/day, respectively, to 5.2 and 11.9 g/person/day, respectively. Only one food category was identified in which employing the NHANES survey data was observed to significantly alter the number of potential consumers identified, and this occurred in infants aged 7 to 11 months. In this population group, 107 infants representing 28.6% of the surveyed population were identified as potential consumer of Olestra using the CSFII data, which included the supplemental children's survey conducted in 1998. Within the NHANES survey data, 89 infants between the ages of 7 and 11 months were identified as potential consumers of Olestra, accounting for 60.5% of this population group.

Table 3-2 Comparison of the Estimated Daily Per Kilogram Body Weight Daily Intake of Olestra From All Proposed Food Uses in the U.S. by Population Group (1994-1996, 1998 USDA CSFII *vs.* 2003-2004, 2005-2006 NHANES Data)

Population Group	% Users		All-User Consumption (mg/kg/day)			
			Mean		90th Percentile	
	CSFII	NHANES	CSFII	NHANES	CSFII	NHANES
Infants						
0 to 6 months	14.2	15.6	96	91	194	169
7 to 12 months	28.6	60.5	76	88	162	193
Toddlers and Children						
1 to 3 Years	89.2	89.7	178	181	400	395
4 to 8 Years	93.2	93.4	175	179	365	396
9t o 13 Years	92.1	92.1	118	130	254	290
Female Teenagers and Adults						
14 to 18 Years	85.7	88.0	75	86	167	204
19 to 30 Years	83.5	89.5	66	69	159	153
31 to 50 Years	89.5	90.6	68	67	156	136
51 to 70 Years	90.2	92.7	60	64	137	141
71 and older	90.6	93.8	62	62	141	141
Male Teenagers and Adults						
14 to 18 Years	89.4	87.9	94	102	214	245
19 to 30 Years	83.9	85.9	69	73	153	179
31 to 50 Years	89.2	91.0	68	68	161	158
51 to 70 Years	90.4	93.9	63	73	138	160
71 and older	91.2	95.6	66	71	152	154
Total Population						
Total Population	85.2	87.5	85	87	195	200

4.0 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 permitted and proposed food-use by the total U.S. population according t0 the NHANES 2003-2004 and 2005-2006 data were estimated to be 5.2 g/person/day (87 mg/kg body weight/day) and 11.9 g/person/day (200 mg/kg body weight/day), respectively. These intake estimates are higher than the estimated mean and 90th percentile intakes of olestra by the total population from the CSFII data, 4.6 g/person/day (85 mg/kg body weight/day) and 10.6 g/person/day (195 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 aged 14 to 18 years, 7.0 g/person/day (102 mg/kg body weight/day), while the highest 90th percentile all-user intake occurred in male adults, 16.2 g/person/day (245 mg/kg body weight/day).

5.0 REFERENCES

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ADDENDUM TO ATTACHMENT V

Representative NHANES 2003-2004, 2005-2006 Food Codes for All Permitted and Proposed Food-Uses of Olestra in the United States

Representative NAHNES 2003-2004, 2005-2006 Food Codes for All Permitted and Proposed Food-Uses of Olestra in the United States

PERMITTED USES

Baked Goods and Baking Mixes

Pre-packaged Ready-to-Eat Cookies
(Reduced-fat, low-fat, and fat-free cookie codes were used as products containing Olestra will be marketed as such)

100% of total fat may be replaced with Olestra
[Olestra] = 7.3 to 30.6%

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
53260030	Cookie, dietetic, chocolate chip
53260150	Cookie, lemon wafer, lowfat
53260200	Cookie, dietetic, oatmeal with raisins
53260300	Cookie, dietetic, sandwich type
53260400	Cookie, dietetic, sugar or plain
54102100	Crackers, graham, lowfat
54102110	Crackers, graham, fat free

Snack Foods

Pre-packaged Ready-to-Heat Unpopped Popcorn
100% of total fat may be replaced with Olestra
[Olestra] = 26.2%

54403010	Popcorn, air-popped (no butter or no oil added)
54403060	Popcorn, popped in oil, lowfat, low sodium
54403070	Popcorn, popped in oil, lowfat

Pre-packaged Ready-to-Eat Savory Snacks
(Reduced-fat, low-fat, and fat-free savory snack codes were used as products containing Olestra will be marketed as such)

100% of total fat may be replaced with Olestra
[Olestra] = 1.3 to 38.4%

54202050	Crackers, saltine, fat free, low sodium
54205100	Cracker, snack, lowfat, 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	Crispbread, rye, no added fat
54328110	Cracker, sandwich-type, peanut butter filled, reduced 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, lowfat, baked without fat
54401170	Salty snacks, corn or cornmeal base, tortilla chips, lowfat, baked without fat, unsalted
54401210	Salty snacks, corn based puffs and twists, cheese puffs and twists, lowfat
54408010	Pretzels, hard
54408030	Pretzel, hard, unsalted
54408040	Pretzels, soft, 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
71202100	White potato, chips, unsalted, reduced fat

PROPOSED USES

Baked Goods and Baking Mixes

Pre-packaged Ready-to-Eat and Ready-to-Heat Bagels
75% of shortening is replaced with Olestra; shortening content of 1.2 to 1.5%
[Olestra] = 1.13%

51180010	Bagel
51180020	Bagel, toasted
51180030	Bagel, with raisins
51180080	Bagel, with fruit other than raisins
51208100	Bagel, whole wheat, 100%, with raisins
51301700	Bagel, wheat
51301750	Bagel, whole wheat, other than 100% or NS as to 100%
51301800	Bagel, wheat, with raisins
51301820	Bagel, wheat, with fruit and nuts
51301900	Bagel, wheat bran
51404500	Bagel, pumpernickel
51501080	Bagel, oat bran
51630000	Bagel, multigrain
51630100	Bagel, multigrain, with raisins

Pre-packaged Ready-to-Eat and Ready-to-Heat Biscuits & English Muffins
75% of shortening is replaced with Olestra; shortening content of 1.1 to 14.1%
[Olestra] = 0.80 to 10.6%

51186010	Muffin, English
51186020	Muffin, English, toasted
51186100	Muffin, English, with raisins
51302500	Muffin, English, wheat bran
51302520	Muffin, English, wheat bran, with raisins
51303010	Muffin, English, wheat or cracked wheat

51303030	Muffin, English, whole wheat, other than 100% or NS as to 100%
51303050	Muffin, English, wheat or cracked wheat, with raisins
51303070	Muffin, English, whole wheat, other than 100% or NS as to 100%, with raisins
51404550	Muffin, English, pumpernickel
51503000	Muffin, English, oat bran
51630200	Muffin, English, multigrain
52101030	Biscuit dough, fried
52101040	Crumpet
52103000	Biscuit, baking powder or buttermilk type, commercially baked
52104040	Biscuit, whole wheat
52104100	Biscuit, cheese
52104200	Biscuit, cinnamon-raisin
52105100	Scone
52105200	Scone, with fruit

Mixtures containing pre-packaged ready-to-eat and ready-to-heat biscuits & English muffins
75% of shortening in the biscuit or English muffin portion is replaced with Olestra; shortening content of 1.2 to 10.0%
(Adjusted for biscuit & English muffin content of 68.0 to 95.0%)
[Olestra] = 5.10 to 6.69%

27515080	Steak sandwich, plain, on biscuit
27520250	Ham on biscuit
27540180	Chicken patty sandwich or biscuit
27560650	Sausage on biscuit
32202020	Egg, cheese, and ham on biscuit
32202025	Egg, cheese and ham on bagel
32202060	Egg and sausage on biscuit
32202110	Egg and ham on biscuit
32202120	Egg, cheese and sausage on bagel

Mixtures containing pre-packaged ready-to-eat and ready-to-heat biscuits & English muffins
75% of shortening in the biscuit or English muffin portion is replaced with Olestra; shortening content of 1.2 to 10.0%
(Adjusted for biscuit & English muffin content of 16.7 to 57.0%)
[Olestra] = 0.14 to 4.28%

27560660	Sausage griddle cake sandwich
27560670	Sausage and cheese on English muffin
32101500	Egg, Benedict
32202010	Egg, cheese, and ham on English muffin
32202030	Egg, cheese, and sausage on English muffin
32202040	Egg, cheese, and beef on English Muffin
32202045	Egg, cheese, and steak on bagel
32202050	Egg, cheese, and sausage on biscuit
32202055	Egg, cheese, and sausage griddle cake sandwich
32202070	Egg, cheese, and bacon on biscuit
32202075	Egg, cheese, and bacon griddle cake sandwich
32202080	Egg, cheese, and bacon on English muffin
32202085	Egg, cheese and bacon on bagel
32202130	Egg and steak on biscuit
32202200	Egg and cheese on biscuit
58128000	Biscuit with gravy

Pre-packaged Ready-to-Eat and Ready-to-Heat Bread
75% of shortening is replaced with Olestra; shortening content of 0.8 to 4.4%

[Olestra] = 0.60 to 3.27%

51101010	Bread, white, toasted
51102010	Bread, white with whole wheat swirl
51102020	Bread, white with whole wheat swirl, toasted
51105010	Bread, Cuban
51105040	Bread, Cuban, toasted
51107010	Bread, French or Vienna
51107040	Bread, French or Vienna, toasted
51108010	Focaccia, Italian flatbread, plain
51108100	Naan, Indian flatbread
51109010	Bread, Italian, Grecian, Armenian
51109040	Bread, Italian, Grecian, Armenian, toasted
51109100	Bread, pita
51109110	Bread, pita, toasted
51111010	Bread, cheese
51111040	Bread, cheese, toasted
51113010	Bread, cinnamon
51113100	Bread, cinnamon, toasted
51119010	Bread, egg, Challah
51119040	Bread, egg, Challah, toasted
51121110	Bread, onion
51122000	Bread, reduced calorie and/or high fiber, white or NFS
51122010	Bread, reduced calorie and/or high fiber, white or NFS, toasted
51122050	Bread, reduced calorie and/or high fiber, Italian
51122100	Bread, reduced calorie and/or high fiber, white or NFS, with fruit and/or nuts
51122300	Bread, white, special formula, added fiber
51123010	Bread, high protein
51127010	Bread, potato
51127020	Bread, potato, toasted
51129010	Bread, raisin
51129020	Bread, raisin, toasted
51133010	Bread, sour dough
51133020	Bread, sour dough, toasted
51134000	Bread, sweetpotato
51135000	Bread, vegetable
51201120	Bread, whole wheat, 100%, with raisins, toasted
51201150	Bread, pita, whole wheat, 100%
51207010	Bread, sprouted wheat
51207020	Bread, sprouted wheat, toasted
51300050	Bread, whole grain white
51300110	Bread, whole wheat, other than 100% or NS as to 100%
51300120	Bread, whole wheat, other than 100% or NS as to 100%, toasted
51300210	Bread, whole wheat, NS as to 100%, with raisins
51300220	Bread, whole wheat, NS as to 100%, with raisins, toasted
51301120	Bread, wheat or cracked wheat, with raisins
51301600	Bread, pita, whole wheat, other than 100% or NS as to 100%
51301620	Bread, pita, wheat or cracked wheat
51302020	Bread, wheat bran, toasted
51302050	Bread, wheat bran, with raisins
51302060	Bread, wheat bran, with raisins, toasted
51401010	Bread, rye
51401020	Bread, rye, toasted
51401030	Bread, marble rye and pumpernickel
51401040	Bread, marble rye and pumpernickel, toasted
51404010	Bread, pumpernickel

51404020	Bread, pumpernickel, toasted
51407010	Bread, black
51501010	Bread, oatmeal
51501020	Bread, oatmeal, toasted
51501040	Bread, oat bran
51501050	Bread, oat bran, toasted
51805010	Bread, sunflower meal
51805020	Bread, sunflower meal, toasted
51806010	Bread, rice
51807000	Injera (American-style Ethiopian bread)

Pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening is replaced with Olestra; shortening content of 4.5 to 14.3%
(Adjusted for bread content of 71.9 to 98.4%)
[Olestra] = 3.23 to 9.27%

51000100	Bread, NS as to major flour
51000110	Toast, NS as to major flour
51101000	Bread, white
51121010	Bread, garlic
51121040	Bread, garlic, toasted
51201010	Bread, whole wheat, 100%
51201020	Bread, whole wheat, 100%, toasted
51301010	Bread, wheat or cracked wheat
51301020	Bread, wheat or cracked wheat, toasted
51301510	Bread, wheat or cracked wheat, reduced calorie and/or high fiber
51301520	Bread, wheat or cracked wheat, reduced calorie and/or high fiber, toasted

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 45.2 to 68.4%)
[Olestra] = 1.36 to 2.05%

14640100	Cheese sandwich, grilled
27500050	Sandwich, NFS
27520300	Ham sandwich, with spread
27540110	Chicken sandwich, with spread
27540170	Chicken patty sandwich, miniature, with spread
27560110	Bologna sandwich, with spread
27560510	Salami sandwich, with spread
27560710	Sausage sandwich
42302010	Peanut butter and jelly sandwich
51804020	Bread, soy, toasted
55301000	French toast, plain

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 30.1 to 44.8%)
[Olestra] = 0.90 to 1.34%

27347230	Chicken or turkey, stuffing, and vegetables (excluding carrots, broccoli, and dark-green leafy), gra
27500200	Wrap sandwich, filled with meat, poultry, or fish, vegetables, and cheese
27500300	Wrap sandwich, filled with meat, poultry, or fish, and vegetables
27511010	Pastrami sandwich
27513010	Roast beef sandwich
27513050	Roast beef sandwich with cheese
27520130	Bacon, chicken, and tomato club sandwich, with lettuce and spread
27520150	Bacon, lettuce, and tomato sandwich with spread
27520310	Ham sandwich with lettuce and spread
27520320	Ham and cheese sandwich, with lettuce and spread
27520330	Ham and egg sandwich
27540120	Chicken salad or chicken spread sandwich
27540130	Chicken barbecue sandwich
27540140	Chicken fillet (breaded, fried) sandwich
27540310	Turkey sandwich, with spread
27550720	Tuna salad sandwich
51601010	Bread, multigrain, toasted
51601020	Bread, multigrain
51601210	Bread, multigrain, with raisins
51601220	Bread, multigrain, with raisins, toasted
51602010	Bread, multigrain, reduced calorie and/or high fiber
58128220	Dressing with chicken or turkey and vegetables
58128250	Dressing with meat and vegetables

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 6.7 to 29.7%)
[Olestra] = 0.27 to 0.89%

13210110	Pudding, bread
13210180	Pudding, Mexican bread (Capirotada)
27246500	Meat loaf made with chicken or turkey
27510950	Reuben sandwich (corned beef sandwich with sauerkraut and cheese), with spread
27516010	Gyro sandwich (pita bread, beef, lamb, onion, condiments), with tomato and spread
27540200	Fajita-style chicken sandwich with cheese, on pita bread, with lettuce and tomato
28110380	Salisbury steak with gravy, macaroni and cheese (frozen meal)
51126010	Bread, milk and honey
51126020	Bread, milk and honey, toasted
53415100	Crisp, apple, apple dessert
58128210	Dressing with oysters
72125260	Spinach and cheese casserole

Mixtures containing pre-packaged ready-to-eat and ready-to-heat bread
75% of shortening in the bread portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for bread content of 0.19 to 10.7%)
[Olestra] = 0.006 to 0.32%

23205010	Veal cutlet or steak, fried, NS as to fat eaten
27150020	Crab, deviled
27214100	Meat loaf made with beef
27214110	Meat loaf made with beef, with tomato-based sauce
27235000	Meat loaf made with venison / deer
27250250	Flounder with crab stuffing
27260010	Meat loaf, NS as to type of meat
27260080	Meat loaf made with beef and pork

27260090	Meat loaf made with beef, veal and pork
27260100	Meat loaf made with beef and pork, with tomato-based sauce
27260510	Liver dumpling
28145100	Turkey with dressing, gravy, vegetable and fruit (diet frozen meal)
28160310	Meat loaf in tomato sauce with potatoes, vegetable (frozen meal)
32301100	Garlic egg soup, Puerto Rican style (Sopa de ajo)
58131110	Ravioli, NS as to filling, with tomato sauce
58131310	Ravioli, meat-filled, no sauce
58131320	Ravioli, meat-filled, with tomato sauce or meat sauce
58131610	Ravioli, cheese and spinach filled, with tomato sauce
58162090	Stuffed pepper, with meat
58162120	Stuffed pepper, with rice, meatless
72116140	Caesar salad (with romaine)

Pre-packaged Ready-to-Eat and Ready-to-Heat Bread Sticks (Hard)
75% of shortening is replaced with Olestra; shortening content of 3.0%
[Olestra] = 2.25%

51184000	Bread sticks, hard
51184100	Bread stick, hard, low sodium
51306000	Bread stick, hard, whole wheat, NS as to 100%

Pre-packaged Ready-to-Eat and Ready-to-Heat Bread Sticks (Soft)
75% of shortening is replaced with Olestra; shortening content of 5.0 to 8.7%
[Olestra] = 3.75 to 6.52%

51184010	Bread stick, soft
51184020	Bread stick, NS as to hard or soft
51184030	Bread stick, soft, prepared with garlic and parmesan cheese

Pre-packaged Ready-to-Eat and Ready-to-Heat Cakes
Cakes without icing
75% of shortening is replaced with Olestra; shortening content of 0.4 to 24.0%
[Olestra] = 0.29 to 17.98%

51165000	Coffee cake, yeast type
51165100	Coffee cake, yeast type, fat free, cholesterol free, with fruit
53102000	Cake, applesauce, NS as to icing
53102100	Cake, applesauce, without icing
53102300	Cake, applesauce, diet, without icing
53102600	Cake, banana, without icing
53102800	Cake, black forest (chocolate-cherry)
53103000	Cake, Boston cream pie
53104100	Cake, carrot, without icing
53104300	Cake, carrot, diet
53104500	Cheesecake
53104520	Cheesecake, diet
53104550	Cheesecake with fruit
53104570	Cheesecake, diet, with fruit
53104600	Cheesecake, chocolate
53106500	Cake, cream, without icing or topping
53107000	Cake, cupcake, NS as to type or icing
53109300	Cake, Dobos Torte (non-chocolate layer cake with chocolate filling and icing)
53110000	Cake, fruit cake, light or dark, holiday type cake
53112000	Cake, ice cream and cake roll, chocolate
53112100	Cake, ice cream and cake roll, not chocolate

53113000	Cake, jelly roll
53115400	Cake, oatmeal, without icing
53115600	Cake, poppyseed, without icing
53116000	Cake, pound, without icing
53116270	Cake, pound, chocolate
53116390	Cake, pound, reduced fat, cholesterol free
53116500	Cake, pumpkin, without icing
53118100	Cake, sponge, without icing
53118300	Cake, sponge, chocolate, without icing
53118410	Cake, rum flavored, without icing (Sopa Borracha)
53118500	Cake, torte
53118550	Cake, tres leche
53119000	Cake, upside down (all fruits)
53120500	Cake, whole wheat, with fruit and nuts, without icing
53122070	Cake, shortcake, biscuit type, with whipped cream and fruit
53122080	Cake, shortcake, biscuit type, with fruit
53123070	Cake, shortcake, sponge type, with whipped cream and fruit
53123080	Cake, shortcake, sponge type, with fruit
53123500	Cake, shortcake, with whipped topping and fruit, diet
53124110	Cake, zucchini, without icing

Pre-packaged ready-to-eat and ready-to-heat cakes, with icing
75% of shortening in the cake portion is replaced with Olestra; shortening content of 1.0 to 16.0%
(Adjusted for cake content of 63.0 to 70.0%)
[Olestra] = 0.006 to 0.32%

53100100	Cake, NS as to type, with or without icing
53102200	Cake, applesauce, with icing
53102700	Cake, banana, with icing
53104260	Cake, carrot, with icing
53104400	Cake, coconut, with icing
53105500	Cake, chocolate, with icing, diet
53107200	Cake, cupcake, NS as to type, with icing
53108100	Cake, cupcake, chocolate, without icing or filling
53108200	Cake, cupcake, chocolate, with icing or filling
53109200	Cake, cupcake, not chocolate, with icing or filling
53109210	Cake, cupcake, not chocolate, with icing or filling, lowfat, cholesterol free
53109270	Cake, cupcake, chocolate, with or without icing, fruit filling or cream filling, lowfat, cholesterol
53114250	Cake, lemon, lowfat, with icing
53115410	Cake, oatmeal, with icing
53115450	Cake, peanut butter, with icing
53116020	Cake, pound, with icing
53116510	Cake, pumpkin, with icing
53118200	Cake, sponge, with icing
53118350	Cake, sweetpotato, with icing
53124120	Cake, zucchini, with icing

Pre-packaged Ready-to-Heat Cookies
75% of shortening is replaced with Olestra; shortening content of 25.7%
[Olestra] = 19.31%

53200100	Cookie, batter or dough, raw, not chocolate

Pre-packaged Ready-to-Eat and Ready-to-Heat Cornbread, Corn Muffins, Tortillas and Taco Shells (Hard and Soft)
75% of shortening is replaced with Olestra; shortening content of 2.1 to 6.4%
[Olestra] = 1.7 to 4.8%

52201000	Cornbread, prepared from mix
52204000	Cornbread stuffing
52206010	Cornbread muffin, stick, round
52208750	Gordita/sope shell, plain, no filling, grilled, no fat added
52208760	Gordita/sope shell, plain, no filling, fried in oil
52209010	Hush puppy
52215000	Tortilla, NFS
52215100	Tortilla, corn
52215200	Tortilla, flour (wheat)
52215260	Tortilla, whole wheat
52215300	Taco shell, corn
52215350	Taco shell, flour
52220110	Cornmeal bread, Dominican style (Arepa Dominicana)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5 to 3.75%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 40.6 to 80.1%)
[Olestra] = 0.76 to 3.0%

53452500	Pastry, mainly flour and water, fried
58100100	Burrito with beef, no beans
58100300	Burrito with beans and rice, meatless
58101400	Soft taco with beef, cheese, and lettuce
58101530	Soft taco with beef, cheese, lettuce, tomato and salsa
58101800	Ground beef with tomato sauce and taco seasonings on a cornbread crust
58104710	Quesadilla with cheese, meatless
58104730	Quesadilla with meat and cheese
58104740	Quesadilla with poultry and cheese
58104820	Taquitos with meat
58104830	Taquitos with chicken

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 26.2 to 39.2%)
[Olestra] = 0.49 to 0.73%

58100110	Burrito with beef and beans
58100130	Burrito with beef and cheese, no beans
58100150	Burrito with beef and potato, no beans
58100160	Burrito with beef, beans, rice, and cheese
58100180	Burrito with pork and beans
58100200	Burrito with chicken, no beans
58100210	Burrito with chicken and beans
58100240	Burrito with chicken, NFS
58100245	Burrito with chicken, beans, cheese, and sour cream
58100250	Burrito with chicken, rice, and cheese
58100255	Burrito with chicken, beans, rice, and cheese

58100310	Burrito with beans, meatless
58100320	Burrito with beans and cheese, meatless
58100340	Burrito with eggs, sausage, cheese and vegetables
58100400	Enchilada with beef, no beans
58100560	Enchilada with ham and cheese, no beans
58100600	Enchilada with chicken, tomato-based sauce
58101200	Flauta, NFS
58101300	Taco or tostada with beef, cheese and lettuce
58101350	Soft taco with beef, cheese, lettuce, tomato and sour cream
58101450	Soft taco with chicken, cheese, and lettuce
58101460	Soft taco with chicken, cheese, lettuce, tomato and sour cream
58104450	Chimichanga with beef and tomato
58104530	Chimichanga with chicken and cheese

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 16.3 to 25.8%)
[Olestra] = 0.30 to 0.48%

58100120	Burrito with beef, beans, and cheese
58100140	Burrito with beef, beans, cheese, and sour cream
58100220	Burrito with chicken, beans, and cheese
58100230	Burrito with chicken and cheese
58100330	Burrito with rice, beans, cheese, sour cream, lettuce, tomato and guacamole, meatless
58100350	Burrito with eggs and cheese, no beans
58100520	Enchilada with beef, beans, and cheese
58100530	Enchilada with beef and cheese, no beans
58100610	Enchilada with chicken and beans, tomato-based sauce
58100620	Enchilada with chicken, beans, and cheese, tomato- based sauce
58100630	Enchilada with chicken and cheese, no beans, tomato- based sauce
58100710	Enchilada with beans, meatless
58100720	Enchilada with beans and cheese, meatless
58100800	Enchilada with cheese, meatless, no beans
58101230	Flauta with beef
58101240	Flauta with chicken
58101310	Taco or tostada with beef, lettuce, tomato and salsa
58101320	Taco or tostada with beef, cheese, lettuce, tomato and salsa
58101510	Taco or tostada with chicken or turkey, lettuce, tomato and salsa
58101520	Taco or tostada with chicken, cheese, lettuce, tomato and salsa
58101540	Taco or tostada with fish, lettuce, tomato, salsa
58104280	Chalupa with beef, cheese, lettuce, tomato and sour cream
58104290	Chalupa with beef, cheese, lettuce, tomato and salsa
58104500	Chimichanga with beef, beans, lettuce and tomato
58104510	Chimichanga with beef, cheese, lettuce and tomato
58104520	Chimichanga with beans and cheese, meatless, with lettuce and tomato
58104550	Chimichanga with chicken, sour cream, lettuce and tomato, no cheese
58104600	Chimichanga with beef and rice
58105000	Fajita with chicken and vegetables
58105050	Fajita with beef and vegetables
58306070	Cheese enchilada (frozen meal)

Mixtures containing pre-packaged ready-to-eat and ready-to-heat cornbread, corn muffins, tortillas or taco shells
75% of shortening in the cornbread, corn muffins, tortillas or taco shell portion is replaced with Olestra; shortening content of 2.5%
(Adjusted for cornbread, corn muffin, tortilla or taco shell content of 1.2 to 15.2%)
[Olestra] = 0.02 to 0.29%

32105100	Egg omelet or scrambled egg, with potatoes and/or onions (Tortilla Espanola, traditional style Spani
32105180	Huevos rancheros
58100360	Chilaquiles, tortilla casserole with salsa, cheese, and egg
58100370	Chilaquiles, tortilla casserole with salsa and cheese, no egg
58101710	Taco or tostada with beans, meatless, with lettuce, tomato and salsa
58101720	Taco or tostada with beans and cheese, meatless, with lettuce, tomato and salsa
58101730	Taco or tostada with beans, cheese, meat, lettuce, tomato and salsa
58101930	Taco or tostada salad with beef and cheese, fried flour tortilla
58101940	Taco or tostada salad, meatless, with cheese, fried flour tortilla
58104260	Chalupa with beans, cheese, lettuce and tomato
58104310	Chalupa with beans, chicken, cheese, lettuce and tomato
58104320	Chalupa with chicken, cheese, lettuce, tomato and sour cream
58104340	Chalupa with chicken, cheese, lettuce, tomato and salsa
58306100	Chicken enchilada (diet frozen meal)
58421080	Sopa de tortilla, Mexican style tortilla soup

Pre-packaged Ready-to-Eat and Ready-to-Heat Croissants
75% of shortening is replaced with Olestra; shortening content of 13.3%
[Olestra] = 10.0%

51166000	Croissant

Mixtures containing pre-packaged ready-to-eat and ready-to-heat croissants
75% of shortening in the croissant portion is replaced with Olestra; shortening content of 13.0 to 13.9%
(Adjusted for croissant content of 90.0 to 100%)
[Olestra] = 9.00 to 10.40%

51166100	Croissant, cheese
51166200	Croissant, chocolate
51166500	Croissant, fruit

Mixtures containing pre-packaged ready-to-eat and ready-to-heat croissants
75% of shortening in the croissant portion is replaced with Olestra; shortening content of 13.3 to 15.8%
(Adjusted for croissant content of 31.5 to 55.8%)
[Olestra] = 3.14 to 11.90%

58127210	Croissant sandwich, filled with ham and cheese
58127270	Croissant sandwich with sausage and egg
58127290	Croissant sandwich with bacon and egg
58127310	Croissant sandwich with ham, egg, and cheese
58127330	Croissant sandwich with sausage, egg, and cheese
58127350	Croissant sandwich with bacon, egg, and cheese

Pre-packaged Ready-to-Eat and Ready-to-Heat Crackers (not snack type)
75% of shortening is replaced with Olestra; shortening content of 3.2 to 10.5%
[Olestra] = 2.40 to 7.88%

51187000	Melba toast
54001000	Crackers, NS as to sweet or nonsweet

Pre-packaged Ready-to-Eat and Ready-to-Heat Doughnuts
Doughnuts without icing or coatings
100% of frying oil is replaced with Olestra; frying oil content of 12.0 to 21.6%
[Olestra] = 12.0 to 21.62%

53520000	Doughnut, NS as to cake or yeast
53520110	Doughnut, cake type
53520120	Doughnut, cake type, chocolate
53520140	Doughnut, cake type, chocolate covered
53520600	Cruller, NFS
53520700	French cruller
53521110	Doughnut, raised or yeast
53521120	Doughnut, raised or yeast, chocolate
53521140	Doughnut, jelly
53521210	Doughnut, custard-filled
53521250	Doughnut, wheat

Mixtures containing pre-packaged ready-to-eat and ready-to-heat doughnuts
100% of frying oil is replaced with Olestra; frying oil content of 5.5 to 17.6%
(Adjusted for doughnut content of 59.3 to 95.2%)
[Olestra] = 5.48 to 17.58%

53520150	Doughnut, cake type, chocolate covered, dipped in peanuts
53520160	Doughnut, cake type, chocolate, with chocolate icing
53521100	Doughnut, raised or yeast, chocolate, with chocolate icing
53521130	Doughnut, raised or yeast, chocolate covered
53521220	Doughnut, chocolate cream-filled
53521230	Doughnut, custard-filled, with icing
53521300	Doughnut, wheat, chocolate covered

Pre-packaged Ready-to-Eat and Ready-to-Heat Muffins
75% of shortening is replaced with Olestra; shortening content of 1.8 to 8.6%
[Olestra] = 1.34 to 6.43%

52301000	Muffin, NFS
52302010	Muffin, fruit and/or nuts
52302020	Muffin, fruit and/or nut, low fat
52302100	Muffin, fruit, fat free, cholesterol free
52302500	Muffin, chocolate chip
52302600	Muffin, chocolate
52303010	Muffin, whole wheat
52303500	Muffin, wheat
52304010	Muffin, wheat bran
52304040	Muffin, bran with fruit, lowfat
52304060	Muffin, bran with fruit, no fat, no cholesterol
52304100	Muffin, oatmeal
52304150	Muffin, oat bran
52304200	Muffin, oat bran with fruit and/or nuts
52306010	Muffin, plain

52306300	Muffin, cheese
52306500	Muffin, pumpkin
52306550	Muffin, zucchini
52306700	Muffin, carrot
52308010	Matzo, fritters
52308020	Matzo ball
52311010	Popover

Pre-packaged Ready-to-Eat and Ready-to-Heat Pancakes, Crepes, and French Toast
75% of shortening is replaced with Olestra; shortening content of 0.08 to 7.3%
[Olestra] = 0.06 to 5.48%

55103000	Pancakes, with fruit
55103100	Pancakes, with chocolate chips
55105200	Pancakes, whole wheat
55105300	Pancakes, sour dough
55101010	Pancakes, reduced calorie, high fiber
55101000	Pancakes, plain
55105100	Pancakes, cornmeal
55105000	Pancakes, buckwheat
58310310	Pancakes and sausage (frozen meal)
55301000	French toast, plain
55301050	French toast sticks, plain
55401000	Crepe, plain

Mixtures containing pre-packaged ready-to-eat and ready-to-heat pancakes, crepes or French toast
75% of shortening in the pancakes, crepes or French toast portion is replaced with Olestra; shortening content of 3.9 to 4.9%
(Adjusted for pancake, crepe or French toast content of 29.0 to 58.1%)
[Olestra] = 0.99 to 1.70%

58120120	Crepe, filled with beef, pork, fish and/or poultry, no sauce on top

Pre-packaged Ready-to-Eat and Ready-to-Heat Pastries, Sweet (pastry portion)
75% of shortening is replaced with Olestra; shortening content of 1.3 to 19.2%
[Olestra] = 0.95 to 14.42%

53400200	Blintz, cheese-filled
53400300	Blintz, fruit-filled
53410100	Cobbler, apple
53410300	Cobbler, berry
53410500	Cobbler, cherry
53410800	Cobbler, peach
53410860	Cobbler, pineapple
53410900	Cobbler, rhubarb
53415100	Crisp, apple, apple dessert
53415120	Fritter, apple
53415300	Crisp, blueberry
53415400	Crisp, cherry
53415500	Crisp, peach
53415600	Crisp, rhubarb
53420000	Cream puff, eclair, custard or cream filled, NS as to icing
53420100	Cream puff, eclair, custard or cream filled, not iced
53420200	Cream puff, eclair, custard or cream filled, iced
53420210	Cream puff, eclair, custard or cream filled, iced, reduced fat
53420250	Cream puff, no filling or icing

53420400	Sopaipilla, without syrup or honey
53420410	Sopaipilla with syrup or honey
53430100	Crepe, dessert type, chocolate-filled
53430200	Crepe, dessert type, fruit-filled
53430250	Crepe suzette
53430750	Tamale, sweet, with fruit
53440000	Strudel, apple
53440300	Strudel, berry
53440600	Strudel, cheese
53441110	Baklava
53441210	Basbousa (semolina dessert dish)
53450000	Turnover or dumpling, apple
53450300	Turnover or dumpling, berry
53450500	Turnover or dumpling, cherry
53450800	Turnover or dumpling, lemon
53451000	Turnover or dumpling, peach
53451750	Turnover, pumpkin
53452100	Pastry, fruit-filled
53452200	Pastry, Italian, with cheese
53452400	Pastry, puff
53452420	Pastry, puff, custard or cream filled, iced or not iced
53452450	Cheese pastry puffs
53452500	Pastry, mainly flour and water, fried
53453150	Empanada, Mexican turnover, fruit-filled
53453170	Empanada, Mexican turnover, pumpkin
53500100	Breakfast pastry, NFS
53510000	Danish pastry, plain or spice
53510100	Danish pastry, with fruit
53510200	Danish pastry, with nuts
53511000	Danish pastry, with cheese
53530000	Breakfast tart
53530010	Breakfast tart, lowfat
58124210	Pastry, cheese-filled

Pre-packaged Ready-to-Eat and Ready-to-Heat Pies, Sweet (pastry portion)
75% of shortening is replaced with Olestra; shortening content of 1.3 to 22.8%
[Olestra] = 0.96 to 17.13%

53300100	Pie, NFS
53300170	Pie, individual size or tart, NFS
53301000	Pie, apple, two crust
53301070	Pie, apple, individual size or tart
53301080	Pie, apple, fried pie
53301500	Pie, apple, one crust
53301750	Pie, apple, diet
53302000	Pie, apricot, two crust
53303000	Pie, blackberry, two crust
53303070	Pie, blackberry, individual size or tart
53303500	Pie, berry, not blackberry, blueberry, boysenberry, huckleberry, raspberry, or strawberry; two crust
53303510	Pie, berry, not blackberry, blueberry, boysenberry, huckleberry, raspberry, or strawberry; one crust
53303570	Pie, berry, not blackberry, blueberry, boysenberry, huckleberry, raspberry, or strawberry, individua
53304000	Pie, blueberry, two crust
53304050	Pie, blueberry, one crust

53305000	Pie, cherry, two crust
53305010	Pie, cherry, one crust
53305070	Pie, cherry, individual size or tart
53305700	Pie, lemon (not cream or meringue)
53305720	Pie, lemon (not cream or meringue), individual size or tart
53306000	Pie, mince, two crust
53306070	Pie, mince, individual size or tart
53307000	Pie, peach, two crust
53307050	Pie, peach, one crust
53307080	Pie, peach, fried pie
53308000	Pie, pineapple, two crust
53308070	Pie, pineapple, individual size or tart
53309000	Pie, raisin, two crust
53310000	Pie, raspberry, one crust
53310050	Pie, raspberry, two crust
53311000	Pie, rhubarb, two crust
53311050	Pie, rhubarb, one crust
53312000	Pie, strawberry, one crust
53313000	Pie, strawberry-rhubarb, two crust
53314000	Pie, strawberry, individual size or tart
53340500	Pie, cherry, made with cream cheese and sour cream
53341000	Pie, banana cream
53341500	Pie, buttermilk
53341750	Pie, chess
53342000	Pie, chocolate cream
53342070	Pie, chocolate cream, individual size or tart
53343000	Pie, coconut cream
53343070	Pie, coconut cream, individual size or tart
53344000	Pie, custard
53345000	Pie, lemon cream
53345070	Pie, lemon cream, individual size or tart
53346000	Pie, peanut butter cream
53346500	Pie, pineapple cream
53347000	Pie, pumpkin
53347070	Pie, pumpkin, individual size or tart
53347600	Pie, squash
53348000	Pie, strawberry cream
53360000	Pie, sweetpotato
53365000	Pie, vanilla cream
53366000	Pie, yogurt, frozen
53370000	Pie, chiffon, not chocolate
53381000	Pie, lemon meringue
53382000	Pie, chocolate-marshmallow
53385000	Pie, pecan
53385070	Pie, pecan, individual size or tart
53385500	Pie, oatmeal
53386000	Pie, pudding, flavors other than chocolate
53386250	Pie, pudding, chocolate, with chocolate coating, individual size
53387000	Pie, Toll house chocolate chip
53390000	Pie, shoo-fly
53391000	Pie shell

Pre-packaged Ready-to-Eat and Ready-to-Heat Pies and Pastries, Meat and Vegetable (pastry portion)
75% of shortening is replaced with Olestra; shortening content of 0.31 to 16.4%
[Olestra] = 0.23 to 12.32%

27311510	Shepherd's pie with beef
27317010	Beef pot pie
27320020	Ham pot pie
27330010	Shepherd's pie with lamb
27347100	Chicken or turkey pot pie
27360050	Meat pie, NFS
28143220	Chicken in barbecue sauce, with rice, vegetable and dessert, reduced fat and sodium (diet frozen mea
41812400	Vegetarian pot pie
58116120	Empanada, Mexican turnover, filled with meat and vegetables
58116210	Meat pie, Puerto Rican style (Pastelon de carne)
58121510	Dumpling, meat-filled
58124500	Pastry, filled with potatoes and peas, fried
58125110	Quiche with meat, poultry or fish
58125120	Spinach quiche, meatless
58125180	Cheese quiche, meatless
58126110	Turnover, meat-filled, no gravy
58126130	Turnover, meat- and cheese-filled, no gravy
58126150	Turnover, meat- and cheese-filled, tomato-based sauce
58126170	Turnover, meat-and vegetable- filled (no potatoes, no gravy)
58126180	Turnover, meat-, potato-, and vegetable-filled, no gravy
58126270	Turnover, chicken- or turkey-, and cheese-filled, no gravy
58126280	Turnover, chicken- or turkey-, and vegetable-filled
58126290	Turnover, meat- and cheese-filled, lower in fat
58126300	Turnover, meat- and cheese-filled, tomato-based sauce, lower in fat
58126400	Turnover, filled with egg, meat and cheese
58127110	Vegetables in pastry
77141010	Potato chicken pie, Puerto Rican style (Pastelon de pollo)

Pre-packaged Ready-to-Eat and Ready-to-Heat Rolls
75% of shortening is replaced with Olestra; shortening content of 0.4 to 5.1%
[Olestra] = 0.27 to 3.86%

51000200	Roll, NS as to major flour
51000300	Roll, hard, NS as to major flour
51150000	Roll, white, soft
51150100	Roll, white, soft, toasted
51152000	Roll, white, soft, reduced calorie and/or high fiber
51153000	Roll, white, hard
51153010	Roll, white, hard, toasted
51154550	Roll, egg bread
51154600	Roll, cheese
51155000	Roll, French or Vienna
51155010	Roll, French or Vienna, toasted
51156500	Roll, garlic
51157000	Roll, hoagie, submarine
51158100	Roll, Mexican, bolillo
51159000	Roll, sour dough
51220000	Roll, whole wheat, 100%
51320010	Roll, wheat or cracked wheat
51320020	Rolls, wheat or cracked wheat, toasted

51320500	Roll, whole wheat, NS as to 100%
51420000	Roll, rye
51421000	Roll, pumpernickel
51502010	Roll, oatmeal
51502100	Roll, oat bran
51620000	Roll, multigrain

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 40.6 to 59.3%)
[Olestra] = 1.22 to 1.78%

27510210	Cheeseburger, plain, on bun
27510220	Cheeseburger, with mayonnaise or salad dressing, on bun
27510290	Double cheeseburger (2 patties), plain, on double-decker bun
27510311	Cheeseburger, 1 oz meat, plain, on miniature bun
27510500	Hamburger, plain, on bun
27510510	Hamburger, with tomato and/or catsup, on bun
27510530	Hamburger, 1/4 lb meat, plain, on bun
27510590	Hamburger, with mayonnaise or salad dressing, on bun
27510600	Hamburger, 1 oz meat, plain, on miniature bun
27540190	Chicken patty sandwich, with lettuce and spread
27550000	Fish sandwich, on bun, with spread
27550100	Fish sandwich, on bun, with cheese and spread
27550750	Tuna salad submarine sandwich, on roll, with lettuce
27560320	Frankfurter or hot dog, plain, on bun

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 30.0 to 39.6%)
[Olestra] = 0.90 to 1.19%

27510230	Cheeseburger, with mayonnaise or salad dressing and tomatoes, on bun
27510240	Cheeseburger, 1/4 lb meat, plain, on bun
27510250	Cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing, on bun
27510280	Double cheeseburger (2 patties), with mayonnaise or salad dressing, on bun
27510300	Double cheeseburger (2 patties), with mayonnaise or salad dressing, on double-decker bun
27510310	Cheeseburger with tomato and/or catsup, on bun
27510340	Double cheeseburger (2 patties), with mayonnaise or salad dressing and tomatoes, on bun
27510360	Cheeseburger with mayonnaise or salad dressing, tomato and bacon, on bun
27510410	Chiliburger, on bun
27510440	Bacon cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun
27510450	Cheeseburger, 1/4 lb meat, with ham, on bun
27510520	Hamburger, with mayonnaise or salad dressing and tomatoes, on bun
27510540	Double hamburger (2 patties), with tomato and/or catsup, on bun
27510550	Double hamburger (2 patties), with mayonnaise or salad dressing and tomatoes, on double-decker bun
27510560	Hamburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun
27510620	Hamburger, 1/4 lb meat, with tomato and/or catsup, on bun
27510700	Meatball and spaghetti sauce submarine sandwich, on roll
27513040	Roast beef submarine sandwich, on roll, with lettuce, tomato and spread
27513070	Roast beef submarine sandwich, on roll, au jus
27515010	Steak sandwich, plain, on roll

27515070	Steak and cheese submarine sandwich, with fried peppers and onions, on roll
27520500	Pork, barbecue sauce, onions and dill pickles on white roll
27540150	Chicken fillet (breaded, fried) sandwich with lettuce, tomato and spread
27540235	Chicken fillet, broiled, sandwich with lettuce, tomato, and spread
27540240	Chicken fillet, (broiled), sandwich, on whole wheat roll, with lettuce, tomato and spread
27540250	Chicken fillet, broiled, sandwich with cheese, on whole wheat roll, with lettuce, tomato and non-may
27540260	Chicken fillet, broiled, sandwich, on oat bran bun, with lettuce, tomato, spread
27540270	Chicken fillet, broiled, sandwich, with lettuce, tomato, and non-mayonnaise type spread
27540280	Chicken fillet, broiled, sandwich with cheese, on bun, with lettuce, tomato and spread
27540290	Chicken submarine sandwich, with lettuce, tomato, and spread
27540350	Turkey submarine sandwich, on roll, with cheese, lettuce, tomato and spread
27541000	Turkey, ham, and roast beef club sandwich
27560340	Frankfurter or hot dog, with catsup and/or mustard, on bun

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 21.7 to 28.9%)
[Olestra] = 0.65 to 0.86%

27510110	Beef barbecue or Sloppy Joe, on bun
27510320	Cheeseburger, 1/4 lb meat, with tomato and/or catsup, on bun
27510330	Double cheeseburger (2 patties), with tomato and/or catsup, on bun
27510350	Cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun
27510370	Double cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, on bun
27510390	Double bacon cheeseburger (2 patties, 1/4 lb meat each), on bun
27510680	Double hamburger (2 patties, 1/4 lb meat each), with tomato and/or catsup, on bun
27510690	Double hamburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing and tomatoes and/o
27515020	Steak and cheese submarine sandwich, on roll, with lettuce and tomato
27515040	Steak and cheese submarine sandwich, plain, on roll
27520160	Bacon, chicken, and tomato club sandwich, on multigrain roll with lettuce and spread
27520360	Ham and cheese sandwich, on bun, with lettuce and spread
27520370	Hot ham and cheese sandwich, on bun
27520510	Pork barbecue or Sloppy Joe, on bun
27560370	Frankfurter or hot dog with chili and cheese, on bun
27560910	Submarine, cold cut sandwich, on bun, with lettuce

Mixtures containing pre-packaged ready-to-eat and ready-to-heat rolls
75% of shortening in the roll portion is replaced with Olestra; shortening content of 4.0%
(Adjusted for roll content of 14.9 to 19.6%)
[Olestra] = 0.43 to 0.59%

27510380	Triple cheeseburger (3 patties, 1/4 lb meat each), with mayonnaise or salad dressing and tomatoes, o
27510430	Double bacon cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing and tomat
27520390	Ham and cheese submarine sandwich, on multigrain roll, with lettuce, tomato and spread

Pre-packaged Ready-to-Eat and Ready-to-Heat Sweet Rolls and Quick Breads
Rolls without icing or frosting
75% of shortening is replaced with Olestra; shortening content of 3.4 to 15.2%
[Olestra] = 2.13 to 11.37%

51160000	Roll, sweet
51160010	Roll, sweet, toasted
51160100	Roll, sweet, cinnamon bun, no frosting
51161000	Roll, sweet, with fruit, no frosting
51161100	Roll, sweet, with fruit and nuts, no frosting
51161200	Roll, sweet, with nuts, no frosting
51161250	Roll, sweet, no topping, Mexican (Pan Dulce)
51167000	Brioche
51168000	Bread, Spanish coffee
51188100	Pannetone (Italian-style sweetbread)
52403000	Bread, nut
52404060	Bread, pumpkin
52405010	Bread, fruit, without nuts
52405100	Bread, fruit and nut
52407000	Bread, zucchini
52408000	Bread, Irish soda

Mixtures containing pre-packaged ready-to-eat and ready-to-heat sweet rolls & quick breads
Rolls with icing or frosting
75% of shortening in the sweet roll portion is replaced with Olestra; shortening content of 1.2 to 7.4%
(Adjusted sweet rolls and quick bread content of 44.6 to 94.7%)
[Olestra] = 0.64 to 3.41%

51160110	Roll, sweet, cinnamon bun, frosted
51161020	Roll, sweet, with fruit, frosted
51161030	Roll, sweet, with fruit, frosted, diet
51161050	Roll, sweet, with nuts, frosted
51161070	Roll, sweet, with fruit, frosted, fat free
51161150	Roll, sweet, with fruit and nuts, frosted
51161260	Roll, sweet, crumb topping, Mexican (Pan Dulce)
51161270	Roll, sweet, sugar topping, Mexican (Pan Dulce)
51161280	Roll, sweet, with raisins and icing, Mexican (Pan Dulce)

Pre-packaged Ready-to-Eat and Ready-to-Heat Waffles
75% of shortening is replaced with Olestra; shortening content of 2.7 to 9.4%
[Olestra] = 1.99 to 7.08%

55201000	Waffle, plain
55202000	Waffle, wheat, bran, or multigrain
55203000	Waffle, fruit
55203500	Waffle, nut and honey
55205000	Waffle, 100% whole wheat or 100% whole grain
55206000	Waffle, oat bran
55211000	Waffle, plain, fat free
55211050	Waffle, plain, lowfat

Cheeses

Natural Cheese Portion of Pre-packaged RTE & RTH Prepared Foods
(Pre-packaged RTE & RTH prepared foods containing reduced-fat, low-fat, and fat-free natural cheese codes were used as products containing olestra will be marketed as such)

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat is replaced with Olestra; butter fat content of 3.4 to 10.5%
(Adjusted for natural cheese content of 50.0 to 64.3%)
[Olestra] = 1.46 to 3.48%

14204020 Cheese, cottage, low-fat, with fruit

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 10.5 to 34.9%
(Adjusted for natural cheese content of 24.4 to 37.0%)
[Olestra] = 0.66 to 8.60%

53104520 Cheesecake, diet
53104570 Cheesecake, diet, with fruit
53104650 Cheesecake, chocolate, reduced-fat
58106900 Pizza with seafood, NS as to type of crust
58106910 Pizza with seafood, thin crust
58108010 Calzone, with meat and cheese
58122210 Gnocchi, cheese

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 10.4 to 47.2%
(Adjusted for natural cheese content of 11.3 to 17.9%)
[Olestra] = 0.31 to 5.62%

53511500 Danish pastry, with cheese, fat-free, cholesterol free
58106210 Pizza, cheese, NS as to type of crust
58106220 Pizza, cheese, thin crust
58106310 Pizza, cheese, with vegetables, NS as to type of crust
58106320 Pizza, cheese, with vegetables, thin crust
58106510 Pizza with meat, NS as to type of crust
58106520 Pizza with meat, thin crust
58106780 Pizza with meat and vegetables, low-fat, thin crust
58106810 Pizza with beans and vegetables, NS as to type of crust
58106820 Pizza with beans and vegetables, thin crust
58106920 Pizza with seafood, thick crust
58108000 Calzone, with cheese, meatless
58108030 Panzerotti, with meat, vegetables, and cheese
58108040 Panzerotti, with vegetables and cheese
58108050 Pizza rolls
58109000 Italian pie, meatless
58124250 Spanakopitta

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 21.6%
(Adjusted for natural cheese content of 6.2 to 10.6%)
[Olestra] = 0.89 to 1.52%

58106230 Pizza, cheese, thick crust
58106330 Pizza, cheese, with vegetables, thick crust

58106360	Pizza, cheese, with fruit, thick crust
58106530	Pizza with meat, thick crust
58106710	Pizza with meat and vegetables, NS as to type of crust
58106720	Pizza with meat and vegetables, thin crust
58106730	Pizza with meat and vegetables, thick crust
58106740	Pizza with meat and fruit, NS as to type of crust
58106750	Pizza with meat and fruit, thin crust
58106760	Pizza with meat and fruit, thick crust
58106830	Pizza with beans and vegetables, thick crust
58107210	White pizza, NS as to type of crust
58107220	White pizza, thin crust
58130320	Lasagna, meatless, with spinach
58130310	Lasagna, meatless
58130020	Lasagna with meat and spinach
58130011	Lasagna with meat
58130140	Lasagna with chicken or turkey

Mixtures containing pre-packaged ready-to-eat natural cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 10.4 to 21.6%
(Adjusted for natural cheese content of 1.4 to 5.4%)
[Olestra] = 0.098 to 0.77%

53105500	Cake, chocolate, with icing, diet
58107230	White pizza, thick crust
58109010	Italian pie with meat
58134623	Tortellini, cheese-filled, meatless, with tomato sauce, canned

Processed Cheese Portion of Pre-packaged RTE & RTH Prepared Foods
(Pre-packaged RTE & RTH prepared foods containing reduced-fat, low-fat, and fat-free processed cheese codes were used as products containing olestra will be marketed as such)

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 21.6%
(Adjusted for processed cheese content of 75.1%)
[Olestra] = 10.82%

14660200	Cheese, nuggets or pieces, breaded, baked, or fried

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 3.5 to 32.0%
(Adjusted for processed cheese content of 21.3 to 32.3%)
[Olestra] = 0.50 to 6.89%

14650150	Cheese sauce made with low-fat cheese
58301050	Lasagna with cheese and meat sauce (diet frozen meal)
58301080	Lasagna with cheese and meat sauce, reduced-fat and sodium (diet frozen meal)
58304200	Ravioli, cheese-filled, with tomato sauce (diet frozen meal)
58304250	Manicotti, cheese-filled, with tomato sauce (diet frozen meal)

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 3.5 to 32.0%
(Adjusted for processed cheese content of 9.2 to 19.1%)
[Olestra] = 0.36 to 2.07%

27550100	Fish sandwich, on bun, with cheese and spread
28110660	Meatballs, Swedish, in gravy, with noodles (diet frozen meal)

28141050	Chicken patty parmigiana, breaded, with vegetable (diet frozen meal)
58145115	Macaroni or noodles with cheese, from boxed mix with already prepared cheese sauce
58301020	Lasagna with cheese and sauce (diet frozen meal)
58301150	Zucchini lasagna (diet frozen meal)
58302030	Macaroni with veal, cheese, and sauce (diet frozen meal)
58302050	Beef and noodles with meat sauce and cheese (diet frozen meal)
58304300	Cannelloni, cheese-filled, with tomato sauce (diet frozen meal)
75412070	Eggplant with cheese and tomato sauce

Mixtures containing pre-packaged ready-to-eat processed cheese
67% of butter fat in the cheese portion is replaced with Olestra; butter fat content of 21.6%
(Adjusted for processed cheese content of 2.5 to 6.9%)
[Olestra] = 0.36 to 0.99%

14610520	Cheese with nuts
28113050	Salisbury steak with vegetables in tomato-based sauce, noodles (diet frozen meal)
28113110	Salisbury steak, baked, with tomato sauce, vegetable (diet frozen meal)
28133210	Veal parmigiana with vegetable (diet frozen meal)
28133340	Veal parmigiana with vegetable, fettuccine alfredo, dessert (frozen meal)
58301030	Veal lasagna (diet frozen meal)
58301130	Tuna lasagna (diet frozen meal)
58304220	Rigatoni with meat sauce and cheese (diet frozen meal)

Confections and Frostings

Pre-packaged Ready-to-Eat Frosting and Icing
100% of shortening is replaced with Olestra; shortening content of 10.81%
[Olestra] = 10.81%

91305010	Icing, chocolate
91305020	Icing, white

Mixtures containing pre-packaged ready-to-eat frosting and icing
100% of shortening in the frosting or icing portion is replaced with Olestra; shortening content of 10.81%
(Adjusted for frosting and icing content of 9.1 to 44.0%)
[Olestra] = 0.98 to 4.76%

51160110	Roll, sweet, cinnamon bun, frosted
51161020	Roll, sweet, with fruit, frosted
51161030	Roll, sweet, with fruit, frosted, diet
51161050	Roll, sweet, with nuts, frosted
51161070	Roll, sweet, with fruit, frosted, fat free
51161150	Roll, sweet, with fruit and nuts, frosted
53100100	Cake, NS as to type, with or without icing
53101200	Cake, angel food, with icing
53101250	Cake, angel food, with fruit and icing or filling
53102000	Cake, applesauce, NS as to icing
53102200	Cake, applesauce, with icing
53102700	Cake, banana, with icing
53102800	Cake, black forest (chocolate-cherry)
53103600	Cake, butter, with icing
53104260	Cake, carrot, with icing
53104400	Cake, coconut, with icing
53105050	Cake, chocolate, devil's food, or fudge, made from home recipe or purchased ready-to-eat, NS as to i

53105200	Cake, chocolate, devil's food, or fudge, standard-type mix (eggs and water added to dry mix), with i
53105260	Cake, chocolate, devil's food, or fudge, with icing, coating, or filling, made from home recipe or p
53105300	Cake, German chocolate, with icing and filling
53105500	Cake, chocolate, with icing, diet
53105750	Cake, chocolate, devil's food, or fudge, pudding type mix, made by "cholesterol free" recipe (water,
53107000	Cake, cupcake, NS as to type or icing
53107200	Cake, cupcake, NS as to type, with icing
53108200	Cake, cupcake, chocolate, with icing or filling
53109200	Cake, cupcake, not chocolate, with icing or filling
53109210	Cake, cupcake, not chocolate, with icing or filling, lowfat, cholesterol free
53109270	Cake, cupcake, chocolate, with or without icing, fruit filling or cream filling, lowfat, cholesterol
53109300	Cake, Dobos Torte (non-chocolate layer cake with chocolate filling and icing)
53114100	Cake, lemon, with icing
53114250	Cake, lemon, lowfat, with icing
53115200	Cake, marble, with icing
53115320	Cake, nut, with icing
53115410	Cake, oatmeal, with icing
53115450	Cake, peanut butter, with icing
53116020	Cake, pound, with icing
53116510	Cake, pumpkin, with icing
53116560	Cake, raisin-nut, with icing
53117200	Cake, spice, with icing
53118200	Cake, sponge, with icing
53118350	Cake, sweetpotato, with icing
53120000	Cake, white, standard-type mix (egg whites and water added), NS as to icing
53120060	Cake, white, made from home recipe or purchased ready-to-eat, NS as to icing
53120200	Cake, white, standard-type mix (egg whites and water added to mix), with icing
53120260	Cake, white, with icing, made from home recipe or purchased ready-to-eat
53120350	Cake, white, pudding-type mix (oil, egg whites, and water added to dry mix), with icing
53121060	Cake, yellow, made from home recipe or purchased ready-to- eat, NS as to icing
53121200	Cake, yellow, standard-type mix (eggs and water added to dry mix), with icing
53121260	Cake, yellow, with icing, made from home recipe or purchased ready-to-eat
53121330	Cake, yellow, pudding-type mix (oil, eggs, and water added to dry mix), with icing
53124120	Cake, zucchini, with icing
53204000	Cookie, brownie, NS as to icing
53204100	Cookie, brownie, with icing
53204600	Cookie, brownie, with peanut butter fudge icing
53204830	Cookie, brownie, lowfat, with icing
53204850	Cookie, brownie, fat free, cholesterol free, with icing
53209010	Cookie, chocolate-covered, sugar wafer, creme- or caramel-filled
53244010	Cookie, butter or sugar, with chocolate icing or filling
53244020	Cookie, butter or sugar, iced, with icing other than chocolate
53420000	Cream puff, eclair, custard or cream filled, NS as to icing
53452420	Pastry, puff, custard or cream filled, iced or not iced
53520140	Doughnut, cake type, chocolate covered
53520160	Doughnut, cake type, chocolate, with chocolate icing
53521100	Doughnut, raised or yeast, chocolate, with chocolate icing
53521230	Doughnut, custard-filled, with icing
54102200	Crackers, graham, sandwich-type, with filling

Fats and Oils

Pre-packaged Ready-to-Eat Mayonnaise
(Reduced-fat, low-fat, and fat-free mayonnaise codes were used as products containing olestra will be marketed as such)

67% of soybean oil is replaced with Olestra; soybean oil content of 5.1 to 79.4%
[Olestra] = 3.40 to 52.90%

83107200	Mayonnaise, made with tofu
83108000	Mayonnaise, imitation
83108100	Mayonnaise, imitation, cholesterol free
83203250	Mayonnaise-type salad dressing, fat-free
83204000	Mayonnaise, low-calorie or diet
83204020	Mayonnaise, reduced calorie or diet, cholesterol-free
83204050	Mayonnaise-type salad dressing, low-calorie or diet
83204060	Mayonnaise-type salad dressing, low-calorie or diet, cholesterol-free

Mixtures containing pre-packaged ready-to-eat mayonnaise
67% of soybean oil in the mayonnaise portion is replaced with Olestra; soybean oil content of 0.2 to 16.3%
(Adjusted for mayonnaise content of 4.2 to 90.8%)
[Olestra] = 0.16 to 10.87%

27540250	Chicken fillet, broiled, sandwich with cheese, on whole wheat roll, with lettuce, tomato and non-mayonnaise
27540270	Chicken fillet, broiled, sandwich, with lettuce, tomato, and non-mayonnaise type spread

Frozen Dairy Desserts and Mixes

Pre-packaged Ready-to-Eat Ice Cream
(Reduced-fat, low-fat, and fat-free ice cream codes were used as products containing olestra will be marketed as such)

67% of butter fat is replaced with Olestra; butter fat content of 1.7 to 9.1%
[Olestra] = 1.13 to 6.07%

13130100	Light ice cream, NFS (formerly ice milk)
13130300	Light ice cream, flavors other than chocolate (formerly ice milk)
13130310	Light ice cream, chocolate (formerly ice milk)
13130320	Light ice cream, no sugar added, NS as to flavor
13130330	Light ice cream, no sugar added, flavors other than chocolate
13130340	Light ice cream, no sugar added, chocolate
13130590	Light ice cream, soft serve, NS as to flavor (formerly ice milk)
13130600	Light ice cream, soft serve, flavors other than chocolate (formerly ice milk)
13130610	Light ice cream, soft serve, chocolate (formerly ice milk)
13130700	Light ice cream, soft serve, blended with candy or cookies
13140680	Light ice cream, sundae, soft serve, not fruit or chocolate topping (without whipped cream) (formerl

Mixtures containing pre-packaged ready-to-eat ice cream
67% of butter fat in the ice cream portion is replaced with Olestra; butter fat Content of 0.6 to 13.5%
(Adjusted for ice cream content of 44.8 to 96.0%)
[Olestra] = 0.51 to 7.83%

13130620	Light ice cream, soft serve cone, flavors other than chocolate (formerly ice milk)
13130630	Light ice cream, soft serve cone, chocolate (formerly ice milk)
13135000	Light ice cream, sandwich (formerly ice milk)
13140100	Light ice cream, bar or stick, chocolate-coated (formerly ice milk)
13140110	Light ice cream, bar or stick, chocolate covered, with nuts (formerly ice milk)
13140500	Light ice cream, cone, flavors other than chocolate (formerly ice milk)
13140550	Light ice cream, cone, chocolate (formerly ice milk)
13140650	Light ice cream, sundae, soft serve, not fruit or chocolate topping, with whipped cream (formerly ic
13140660	Light ice cream, sundae, soft serve, chocolate or fudge topping (without whipped cream) (formerly ic
13140670	Light ice cream, sundae, soft serve, fruit topping (without whipped cream) (formerly ice milk)
13140700	Light ice cream, creamsicle or dreamsicle (formerly ice milk)
13140900	Light ice cream, fudgesicle (formerly ice milk)
13161630	Light ice cream, bar or stick, with low-calorie sweetener, chocolate-coated (formerly ice milk)

Pre-packaged Ready-to-Eat Frozen Yogurt
(Reduced-fat, low-fat, and fat-free yogurt codes were used as products containing olestra will be marketed as such)

67% of butter fat is replaced with Olestra; butter fat content of 3.6%
[Olestra] = 2.40%

11459990	Yogurt, frozen, NS as to flavor, NS as to type of milk
11460000	Yogurt, frozen, flavors other than chocolate, NS as to type of milk
11460100	Yogurt, frozen, chocolate, NS as to type of milk
11460150	Yogurt, frozen, NS as to flavor, lowfat milk
11460160	Yogurt, frozen, chocolate, lowfat milk
11460170	Yogurt, frozen, flavors other than chocolate, lowfat milk
11460200	Yogurt, frozen, chocolate, nonfat milk
11460250	Yogurt, frozen, flavors other than chocolate, with sorbet or sorbet-coated
11460300	Yogurt, frozen, flavors other than chocolate, nonfat milk
11460400	Yogurt, frozen, chocolate, nonfat milk, with low-calorie sweetener
11460410	Yogurt, frozen, flavors other than chocolate, nonfat milk, with low-calorie sweetener
11461270	Yogurt, frozen, cone, flavors other than chocolate, lowfat milk
11461280	Yogurt, frozen, cone, chocolate, lowfat milk

Grain Products and Pastas

Pre-packaged Ready-to-Eat Breakfast, Granola, and Nutritional Bars
75% of shortening is replaced with Olestra; shortening content of 2.7 to 16.0%
[Olestra] = 2.03 to 12.0%

41435110	High protein bar, candy-like, soy and milk base
53540000	Breakfast bar, NFS
53540200	Breakfast bar, cereal crust with fruit filling, lowfat
53540250	Breakfast bar, cereal crust with fruit filling, fat free
53540500	Breakfast bar, date, with yogurt coating
53540600	Milk 'n Cereal bar

53540700	Kellogg's Special K bar
53541200	Meal replacement bar
53542100	Granola bar, oats, sugar, raisins, coconut
53542200	Granola bar, oats, fruit and nuts, lowfat
53542210	Granola bar, nonfat
53543100	Granola bar, peanuts, oats, sugar, wheat germ
53544200	Granola bar, chocolate-coated
53544210	Granola bar, with coconut, chocolate-coated
53544220	Granola bar with nuts, chocolate-coated
53544250	Granola bar, coated with non-chocolate coating
53544300	Granola bar, high fiber, coated with non-chocolate yogurt coating
53544400	Granola bar, with rice cereal
53544450	PowerBar (fortified high energy bar)

Pre-packaged Ready-to-Eat and Ready-to-Heat Pizza Crust
75% of shortening is replaced with Olestra; shortening content of 2.1 to 4.9%
[Olestra] = 1.54 to 3.64%

58106210	Pizza, cheese, NS as to type of crust
58106220	Pizza, cheese, thin crust
58106230	Pizza, cheese, thick crust
58106310	Pizza, cheese, with vegetables, NS as to type of crust
58106320	Pizza, cheese, with vegetables, thin crust
58106330	Pizza, cheese, with vegetables, thick crust
58106360	Pizza, cheese, with fruit, thick crust
58106510	Pizza with meat, NS as to type of crust
58106520	Pizza with meat, thin crust
58106530	Pizza with meat, thick crust
58106710	Pizza with meat and vegetables, NS as to type of crust
58106720	Pizza with meat and vegetables, thin crust
58106730	Pizza with meat and vegetables, thick crust
58106740	Pizza with meat and fruit, NS as to type of crust
58106750	Pizza with meat and fruit, thin crust
58106760	Pizza with meat and fruit, thick crust
58106780	Pizza with meat and vegetables, lowfat, thin crust
58106820	Pizza with beans and vegetables, thin crust
58106830	Pizza with beans and vegetables, thick crust
58106910	Pizza with seafood, thin crust
58106920	Pizza with seafood, thick crust
58107030	Pizza, no cheese, NS as to type of crust
58107050	Pizza, no cheese, thin crust
58107100	Pizza, no cheese, thick crust
58107220	White pizza, thin crust
58107230	White pizza, thick crust

<u>Soft Candy</u>

Pre-packaged Ready-to-Eat Chocolate Confections (chocolate portion)
100% of cocoa butter is replaced with Olestra; cocoa butter content of 15.0 to 21.5%
[Olestra] = 15.0 to 21.5%

91703010	Caramel, chocolate-flavored roll
91703150	Toblerone, milk chocolate with honey and almond nougat
91705010	Chocolate, milk, plain
91705020	Chocolate, milk, with cereal
91705040	Chocolate, milk, with nuts, not almond or peanuts

91705050	Chocolate, milk, with fruit and nuts
91705060	Chocolate, milk, with almonds
91705070	Chocolate, milk, with peanuts
91705200	Chocolate, semi-sweet morsel
91705300	Chocolate, sweet or dark
91705400	Chocolate, white
91705410	Chocolate, white, with almonds
91705420	Chocolate, white, with cereal
91705500	Mexican chocolate (tablet)
91734200	Reese's Pieces
91734300	~Reese Sticks~
91734400	~Reese's Fast Break~
91746010	Sugar-coated chocolate discs
91746100	M & M's Plain Chocolate Candies
91746120	Sixlets
91746150	Easter egg, candy coated chocolate
91760500	Truffles

100% of cocoa butter is replaced with Olestra; cocoa butter content of 6.0 to 13.7%
[Olestra] = 6.0 to 13.7%

91700500	M & M's Almond Chocolate Candies
91701010	Almonds, chocolate covered
91703060	Caramel with nuts, chocolate covered
91703070	Rolo
91703200	TWIX Cookie Bars
91703250	TWIX Chocolate Fudge Cookie Bars
91703300	TWIX Peanut Butter Cookie Bars
91703400	Whatchamacallit
91705030	Kit Kat
91705090	Chocolate with fondant and caramel
91706000	Coconut candy, chocolate covered
91707010	Fondant, chocolate covered
91709000	Gumdrops, chocolate covered
91713030	Fudge, chocolate
91713040	Fudge, chocolate, with nuts
91715000	Fudge, caramel and nut, chocolate-coated
91715100	SNICKERS Bar
91715200	Baby Ruth
91715300	100 GRAND Bar
91718050	Honey-combed hard candy with peanut butter, chocolate covered
91718100	Butterfinger
91723010	Marshmallow, chocolate covered
91726110	Nougat, with caramel, chocolate covered
91726130	MILKY WAY Bar
91726140	MILKY WAY DARK Bar
91726150	MARS Bar
91726410	Nougat, chocolate covered
91726420	3 MUSKETEER Bar
91727010	Nuts, chocolate covered, not almonds or peanuts
91731000	Peanuts, chocolate covered
91731010	M & M's Peanut Chocolate Candies
91731060	M & M's Peanut Butter Chocolate Candies
91733200	Peanut Bar, chocolate covered
91734000	Peanut butter, chocolate covered
91734100	Reese's Peanut Butter Cup

91739010	Raisins, chocolate covered
91770030	Dietetic or low calorie candy, chocolate covered

Mixtures containing pre-packaged ready-to-eat chocolate confections
100% of cocoa butter is replaced with Olestra; cocoa butter content of 2.1 to 5.8%
(Adjusted for chocolate content of 30.0 to 64.0%)
[Olestra] = 2.15 to 5.80%

91703040	Caramel, chocolate covered
91703600	Espresso coffee beans, chocolate-covered
91760100	Toffee, chocolate covered
91760200	Toffee, chocolate-coated, with nuts

OLESTRA AMENDMENT GRAS NOTICE

APPENDIX C:

CAROTENOIDS

January 18, 2010

APPENDIX C:

CAROTENOIDS

Table of Contents

Page

1.0 BACKGROUND C-3
1.1 Introduction C-3

2.0 β-CAROTENE C-8
2.1 Introduction C-8
2.2 Statements and Opinions of Authoritative Organizations on β-Carotene and Risk of Cancer or Cardiovascular Disease C-8
2.3 Review of Recently Published Scientific Literature Pertaining to β-Carotene and Risk of Cancer or Cardiovascular Disease C-9
2.3.1 Cancer Risk C-10
2.3.2 Cardiovascular Disease Risk C-17

3.0 LYCOPENE C-21
3.1 Introduction C-21
3.2 Authoritative Body Statements and Opinions on Lycopene and Cancer Risk C-22
3.3 Review of Scientific Literature Pertaining to Lycopene and Cancer Risk C-22
3.3.1 Review Articles on Lycopene and Cancer Risk C-23
3.3.2 Meta-Analyses and Pooled Analyses on Lycopene and Cancer Risk C-24
3.3.3 Primary Research Articles on Lycopene and Cancer Risk C-26

4.0 β-CRYPTOXANTHIN C-32
4.1 Introduction C-32
4.2 Authoritative Body Statements and Opinions on β-Cryptoxanthin and Cancer Risk C-33
4.3 Review of Scientific Literature Pertaining to β-Cryptoxanthin and Cancer Risk C-33
4.3.1 Review Articles on β-Cryptoxanthin and Cancer Risk C-33
4.3.2 Meta-Analyses and Pooled Analyses on β-Cryptoxanthin and Cancer Risk C-34
4.3.3 Primary Research Articles on β-Cryptoxanthin and Cancer Risk C-35

5.0 α-CAROTENE C-40
5.1 Introduction C-40
5.2 Authoritative Body Statements and Opinions on α-Carotene and Cancer Risk C-40
5.3 Review of Scientific Literature Pertaining to α-Carotene and Cancer Risk C-40
5.3.1 Review Articles on α-Carotene and Cancer Risk C-41

5.3.2 Meta-Analyses and Pooled Analyses on α-Carotene and Cancer Risk C-41
5.3.3 Primary Research Articles on α-Carotene and Cancer Risk C-42

6.0 REFERENCES C-47

ATTACHMENT I Tabular Summary from Human Intervention and Observational Studies Assessing the Health Effects of β-Carotene, Lycopene, β-Cryptoxanthin, and α-Carotene

List of Tables

Table 1.1-1 Effects of Olestra and Other Sucrose Polyesters on Serum Carotenoid Levels C-4
Table 1.1-2 Position Statements/Recommendations Regarding Carotenoids from Authoritative Scientific and Regulatory Organizations C-5
Table 2.3.1.3-1 Summary of Observational Studies Assessing β-Carotene Intakes or Circulating Levels with Cancer Risk C-13
Table 2.3.1.3-2 β-Carotene and Cancer Risk – A Summary of Findings by Study Type C-17
Table 2.3.2.3-1 Summary of Observational Studies Assessing β-Carotene Intakes or Circulating Levels with Cardiovascular Disease Risk C-20
Table 2.3.2.3-2 β-Carotene and CVD Risk – A Summary of Findings by Study Type C-21
Table 3.3.3-1 Summary of Studies Assessing Lycopene Intakes or Circulating Levels with Cancer Risk C-28
Table 3.3.3-2 Lycopene and Cancer Risk – A Summary of Findings by Study Type C-32
Table 4.3.3-1 Summary of Studies Assessing β-Cryptoxanthin Intake or Circulating Levels with Cancer Risk C-36
Table 4.3.3-2 β-Cryptoxanthin and Cancer Risk – A Summary of Findings by Study Type C-39
Table 5.3.3-1 Summary of Studies Assessing α-Carotene Intake or Circulating Levels with Cancer Risk C-43
Table 5.3.3-2 α-Carotene and Cancer Risk – A Summary of Findings by Study Type C-46

1.0 BACKGROUND

1.1 Introduction

Co-consumption of olestra with foods rich in the fat-soluble vitamins (vitamins A, D, E, and K) or carotenoids results in a reduction in the absorption of these nutrients, as evidenced by reduced serum vitamin and carotenoid levels (Jones *et al.,* 1991a; Weststrate and van het Hof, 1995; Koonsvitsky *et al.,* 1997; Schlagheck *et al.,* 1997a,b; Kelly *et al.,* 1998; Thornquist *et al.,* 2000; Broekmans *et al.,* 2003; Tulley *et al.,* 2005; Neuhouser *et al.,* 2006). To compensate for any interference with the absorption of fat-soluble vitamins, the fat-soluble vitamins must be added to all products containing olestra, in accordance with 21 CFR 172.867(d) (U.S. FDA, 2008a). Data collected in the Olestra Post-Marketing Surveillance Study (OPMSS) as well as in human experimental studies conducted following the market introduction of olestra in the U.S. indicate that the vitamin restoration levels specified in 21 CFR 172.867(d) are sufficient to prevent reductions in serum levels of the fat-soluble vitamins (Jones *et al.,* 1991a,b; Koonsvitsky *et al.,* 1997; Schlagheck *et al.,* 1997b; Kelly *et al.,* 1998; Thornquist *et al.,* 2000; Broekmans *et al.,* 2003; Neuhouser *et al.,* 2006; U.S. FDA, 2008a).

Unlike the fat-soluble vitamins, carotenoids are not added to olestra-containing products. There is strong consensus amongst human experimental studies that olestra is associated with reductions in serum carotenoid levels (Table 1.1-1); however, in all of these studies, there were no apparent ill-health effects (Weststrate and van het Hof, 1995; Koonsvitsky *et al.,* 1997; Schlagheck *et al.,* 1997a,b; Kelly *et al.,* 1998; Thornquist *et al.,* 2000; Broekmans *et al.,* 2003; Tulley *et al.,* 2005; Neuhouser *et al.,* 2006). In the longest intervention trial [a 1-year study involving 380 subjects (stratified according to habitual fruit and vegetable consumption)], the daily consumption of 10 g sucrose polyester together with 7 g olestra for 1 year was not associated with adverse effects on markers of oxidative stress, cardiovascular health, immune status, or macular pigment optical density or eye health, despite serum carotenoid reductions from baseline of 13 to 33% (Broekmans *et al.,* 2003). Although this study suggests that olestra-induced reductions in serum carotenoid levels are inconsequential to health, the length of this intervention trial may not have been sufficient to assess the effects of chronically reduced serum carotenoid levels on diseases which generally take years to develop (*e.g.,* cancer, cardiovascular disease, *etc.*).

Table 1.1-1 Effects of Olestra and Other Sucrose Polyesters on Serum Carotenoid Levels

Reference	Study Design	Study Population and Final Sample Size	Intervention	Duration	Significant Effects on Carotenoids
Weststrate and van het Hof, 1995	Randomized, double-blind, placebo-controlled, crossover	21 healthy male and female subjects 23 to 55 years of age	12.4 g/day SPE *vs.* TG in margarine consumed with main meal	1 month[1]	↓ in all carotenoids; β-carotene and lycopene ↓ to 66 and 48% of control
	Randomized, double-blind, placebo-controlled, parallel	53 healthy male and female subjects 19 to 64 years of age	3 g/day SPE *vs.* TG in margarine consumed with main meal	1 month	β-carotene and lycopene ↓ to 63 and 66% of control
Koonsvitsky *et al.,* 1997	Parallel, placebo-controlled, double-blind	132 healthy male and female subjects 18 to 65 years of age	18 g/day olestra or TG delivered in 1 frozen dessert and 3 cookies	4 months	Total carotenoids ↓ to 68% of control
Kelly *et al.,* 1998	Crossover	83 healthy male and female subjects 18 to 65 years of age	27 g/day SPE *vs.* TG in various foods	3 months per intervention[1]	All carotenoids ↓ to 58 to 75% of control
Schlagheck *et al.,* 1997a	Randomized, double-blind, placebo-controlled, parallel	88 healthy male and female subjects 18 to 44 years of age	0, 8, 20, or 32 g/day olestra in cookies, chips, muffins, biscuits	2 months	Dose-dependent ↓; total carotenoids were 49, 39, and 32% of control (1997a) and 53, 42, and 38% of control (1997b)
Schlagheck *et al.,* 1997b		102 healthy male and female subjects 18 to 44 years			
Broekmans *et al.,* 2003	Randomized, double-blind, placebo-controlled, parallel	341 generally healthy male and female subjects 18 to 75 years of age[2]	0, 7, 10, or 17 g/day olestra (in chips) and SPE (in margarine)	12 months	13 to 33% ↓ in all carotenoids; carotenes and lycopene most affected
Tulley *et al.,* 2005	Randomized, double-blind, parallel	37 healthy overweight males 21 to 60 years of age with a BMI of 27-35 kg/m^2	Regular-fat diet (33% energy), low-fat diet (25% energy), or low-fat diet + 20 to 45 g/day olestra[3]	9 months	↓ from baseline in β-carotene (by 54%), lycopene (by 47%), and lutein+zeaxanthin (by 29%)
Thornquist *et al.,* 2000 (OPMSS)	Population-based cross-sectional study	931 subjects 18 to 55+ years of age; 714 non-olestra consumers and 217 olestra consumers[4]	NA	12 months	No significant trends across olestra intake groups
	Population-based cohort study	398 subjects 18 to 55+ years of age; 262 non-olestra consumers and 136 olestra consumers[4]	NA	12 months	14.5% ↓ in total carotenoids in the highest olestra intake group

Table 1.1-1 Effects of Olestra and Other Sucrose Polyesters on Serum Carotenoid Levels

Reference	Study Design	Study Population and Final Sample Size	Intervention	Duration	Significant Effects on Carotenoids
Neuhouser *et al.,* 2006	Population-based cross-sectional and cohort studies[5]	3,728 adults, mean age of 44.9±15.6 years; 2,963 non-olestra consumers and 765 olestra consumers[6]	NA	12 months	Dose-dependent ↓ in all carotenoids except lutein+zeaxanthin.
		272 adolescents, mean age of 14.7 ± 1.6 years; 244 non-olestra consumers and 108 olestra consumers[7]			

[1] No washout period was included; however, there was no effect of treatment order.
[2] The cut-offs for cholesterol and triglycerides were set quite high in the subject exclusion criteria, and so subjects permitted into the trial were either normo- or hyperlipidemic.
[3] All subjects were required to take a daily multivitamin (Centrum™); carotenoids present were β-carotene (2.24 μmol) and lutein (0.44 μmol)
[4] Low, moderate, and heavy olestra intakes were estimated to be >0 to <0.4, ≥0.4 to <2.0, and ≥2.0 g/day, respectively.
[5] Authors combined results from the clinic cross-sectional and cohort studies.
[6] The mean daily olestra intake was 0.78 ± 1.39 g.
[7] The mean daily olestra intake was 0.74 ± 1.0 g.

Olestra is currently approved for use in pre-packaged ready-to-eat savory snacks, pre-packaged ready-to-heat unpopped popcorn, and pre-packaged ready-to-eat cookies. The 1994-1996 CSFII and the 1998 Supplemental Children's Survey indicate that savory snacks, popcorn, and cookies are consumed mostly as snacks (*i.e.,* in-between meals) as opposed to with meals. In this GRAS amendment, olestra is being proposed for use in several categories of foods that may be co-consumed with main meals; thus, use of olestra in the proposed food categories will result in greater reductions in serum carotenoid levels than the current approved uses of olestra in savory snacks, popcorn, and cookies.

To ensure that reductions in serum carotenoid levels will not be associated with ill health effects, the scientific literature regarding the role of carotenoids in the maintenance of health and in reducing the risk of disease has been reviewed. To this end, position statements of authoritative scientific and regulatory organizations on 6 of the most commonly consumed carotenoids (β-carotene, lycopene, β-cryptoxanthin, α-carotene, lutein, and zeaxanthin) were compiled (Table 1.1-2). Although these statements do not provide definitive support that carotenoids reduce the risk of disease(s), they also do not rule out such a benefit. Thus, in order to ensure that all data from new and evolving science were considered, a systemic review of the more recent literature (*i.e.,* human studies published in or subsequent to 2003) was conducted for β-carotene, lycopene, β-cryptoxanthin, and α-carotene. The totality of evidence from these studies and statements was considered to determine whether these carotenoids are important in reducing the risk of chronic diseases in humans. Given that the scientific literature regarding the roles of lutein and zeaxanthin in the maintenance of eye health is rapidly evolving, the totality of evidence (*i.e.,* literature search *was not* limited to articles published in or subsequent to 2003) from human intervention and observational studies was considered to determine whether these carotenoids are important in reducing the risk of age-related cataract or macular degeneration or improving visual performance (see **Appendix E**).

Table 1.1-2 Position Statements/Recommendations Regarding Carotenoids from Authoritative Scientific and Regulatory Organizations

Authoritative Organization	Reference	Subject of Position Statement/ Recommendation	Position Statement/ Recommendation
U.S. FDA, CFSAN, Office of Nutritional Products, Labeling, and Dietary Supplements[1]	U.S. FDA, 2005a	Lutein and zeaxanthin and ARMD and cataract formation	There is no credible scientific evidence to support qualified health claims for consumption of lutein and/or zeaxanthin and reduced risk of ARMD or cataract formation.
U.S. FDA, CFSAN, Office of Nutritional Products, Labeling, and Dietary Supplements[2]	U.S. FDA, 2005b	Lycopene and prostate cancer	There is no credible scientific evidence to support claims about consumption of lycopene (as a component of tomatoes, tomato products, or fruits and vegetables) and a reduced risk of prostrate cancer.[3]
U.S. FDA, CFSAN, Office of Nutritional Products, Labeling, and Dietary Supplements[4]	U.S. FDA, 2005c	Lycopene and cancers	There is no credible scientific evidence supporting a relationship between consumption of lycopene, either as a food ingredient, a component of food, or as a dietary supplement, and reduced risk of cancer, prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer.[5]
U.S. FDA	U.S. FDA, 1998	β-carotene	Under the Food and Drug Administration Modernization Act (FDAMA), a health claim on food labels for β-carotene and reduced risk of atherosclerosis, coronary heart disease, and certain cancers was evaluated but was denied due to a lack of consistent, authoritative statements by national scientific bodies.
World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR)[6]	WCRF/AICR, 2007	Carotenoids, β-carotene, lycopene	•Foods containing carotenoids[7] probably protect against cancers of the mouth, pharynx, and larynx, and also lung. •Foods containing lycopene[7,8] probably protect against prostate cancer. •Foods containing the carotenoid β-carotene[9] probably protect against esophageal cancer. •"Vegetables, fruits… are sources of a wide variety of micronutrients and other bioactive compounds. Foods containing several of these constituents have been identified in the systematic literature reviews, on which this chapter is based, as being associated with cancer risk…it is not possible to ascribe the association between these foods and lower cancer risk to a causal effect of specific compounds with confidence, as each foods contains a complex mixture of different constituents, all of which might also contribute to any effect." •"The best source of nourishment is food and drinks, not supplements."

Table 1.1-2 Position Statements/Recommendations Regarding Carotenoids from Authoritative Scientific and Regulatory Organizations

Authoritative Organization	Reference	Subject of Position Statement/ Recommendation	Position Statement/ Recommendation
World Health Organization (WHO), International Agency for Research on Cancer (IARC)	WHO/IARC, 1998	β-carotene and other carotenoids	• "Until further information becomes available on how β-carotene and other carotenoids influence the processes leading to cancer, none of these substances should be promoted to the general population as a tumor-preventative treatment." • "It appears, at present, that cancer prevention by fresh fruits and vegetables remains more effective than taking one or several of their constituents as dietary supplements."
Food and Nutrition Board, Institute of Medicine	IOM, 2000	β-carotene and other carotenoids	• "A large body of observational epidemiological evidence suggests that higher blood concentrations of β-carotene and other carotenoids obtained from food are associated with lower risk of several chronic diseases. This evidence, although consistent, cannot be used to establish a requirement for β-carotene or carotenoid intake because the observed effects may be due to other substances found in carotenoid-rich food, or to other behavioral correlates of increased fruit and vegetable consumption." • "The only clear function of certain carotenoids that is firmly linked to a health outcome is the provitamin A activity of some dietary carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) and their role in the prevention of vitamin A deficiency."
American Cancer Society	Kushi *et al.,* 2006	Carotenoids, β-carotene, lycopene	• "To reduce cancer risk, the best advice presently is to consume antioxidants through food sources rather than supplements." • "Evidence that vegetable and fruit consumption reduces cancer risk has led to attempts to isolate specific nutrients and administer them in very high doses. Most of these attempts have been unsuccessful in preventing cancer or its precursor lesions, and in some cases, have had adverse effects." • "Several studies have reported that consumption of tomato products reduces the risk of some cancers. It is uncertain, however, whether lycopene is the micronutrient responsible for this association." • "Consuming vegetables and fruits that contain β-carotene may be helpful, but high-dose β-carotene supplements should be avoided."

Table 1.1-2 Position Statements/Recommendations Regarding Carotenoids from Authoritative Scientific and Regulatory Organizations

Authoritative Organization	Reference	Subject of Position Statement/ Recommendation	Position Statement/ Recommendation
American Heart Association	Lichtenstein *et al.*, 2006	Antioxidants	•"Antioxidant vitamin supplements or other supplements such as selenium to prevent CVD are not recommended. Nevertheless, food sources of antioxidant nutrients, principally from a variety of plant-derived foods such as fruits, vegetables, whole grains, and vegetable oils are recommended."

Abbreviations: AICR, American Institute for Cancer Research; ARMD, age-related macular degeneration; CFSAN, Center for Food Safety and Applied Nutrition; CVD, cardiovascular disease; FDAMA, Food and Drug Administration Modernization Act; IARC, International Agency for Research on Cancer; U.S. FDA, United States Food and Drug Administration; WCRF, World Cancer Research Fund; WHO, World Health Organization.

[1] The Oregon Health Sciences Evidence-Based Practice Center assisted FDA by doing an independent scientific review.

[2] Qualified Health Claim petition was filed by the Lycopene Health Claim Coalition (H.J. Heinz Company, LycoRed Natural Products Industries, Ltd., The Morningstar Company, and The Prostate Cancer Foundation).

[3] The FDA issued letters of enforcement discretion for qualified health claims regarding consumption of tomatoes and/or tomato sauce and a reduced risk in prostate cancer.

[4] Qualified Health Claim petition was filed by American Longevity, Inc.

[5] The FDA issued letters of enforcement discretion for qualified health claims regarding consumption of tomatoes and/or tomato sauce and a reduced risk of prostate, gastric, ovarian, and pancreatic cancers.

[6] Judgments were graded based on the strength of evidence as convincing, probable, limited – suggestive, or substantial effect on risk unlikely. Only relationships regarding carotenoids and cancer risk that were determined to be probable are shown.

[7] Includes both foods naturally containing the constituent and foods which have the constituent added.

[8] Mostly contained in tomato and tomato products. Also fruits such as grapefruit, watermelon, guava, and apricot.

[9] The evidence is derived from studies using supplements and foods containing β-carotene.

2.0 B-CAROTENE

2.1 Introduction

β-Carotene is one of the most abundant carotenoids in the human diet. The main dietary sources of β-carotene are carrots, apricots, mangoes, red pepper, kale, spinach, and broccoli (Osganian *et al.*, 2003).

β-Carotene is a provitamin as it can be converted to retinol, the active form of vitamin A. Retinol is subsequently converted to retinoic acid, which is used for processes involving growth and cell differentiation. According to the Food and Nutrition Board of the National Academies' Institute of Medicine (IOM), 2 µg of supplemental β-carotene (in oil) or 12 µg of dietary β-carotene are equivalent to 1 µg of retinol (IOM, 2001). That the average conversion factor of β-carotene (in oil) to retinol is 2:1 was based primarily on a study conducted by Sauberlich *et al.* (1974) in which 8 healthy male volunteers were depleted of vitamin A over 359 to 771 days and then repleted with either vitamin A (n=5) or β-carotene (n=3). Several recent studies have demonstrated that these standard conversion factors may overestimate the amount of β-carotene converted to retinol (Tang *et al.,* 2000*,* 2003*,* 2005). Cumulatively, these studies suggest that in healthy individuals, the average conversion factor, by weight, of β-carotene to retinol is 15:1 to 21:1 (from food) and 4:1 to 9:1 (when administered in oil), and it has been suggested that the conversion of β-carotene to retinol is less efficient in a population with normal vitamin A status than in subjects who are vitamin A deficient or depleted.

2.2 Statements and Opinions of Authoritative Organizations on β-Carotene and Risk of Cancer or Cardiovascular Disease

In 1998, the FDA evaluated a health claim for β-carotene and reduced risk of atherosclerosis, coronary heart disease, and certain cancers; however, the claim was denied because of a lack of consistent, authoritative statements by national scientific bodies (U.S. FDA, 1998). Similarly, the World Health Organization (WHO), International Agency for Research on Cancer (IARC) stated that β-carotene and other carotenoids should not be promoted as a tumor-preventative treatment until further information becomes available on the mechanisms by which these substances influence the processes leading to cancer (WHO/IARC, 1998).

In a recent statement issued by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), it was noted that foods containing β-carotene, including foods naturally containing β-carotene and foods which have added β-carotene, probably protect against esophageal cancer (WCRF/AICR, 2007). The IOM stated that consistent "observational epidemiological evidence suggests that higher blood concentrations of β-carotene and other carotenoids obtained from food are associated with lower risk of several chronic diseases"; however, the evidence "cannot be used to establish a requirement for β-carotene or carotenoid

intake because the observed effects may be due to other substances found in carotenoid-rich food, or to other behavioral correlates of increased fruit and vegetable consumption" (IOM, 2000).

While the American Cancer Society indicated that consuming β-carotene-containing fruits and vegetables may be helpful in reducing cancer risk, it stated that the use of high dose β-carotene supplements should be avoided (Kushi *et al.*, 2006).

A summary of the authoritative body position statements and recommendations regarding β-carotene is provided in Table 1.1-2.

2.3 Review of Recently Published Scientific Literature Pertaining to β-Carotene and Risk of Cancer or Cardiovascular Disease

Literature searches were conducted to identify recently published articles pertaining to the effects of β-carotene on risk of cancer or cardiovascular disease (CVD). Reviews, meta-analyses, pooled analyses, and primary intervention and observational studies in humans published from 2003 to the present were identified.

The literature searches were conducted using the following databases: Medline, ToxFile, AGRIS, Agricola, FSTA, Foodline, Biosis Previews, NTIS, and EMBASE.

For studies that evaluated cancer endpoints, the following search terms were used: [beta()carotene OR 7235-40-7] AND [publication year=2003:2008] AND [human OR humans OR subject OR subjects OR patient? OR clinical? OR volunteer? OR double()blind OR epidemiol? OR case()(stud? OR control?) OR cohort? OR intervention?()stud? OR observation?()stud? OR meta()analys?s]. Within the obtained results, records including the following terms were searched: cancer OR tumor? OR tumour? OR neoplas?. Duplicate search records were removed. From the list of unique records, results were limited to those containing the term "carotene" in the title. [Note: The question mark, "?", allows for truncation.]

To identify studies that evaluated CVD endpoints, the following search terms were used: [beta()carotene OR 7235-40-7] AND [publication year=2003:2008] AND [human OR humans OR subject OR subjects OR patient? OR clinical? OR volunteer? OR double()blind OR epidemiol? OR case()(stud? OR control?) OR cohort? OR intervention?()stud? OR observation?()stud? OR meta()analys?s]. CVD studies within these records were identified using the terms: heart()disease? OR cardiovascular(2w)disease? OR coronary()disease OR atherosclerosis OR arteriosclerosis OR myocardial()infarction OR ischemia OR cholesterol OR lipoprotein. Results were limited to records containing "carotene" in the title and duplicates were removed.

Although the literature searches identified only studies in which the term "carotene" was in the title, references in these publications were checked for relevant studies that were not identified in the original search. Additionally, studies identified in the literature searches for other carotenoids that included assessments of β-carotene were included in this evaluation.

Reviews, meta-analyses, pooled analyses, and primary research studies were critically reviewed to determine if the findings were consistent with the authoritative body position statements regarding β-carotene.

2.3.1 Cancer Risk

2.3.1.1 Review Articles

Dagnelie *et al.* (2004) conducted a review of prospective cohort and intervention studies on potential dietary risk factors for prostate cancer. Studies published between 1966 and September 2003 were included in the review. Based on results from 4 intervention studies in which β-carotene was provided at doses of 20 to 50 mg daily or on alternate days with a follow-up period of up to 12.9 years, the authors stated that β-carotene supplementation does not affect prostate cancer risk, but it may reduce incidence in men with low baseline β-carotene levels and increase incidence in those with high baseline levels. Serum levels of β-carotene were not associated with prostate cancer risk in one prospective cohort study, but were associated with an increased risk in another study. Five studies were identified in which β-carotene intake was measured using dietary questionnaires or interviews; none showed an association between β-carotene intake and prostate cancer risk. The authors concluded that the available studies failed to show a consistent association between β-carotene and prostate cancer risk.

2.3.1.2 Meta-Analyses and Pooled Analyses

One meta-analysis and 3 pooled analyses related to β-carotene and the risk of developing cancer were identified.

Bjelakovic *et al.* (2004) published a systematic review and meta-analysis of randomized clinical trials (up to February 2003) that assessed the efficacy of antioxidant supplements in preventing gastrointestinal cancers. In 5 identified trials that tested β-carotene supplementation alone (15 to 50 mg everyday or on alternate days for 1 to 12 years), no significant effect on esophageal, gastric, colorectal, or pancreatic cancers was reported, using either the fixed-effect or random-effects meta-analyses models. Additionally, β-carotene supplementation did not significantly affect mortality.

Männistö *et al.* (2007) conducted a pooled analysis of 11 cohort studies conducted in North America and Europe that assessed the effects of dietary carotenoid intake on colorectal cancer

risk. Baseline intakes of specific carotenoids, including β-carotene, were estimated using food frequency questionnaires, and the follow-up period for each study ranged from 6 to 20 years (between 1980 and 2003). Of the 702,647 participants in the studies, 7,885 incident cases of colorectal cancer were diagnosed. The pooled multivariate relative risk of colorectal cancer comparing the highest and lowest quintile of β-carotene intake was 0.96 (95% confidence interval: 0.85 to 1.09, p value for trend: 0.39). Statistically significant between-studies heterogeneity was reported for the 5th quintile of β-carotene intake. Analysis of tumor subsites revealed no significant association between β-carotene intake and cancers of the colon, proximal colon, or rectum, although there was an inverse association between β-carotene intake and distal colon cancer risk. The authors concluded that the pooled data did not support an association between β-carotene intake and colorectal cancer risk.

In another pooled analysis, primary data from 10 prospective cohort studies in North America and Europe were evaluated to determine the relationship between intakes of major carotenoids and the risk of invasive epithelial ovarian cancer (Koushik *et al.*, 2006). Intakes were assessed using food frequency questionnaires administered at baseline in each study. During a follow-up of 7 to 22 years across studies, 2,012 cases of ovarian cancer occurred among the 521,911 subjects. Multivariate analyses revealed no association between β-carotene intake and ovarian cancer (relative risk comparing the highest and lowest quintile of intake: 0.95, confidence interval: 0.82 to 1.10, p value for trend: 0.25), and there was no evidence of statistically significant heterogeneity between studies. Additionally, associations did not vary significantly by histological type of ovarian cancer or by population subgroup. It was concluded that consumption of the major carotenoids during adulthood was not associated with ovarian cancer risk.

Männistö *et al.* (2004) also conducted a pooled analysis of 7 cohort studies in North America and Europe to determine the association between dietary β-carotene intakes and lung cancer risk, as part of the Pooling Project of Prospective Studies of Diet and Cancer. Dietary intakes were estimated using dietary questionnaires administered at baseline. During the follow-up period, which ranged from 7 to 16 years across studies, 3,155 incident lung cancer cases were diagnosed among the 399,765 subjects. In the multivariate analyses, no significant association between β-carotene intake and lung cancer risk was reported (relative risk comparing the highest and lowest quintile: 0.98; confidence interval: 0.87 to 1.11; p value for trend: 0.47). Similarly, analysis of lung cancer by cell type revealed no significant association with β-carotene intake. It was concluded from the results of the pooled analysis that higher dietary intakes of β-carotene were not associated with reduced risk of lung cancer. The authors also stated that the findings did not suggest that higher β-carotene intake in the context of normal diets would increase lung cancer risk.

2.3.1.3 Primary Research Articles

Pertinent data from primary research articles can be found in **Attachment I** to **Appendix C**. A search of the scientific literature revealed 1 placebo-controlled intervention study that evaluated the effects of β-carotene supplementation on upper aerodigestive tract cancer risk (Wright *et al.*, 2007). β-Carotene, when provided at doses of 20 mg/day for 5 to 8 years, had no significant effect on the risk of cancers of the oral cavity/pharynx, esophagus, or larynx.

A total of 38 observational studies (reported in 37 publications) were identified in which dietary intakes or circulating levels of β-carotene were assessed and quantified (*i.e.*, tertiles, quartiles, or quintiles of intake or blood levels) and their possible relation to cancer risk determined. Eleven studies assessed the potential relationship between β-carotene and prostate cancer risk (Goodman *et al.*, 2003; Huang *et al.*, 2003; Bosetti *et al.*, 2004; Wu *et al.*, 2004; Chang *et al.*, 2005; Jian *et al.*, 2005; McCann *et al.*, 2005; Kirsh *et al.*, 2006a; Key *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a), 7 studies assessed colon, rectal, or colorectal cancer risk (Chiu *et al.*, 2003; Erhardt *et al.*, 2003; Satia-Abouta *et al.*, 2003; Murtaugh *et al.*, 2004; Nkondjock and Ghadirian, 2004; Senesse *et al.*, 2005; Wakai *et al.*, 2005), and 4 studies assessed breast cancer risk (Cho *et al.*, 2003; Sesso *et al.*, 2005; Tamimi *et al.*, 2005; Huang *et al.*, 2007). Three studies each assessed gastric cancer risk (Abnet *et al.*, 2003; Jenab *et al.*, 2006; Larsson *et al.*, 2007), lung cancer risk (Goodman *et al.*, 2003; Wright *et al.*, 2003; Yuan *et al.*, 2003), and skin cancer risk (Fung *et al.*, 2003; Dorgan *et al.*, 2004; Schaumberg *et al.*, 2004). The remaining 7 studies assessed associations with cancers of the bladder (Hung *et al.*, 2006), esophagus (Abnet *et al.*, 2003; De Stefani *et al.*, 2006) ovaries (Zhang *et al.*, 2007b), and pancreas (Nkondjock *et al.*, 2005); with tobacco-related cancer (Touvier *et al.*, 2005); and with cancer mortality (Buijsse *et al.*, 2005). A summary of these studies is presented in Table 5.3.1.3-1 (for more extensive tabular summaries of study findings, see **Attachment I** to **Appendix C**).

Table 2.3.1.3-1 Summary of Observational Studies Assessing β-Carotene Intakes or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Prostate cancer					
Kirsh *et al.*, 2006a	Cohort	Dietary intake *via* FFQ at baseline only	NS	NS	NS
Bosetti *et al.*, 2004	Case-control	Dietary intake *via* FFQ	↓ (p=0.017)	0.72 (0.55-0.94)	NS
Chang *et al.*, 2005	Case-control	Plasma β-carotene	↓ (p value NR)	NR	NR
Goodman *et al.*, 2003	Nested case-control	Serum β-carotene	NS	NS	NS
Huang *et al.*, 2003	Nested case-control	Serum β-carotene	NS	NS	NS
Jian *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	0.34 (0.17-0.69)	0.42 (0.21-0.83)
Key *et al.*, 2007	Nested case-control	Plasma β-carotene	NS	NS	NS
McCann *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Peters *et al.*, 2007	Nested case-control	Serum β-carotene	NS	NS	NS
Wu *et al.*, 2004	Nested-case-control	Serum β-carotene	NS	NS	NS
Zhang *et al.*, 2007a	Case-control	Plasma β-carotene	NS	NS	NS
Colon, rectal, or colorectal cancer					
Chiu *et al.*, 2003	Case-control	Dietary intake *via* FFQ	Men: ↓ (p<0.01)	0.5 (0.3-0.7)	0.6 (0.5-0.9)
			Women: ↓ (p=0.02)	0.6 (0.4-0.9)	0.7 (0.5-0.9)
Erhardt *et al.*, 2003	Case-control	Plasma β-carotene	NS	NR	NR
Murtaugh *et al.*, 2004	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Nkondjock and Ghadirian, 2004	Case-control	Dietary intake *via* FFQ	NS in ever smokers	NS	NS
			↓ in never smokers (p=0.02)	0.44 (0.21-0.92)	NS
Satia-Abouta *et al.*, 2003	Case-control	Dietary intake *via* FFQ	↓ in Caucasians (p=0.05)	0.5 (0.3-0.9)	NS
			↓ in African-Americans (p=0.009)	0.6 (0.3-0.9)	NS
Senesse *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS

Table 2.3.1.3-1 Summary of Observational Studies Assessing β-Carotene Intakes or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Wakai *et al.*, 2005	Nested case-control	Serum β-carotene	NS in men	NS	NS
			↑ in women (p=0.040)	NS	NS
Breast cancer					
Cho *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline and 4 years later	NS	NS	NS
Sesso *et al.*, 2005	Cohort and nested case-control	Dietary intake *via* FFQ at baseline only, and plasma β-carotene	NS	NS	NS
Huang *et al.*, 2007	Case-control	Dietary intake *via* FFQ	↓ (p=0.01)	0.38 (0.21-0.71)	0.36 (0.20-0.66)
Tamimi *et al.*, 2005	Nested case-control	Plasma β-carotene	↓ (p=0.01)	NS	NS
Gastric cancer					
Abnet *et al.*, 2003	Nested case-control	Serum β-carotene	NS	NS	NS
Larsson *et al.*, 2007	Cohort	Dietary intake *via* FFQ at baseline only	NS ↓ (p=0.07)	0.55 (0.32-0.94)	NS
Jenab *et al.*, 2006	Nested case-control	Serum β-carotene	NS	NS	NS
Lung cancer					
Yuan *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline only	NS	NS	NS
Goodman *et al.*, 2003	Nested case-control	Serum β-carotene	NS	NS	NS
Wright *et al.*, 2003	Case-control	Dietary intake *via* FFQ	NS in never/former smokers	NS	NS
			↓ in current smokers (p=0.02)	0.54 (0.32-0.90)	0.59 (0.37-0.95)
Skin cancer					
Dorgan *et al.*, 2004	Cohort	Serum β-carotene	Basal cell carcinoma: NS	NS	NS
			Squamous cell carcinoma: NS ↑ (p=0.06)	NS	NS
Fung *et al.*, 2003	Cohort	Dietary intake *via* FFQ	NS	NS	NS
Schaumberg *et al.*, 2004	Nested case-control	Plasma β-carotene	NS	NS	NS

Table 2.3.1.3-1 Summary of Observational Studies Assessing β-Carotene Intakes or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Bladder cancer					
Hung *et al.*, 2006	Case-control	Plasma β-carotene	↓ (p=0.047)	0.11 (0.04-0.80)	0.15 (0.03-0.83)
Esophageal cancer					
Abnet *et al.*, 2003	Nested case-control	Serum β-carotene	NS	NS	NS
De Stefani *et al.*, 2006	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Ovarian cancer					
Zhang *et al.*, 2007b	Case-control	Dietary intake *via* FFQ	↓ (p<0.01)	0.51 (0.31-0.84)	0.46 (0.29-0.73)
Pancreatic cancer					
Nkondjock *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Tobacco-related cancer					
Touvier *et al.*, 2005	Cohort	Dietary intake *via* FFQ at baseline only	↓ in never smokers (p=0.03)	NS	0.72 (0.57-0.92)
			NS ↑ in ever smokers (p=0.09)	2.14 (1.16-3.97)	1.43 (1.05-1.96)
Cancer mortality					
Buijsse *et al.*, 2005	Cohort	Plasma carotene (α and β)	↓ (p NR)	NR	NR

Abbreviations: ↓, decreased; ↑, increased; CI, confidence intervals; FFQ, food frequency questionnaire; NR, not reported; NS, not significant; OR, odds ratio; RR, relative risk

For prostate cancer risk, 2 of the 11 studies indicated a statistically significant trend for a protective effect of β-carotene, one in which dietary intake was assessed (Bosetti *et al.*, 2004) and one in which plasma levels were assessed but for which the actual statistical value of the trend was not reported (Chang *et al.*, 2005). Another study reported a decreased incidence of prostate cancer in the highest centile and in an intermediate centile of dietary β-carotene intake (Jian *et al.*, 2005). None of the other 8 studies reported any significant change in prostate cancer risk associated with high β-carotene intake (McCann *et al.*, 2005; Kirsh *et al.*, 2006) or circulating levels (Goodman *et al.*, 2003; Huang *et al.*, 2003; Wu *et al.*, 2004; Key *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a).

Of the 7 studies examining colon, rectal, or colorectal cancer risk, statistically significant trends for decreased risk of colon cancer were reported for Chinese men and women (Chiu *et al.*, 2003) and for Caucasians and African-Americans (Satia-Abouta *et al.*, 2003) consuming high

amounts of β-carotene. Conversely, Wakai *et al.* (2005) reported no change in risk in men but an increased trend for colorectal cancer risk in women with high serum β-carotene (p=0.04). Nkondjock and Ghadarian (2004) reported a statistically significant trend for decreased colon cancer risk only in subjects consuming high amounts of β-carotene and who had never smoked; no such relationship was observed in ever-smokers. None of the other 3 studies reported any significant change in risk associated with dietary intake (Murtaugh *et al.*, 2003; Senesse *et al.*, 2005) or circulating levels (Erhardt *et al.*, 2003) of β-carotene.

Four studies examined breast cancer risk, and 2 of these reported statistically significant trends for decreased risk associated with high dietary intake (Huang *et al.*, 2007) or circulating levels (Tamimi *et al.*, 2005) of β-carotene. The other 2 studies did not report a change in risk associated with high dietary intake (Cho *et al.*, 2003; Sesso *et al.*, 2005) or circulating levels (Sesso *et al.*, 2005). For each of gastric, lung, and skin cancer, 3 studies were identified in which risks were determined in relation to β-carotene dietary intake or circulating levels. For gastric cancer risk, 1 of the 3 studies reported a significant trend for decreased risk with high dietary intake (Larsson *et al.*, 2007) while the other 2 did not report any association with serum β-carotene levels (Abnet *et al.*, 2003; Jenab *et al.*, 2006). Similarly, the risk of lung cancer was found to be decreased in 1 study that assessed dietary intake levels (Wright *et al.*, 2003) but not in another (Yuan *et al.*, 2003), and risk also was not altered in the study that assessed circulating β-carotene levels (Goodman *et al.*, 2003). Finally, the risk of skin cancer was not decreased in 2 of the studies that assessed dietary (Fung *et al.*, 2003) or circulating levels (Schaumberg *et al.*, 2004) and the risk of squamous cell carcinoma was found to be increased (p=0.06) with higher serum β-carotene (Dorgan *et al.*, 2004). Neither of the studies that assessed esophageal cancer risk reported an effect associated with serum β-carotene (Abnet *et al.* 2003) or with dietary β-carotene (De Stefani *et al.* 2006).

A significant reduction in ovarian cancer risk was reported to be associated with high dietary β-carotene intake (Zhang *et al.*, 2007b) while no such association was found in a study of pancreatic cancer (Nkondjock *et al.*, 2005). Tobacco-related cancer risk was reported to be decreased in never smokers and increased in ever-smokers with high dietary β-carotene intakes (Touvier *et al.*, 2005), and a decrease in overall cancer mortality was found to be associated with high plasma carotene levels (α- and β-carotene) in a study by Buijsse *et al.* (2005).

As can be seen from Table 2.3.1.3-2, 38 studies (in 37 publications) were identified in which risk of cancer was assessed as a function of dietary intake or circulating levels of β-carotene. Of these 38 studies, 12 supported a significant reduction in risk of various cancers with increased intake or circulating level of β-carotene, and of these 12 supporting studies, 10 were case-control studies. Because, in case-control studies, dietary intakes are assessed retrospectively, there is large potential for recall bias, which tends to bias associations *away from the null*. Another limitation of case-control studies is that temporality (*i.e.,* whether low β-carotene intakes/circulating levels preceded the disease or whether the disease caused reductions in

intakes/circulating levels) cannot be established. Since cancer is associated with increased cell death and apoptosis (*i.e.,* oxidative stress), reduced circulating levels of β-carotene may be a consequence of the disease, rather than a risk factor for the disease.

Table 2.3.1.3-2 β-Carotene and Cancer Risk – A Summary of Findings by Study Type

Study Type	Exposure	Cancer Type[1]	Proportion of Studies Reporting Significant Risk Reduction[2,3]
Randomized controlled trial	Supplementation (20 mg/day for 5 to 8 years)	Upper aerodigestive tract	0/1 (0%)
Cohort	Circulating Levels	Skin	0/1 (0%)
	Dietary Intake	Prostate, **gastric**, **tobacco-related**, skin, lung, and breast (n=2)	2/7 (28.6%)
Case-control	Circulating Levels	Prostate (n=7), colon, rectal or colorectal (n=2), **breast** (n=2), gastric (n=2), lung, skin, **bladder**, and esophageal/upper aerodigestive tract.	2/17 (11.8%)
	Dietary Intake	**Colon, rectal, or colorectal** (n=5), **prostate** (n=3), **breast**, **ovarian**, **lung**, aerodigestive tract, and pancreatic	8/13 (61.5%)

[1] Bolded cancers are those for which significant reductions in risk with increased intake/circulating levels of β-carotene were reported.
[2] Significance was defined as P<0.05 between the treatment and placebo groups, or, for observational studies, as P<0.05 for the trend, the highest centile *versus* the lowest centile, or an intermediate centile *versus* the lowest centile.
[3] The study by Sesso *et al.* (2005) is counted both as a cohort dietary intake study and as a case-control circulating level study.

2.3.2 Cardiovascular Disease Risk

2.3.2.1 Review Articles

In a review of carotenoids and cardiovascular health, Voutilainen *et al.* (2006) identified 14 observational prospective or case-control studies that assessed the association of β-carotene (dietary intake, plasma or serum levels, or adipose tissue levels) with the risk of CVD and atherosclerosis. In 5 of 6 intake studies, β-carotene intake was associated with decreased risk of CVD outcomes, including coronary artery disease (CAD), myocardial infarction (MI), and stroke. Of 6 studies that included measurements of plasma or serum β-carotene, an inverse association between plasma or serum levels and CVD risk was observed in 4 studies, but no association was reported in 2 studies. Studies that measured adipose tissue levels of β-carotene revealed no association with risk of MI in 1 study but a reduced risk of MI with increasing β-carotene concentrations in a second study. The authors also reviewed 7 intervention studies in which subjects were provided 20 to 50 mg β-carotene/day with a follow-up period ranging from 4 to 12 years. In 3 of the 5 primary prevention studies identified, β-carotene supplementation increased ischemic heart disease, stroke mortality, first major

coronary event, or CVD mortality. No effect of β-carotene supplementation on CVD mortality was reported in the other 2 studies. A significant increase in the risk of a fatal coronary event was reported in one secondary prevention study; however, no effect on fatal or non-fatal vascular events was noted in a second study. The authors concluded that the consumption of supplemental carotenoids for heart disease treatment or prevention cannot be recommended.

2.3.2.2 Meta-Analyses and Pooled Analyses

Vivekananthan *et al.* (2003) reported the findings of a meta-analysis of randomized trials on the use of vitamin E or β-carotene for the prevention of CVD. Eight randomized trials of β-carotene treatment, all of which included 1,000 or more patients, were analyzed. Four studies were primary prevention trials or were among low-risk patients, while the remaining 4 studies were secondary prevention studies conducted in patients with known or documented vascular disease, active tobacco use or asbestos exposure, or documented history of previous malignant disease. β-Carotene was provided at doses ranging from 15 to 50 mg/day, with a follow-up period of 2.1 to 12.0 years across studies. In total, 138,113 patients were included in the meta-analysis. Cardiovascular death was assessed in 131,551 patients in 6 studies. The odds ratios for cardiovascular death with β-carotene supplementation was slightly increased (1.1; confidence interval: 1.03 to 1.17; p=0.003). In the 3 trials in which all-cause cerebrovascular accident was evaluated, there was no significant difference between β-carotene and placebo-treated patients. It was concluded that the use of supplements containing β-carotene should be discouraged due to the small but significant increase in cardiovascular death risk.

Knekt *et al.* (2004) conducted a pooled analysis of 9 prospective cohort studies that included information on dietary intakes of β-carotene, other carotenoids, vitamin E, and vitamin C, and the risk of coronary heart disease. Intakes were assessed using a food-frequency questionnaire, dietary history interview, or food records. Median dietary intakes of β-carotene across studies ranged from 813 to 4,030 µg/day. A total of 147,585 participants with β-carotene intake measures were included in the analysis. There were 2,801 incidences of coronary heart disease (including non-fatal myocardial infarction and coronary death) and 1,084 incidences of mortality. A significant inverse association was observed between dietary β-carotene intake and coronary heart disease risk using an age- and energy-adjusted model (relative risk comparing the highest to lowest quintile of intake: 0.84; confidence interval: 0.74 to 0.95; p for trend: 0.01); however, significance disappeared in multivariate models adjusted for potential non-dietary and dietary confounding factors. The association between overall β-carotene intake (dietary and supplemental) and coronary heart disease risk was non-significant. Based on the findings of this pooled analysis, the authors stated that the risk reductions for major coronary heart disease events at high carotenoid intakes appear to be small.

2.3.2.3 Primary Research Articles

Pertinent data from primary research studies can be found in **Attachment I** to **Appendix C**. One secondary prevention trial was identified in which β-carotene supplementation was assessed for its efficacy in reducing the risk of major CVD, which included MI, revascularization, stroke, transient ischemic attack, and CVD death (Cook *et al.*, 2007). Study participants included female health professionals with a reported history of CVD or at least 3 cardiac risk factors. Supplementation with 50 mg β-carotene on alternate days for a mean period of 9.4 years had no significant effect on the primary combined endpoint of major CVD or on the individual outcomes.

A total of 3 observational cohort studies that assessed the relationship between plasma or dietary β-carotene and CVD were identified. In the 1 study that measured plasma β-carotene levels, a significant decrease in CVD mortality risk (including total and from stroke) was reported with increasing β-carotene levels; however, no significant reduction in risk of mortality from heart disease was observed (Ito *et al.*, 2006). Two studies were identified in which the relationship between dietary β-carotene intake and CVD risk was evaluated (Osganian *et al.*, 2003; Buijsse *et al.*, 2008). In both studies, an inverse association between dietary β-carotene intake and cardiovascular mortality or total CAD (which included non-fatal MI and fatal CAD) was reported; the association was reported to be significant in 1 study (Osganian *et al.,* 2003), and in the other study, the significance of the association was not reported (Buijsse *et al.,* 2008).

There were 3 case-control studies in which the relationship between plasma, adipose tissue, or dietary β-carotene and CVD risk were identified. In 1 study (Hak *et al.*, 2003), risk of myocardial infarction was significantly reduced in an intermediate centile *versus* the lowest centile, while an inverse association between adipose tissue β-carotene levels (but not dietary intake) and MI risk was noted in another study (Kabagambe *et al.*, 2005). Decreased risk of MI with increasing β-carotene intake was reported by Tavani *et al.* (2006).

An abbreviated summary of these studies is provided in Table 2.3.2.3-1 (for more extensive tabular summaries of study findings, see **Attachment I** to **Appendix C**). In Table 2.3.2.3-2, study results are summarized according to study type.

Table 2.3.2.3-1 Summary of Observational Studies Assessing β-Carotene Intakes or Circulating Levels with Cardiovascular Disease Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs*. Lowest Centile (OR or RR and 95% CI)	Intermediate *vs*. Lowest Centile (OR or RR and 95% CI)
Myocardial infarction					
Hak *et al.*, 2003	Nested case-control	Plasma β-carotene	NS	NS	0.60 (0.36-0.98)
Kabagambe *et al.*, 2005	Case-control	Adipose tissue β-carotene	↓ (p=0.02)	0.70 (0.51-0.96)	0.74 (0.55-0.99)
		Dietary intake *via* FFQ	NS	NS	NS
Tavani *et al.*, 2006	Case-control	Dietary intake *via* FFQ at baseline only	↓ (p=0.037)	NS	NS
CVD mortality					
Buijsse *et al.*, 2008	Cohort	Dietary intake *via* FFQ	↓ (p NR)	NR	NR
Ito *et al.*, 2006	Cohort	Serum β-carotene	CVD mortality: ↓ (p=0.007)	NR	NR
			Heart disease mortality: NS	NR	NR
			Stroke mortality: ↓ (p=0.002)	NR	NR
CAD					
Osganian *et al.*, 2003	Cohort	Dietary intake *via* FFQ	↓ (p=0.05)	0.74 (0.59-0.93)	0.69 (0.56-0.85)

Abbreviations: ↓, decreased; ↑, increased; CAD, coronary artery disease; CVD, cardiovascular disease; FFQ, food frequency questionnaire; NR; not reported; NS, not significant.

Table 2.3.2.3-2 β-Carotene and CVD Risk – A Summary of Findings by Study Type

Study Type	Exposure	Endpoint[1]	Proportion of Studies Reporting Significant Risk Reduction[2]
Randomized controlled trial	Supplementation (50 mg/day for approximately 9.4 years)	Recurrent CVD (myocardial infarction, revascularization, stroke, transient ischemic attack) or CVD death	0/1 (0%)
Cohort	Circulating Levels	**CVD mortality**, heart disease mortality, **stroke mortality**	1/1 (100%)
	Dietary Intake	CVD mortality, **CAD**	1/2 (50.0%)
Case-control	Circulating Levels/Adipose Tissue Levels	**Myocardial infarction** (n=2)	2/2 (100.0%)
	Dietary Intake	Myocardial infarction (n=2)	1/2 (50.0%)

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease.
[1] Bolded items are those for which significant reductions in risk with increased intake/circulating levels of β-carotene were reported.
[2] Significance was defined as P<0.05 between the treatment and placebo groups, or, for observational studies, as P<0.05 for the trend, the highest centile *versus* the lowest centile, or an intermediate centile *versus* the lowest centile.

2.3.2.4 Summary

In a published review of intervention studies, β-carotene supplementation increased CVD risk in 3 of 5 primary prevention trials and 1 of 2 secondary prevention trials, while no effect was reported in the remaining 2 primary prevention trials and in 1 secondary prevention trial. A meta-analysis of randomized controlled trials assessing the effects of β-carotene on CVD risk demonstrated a small but significant increase in the risk of death from CVD. Conversely, the human intervention study published subsequent to 2003 failed to show a significant decrease in CVD risk. Data reported in observational studies are inconsistent, with some showing a significant decrease in CVD risk with increased dietary intakes or plasma levels of β-carotene, and others showing no effect. Observational studies are associated with several methodological limitations, and findings from human intervention trials take precedence over findings from observational studies in establishing causality. Data from human intervention trials suggest that β-carotene supplementation either increases or has no effect on CVD risk.

3.0 LYCOPENE

3.1 Introduction

Lycopene, as with the other major dietary carotenoid antioxidants, is synthesized by plants and microorganisms but not by animals or humans. It is present at various levels in a number of foods including tomatoes and tomato-based products, watermelon, guava, grapefruit, papaya, and others (Holden *et al.*, 1999). The biological activity of lycopene has been attributed primarily to its antioxidant properties, although other effects including facilitation of gap junction communication, immune system stimulation, and cell cycle regulation have been proposed

(Rao *et al.*, 2006). Of note, lycopene lacks a β-ionic ring structure and therefore lacks the provitamin A activity that is common to other carotenoids such as β-carotene.

Lycopene is absorbed in the intestines by passive diffusion where it is incorporated into chylomicrons and transported *via* the lymphatic system to the liver. Bioavailability ranges from 10 to 30%, although a number of biological and lifestyle factors have been identified that influence the absorption of lycopene, including age, gender, hormonal status, blood lipid levels, smoking, alcohol consumption, and others (Rao *et al.*, 2006). Lycopene is incorporated into lipoproteins in the liver and distributed throughout the body *via* the circulation. Tissue concentrations of lycopene vary greatly with the highest concentrations observed in the testes, adrenal glands, liver, and prostate; measurable lycopene levels have also been reported for breast, colon, kidney, lung, ovary, pancreas, skin, and stomach. Concentrations of lycopene in the plasma and tissues of humans generally reflect dietary intake (Rao *et al.*, 2006).

3.2 Authoritative Body Statements and Opinions on Lycopene and Cancer Risk

Lycopene has been touted as a beneficial agent for the promotion and maintenance of health, and particularly as a potential protective agent against a variety of cancers. Indeed, 2 health claim petitions were submitted to the FDA in 2004 regarding consumption of tomatoes, tomato-based products, and/or lycopene and a reduced risk of a variety of cancers including prostate, gastric, ovary, lung, pancreatic, colorectal, breast, and other cancers. A number of statements and recommendations from authoritative bodies and regulatory agencies that pertain to the potential beneficial health effects of lycopene have been published or made available to the public through electronic dissemination. In general, these statements conclude that there is no credible scientific evidence to support lycopene (alone or as a component of lycopene-containing foods such as tomatoes and tomato-based products) as a protective agent against any form of cancer. The FDA issued letters of enforcement discretion (U.S. FDA, 2005b,c) for the 2 health claim petitions noted above that outlined a number of flaws and data gaps in the studies that were submitted in support of the health claim petitions. Statements by the WCRF/AICR, the IARC, the Food and Nutrition Board of the Institute of Medicine, and the American Cancer Society (Table 1.1-2) similarly indicate that while beneficial health effects have been documented for lycopene-containing foods such as tomatoes and tomato products, it is not possible to discern whether the observed beneficial effects are due to lycopene, other nutrients in lycopene-containing products, lifestyle factors associated with consumption of lycopene-containing products, a combination of these, or other factors altogether.

3.3 Review of Scientific Literature Pertaining to Lycopene and Cancer Risk

As some of the authoritative body statements described above are several years old, a literature search was conducted to identify articles that relate to the effects of lycopene on cancer risk that have been recently published in the scientific literature. Specifically, this search focused on

identifying articles published in the last 5 years (*i.e.*, from 2003 to the present) and aimed to identify reviews, meta-analyses, and primary intervention and observational studies in humans. The search terms that were used included [(lycopene OR 502-65-8) AND (human OR humans OR subject OR subjects OR patient? OR clinical? OR volunteer? OR double OR blind OR double blind OR epidemiol OR case OR stud? OR control OR cohort? OR intervention? OR observation? OR meta OR analysis) AND (cancer? OR tumor? OR tumour? OR neoplas?)]. The search identified these terms in the title or abstract of articles contained in the following databases: Medline, ToxFile, AGRIS, Agricola, FSTA, Foodline, Biosis Previews, NTIS, and EMBASE. For the primary studies that were identified, a critical assessment of the methodologies and endpoints described in the publications was performed. The results of the literature search and the assessment of the data contained in the articles that were identified are described in the following sections.

3.3.1 Review Articles on Lycopene and Cancer Risk

The vast majority of the review articles identified were concerned with the potential effects of lycopene on prostate cancer risk. Dagnelie *et al.* (2004) conducted a review of prospective cohort and intervention studies on potential dietary risk factors for prostate cancer that were published between 1966 and September 2003. The authors identified a total of 5 studies that matched their search criteria. Two of these studies were cohort studies in which serum levels of lycopene were measured, and both reported a reduced risk (defined by Dagnelie *et al.* as a relative risk estimate <0.80) of prostate cancer with elevated blood levels of lycopene. In 3 other cohort studies in which dietary lycopene was estimated using questionnaires or interviews, a decreased risk associated with increased lycopene intake was observed in one study but no change in risk was observed in the other two. Thus, the authors concluded that the available studies suggest a possible protective effect of tomatoes/lycopene in reduced prostate cancer risk (Dagnelie *et al.*, 2004).

Kristal (2004) reviewed the experimental and epidemiological evidence for vitamin A, retinoids, and carotenoids as chemopreventive agents for prostate cancer. Details of the review method were not provided, but the author indicated that 5 prospective studies and 3 case-control studies were identified in which plasma lycopene and prostate cancer risk were assessed. Overall, the epidemiological evidence for a protective effect of tomato products and/or lycopene on prostate cancer risk was suggested to be modest, and the author concluded that there is “currently little support from animal or human experimental studies for their use as chemopreventive agents” (Kristal, 2004). Fraser *et al.* (2005) also assessed the potential utility of lycopene as a protective agent against prostate cancer by reviewing cohort, nested case-control, and case-control studies identified in searches of PubMed and other databases. The results of 13 studies were assessed, including 2 cohort, 3 nested case-control, and 8 case-control studies, all of which demonstrated either a null effect or some degree of a protective effect of lycopene. The authors concluded that although there is emerging evidence for a protective effect of lycopene,

it is premature to recommend pharmacologic supplementation of lycopene as the "protective effect of pure lycopene in the absence of other compounds within tomatoes cannot be substantiated" (Fraser *et al.*, 2005).

Several other reviews of chemoprevention strategies for prostate cancer include excerpts on the potential benefits of lycopene (Neill and Fleshner, 2006; Gupta, 2007; Syed *et al.*, 2007; Thompson, 2007; Cheung *et al.*, 2008). None of these reviews, however, indicate that lycopene is a bona fide protective factor against prostate cancer. Rather, they all suggest that study results pertaining to the potential effects of lycopene on prostate cancer risk are promising but unclear and that tomatoes or tomato-based products, rather than lycopene itself, may be preferable as a modifiable dietary factor to reduce prostate cancer risk.

Three additional review articles were identified, 2 of which assessed the effects of lycopene on lung and breast cancer, respectively, and one of which provided a summary of the FDA's review of the qualified health claims for tomatoes and lycopene described above. The review by Ruano-Ravina *et al.* (2006) evaluated articles published between 1994 and October 2003 that reported the results of cohort and case-control studies pertaining to lycopene and lung cancer, although case-control studies with less than 300 subjects were not assessed. The authors indicated that of the 7 studies that were reviewed, only one reported a statistically significant protective effect of lycopene against lung cancer. Wane and Lengacher (2006) performed an integrative review of lycopene and breast cancer that focused on analyzing the published literature regarding lycopene, its antioxidant capacity, and its nutritive and physiologic effects on breast cancer. As such, the authors included a total of 40 articles reporting cell, animal, and human studies that fit these criteria and that were published between 1990 and 2004. The overall conclusion from the review was that effects of lycopene on breast cancer are difficult to assess given the "multiple nutritional variables studied that affected statistical interpretation and application" (Wane and Lengacher, 2006). Finally, the review by Kavanaugh *et al.* (2007) is a published summary of the approach and conclusions reached by the FDA with regard to its assessment of the qualified health claims for tomatoes and lycopene that were submitted to the agency in 2004. In summary, this review concluded that there was "no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric, and pancreatic cancers" (Kavanaugh *et al.*, 2007).

3.3.2 Meta-Analyses and Pooled Analyses on Lycopene and Cancer Risk

One meta-analysis and 3 pooled analyses related to lycopene and cancer risk were identified. Each of these analyses is described briefly below.

The meta-analysis by Etminan *et al.* (2004) evaluated the role of tomato products and lycopene in the prevention of prostate cancer in 11 case-control and 10 cohort studies published up to March 2003. Measurements of tomato and/or lycopene intake or of serum lycopene concentrations were evaluated based on quartiles or quintiles (depending on how they were reported in the original studies), and pooled relative risk ratios were determined for raw tomatoes, cooked tomatoes, lycopene intake, and serum lycopene. When assessed together, a pooled analysis of the results of 7 case-control and 3 cohort studies in which lycopene intake was reported revealed a significant effect of high lycopene intake (corresponding to the 5th quintile of distribution) on prostate cancer risk (RR: 0.89, 95% CI: 0.81-0.98). When assessed separately, a statistically significant effect of high lycopene intake was observed only for the cohort studies (RR: 0.84, 95% CI: 0.75-0.95). For studies that included measurements of serum lycopene, a pooled analysis of the 2 case-control and 5 cohort studies resulted in a significant effect of moderate (corresponding to the 2nd, 3rd, and 4th quintiles of the distribution) and high serum lycopene concentrations on prostate cancer risk (RR: 0.85, 95% CI: 0.75-0.97 and RR: 0.74, 95% CI: 0.59-0.92, respectively). Assessment of the case-control and cohort studies separately revealed a significant effect of high serum lycopene concentration on the risk of prostate cancer (RR: 0.55, 95% CI: 0.32-0.94 for case-control studies and RR: 0.78, 95% CI: 0.61-1.00 for cohort studies). The authors stated that despite the preventive effects of lycopene reported in the meta-analysis, the existing evidence is insufficient to recommend lycopene supplementation for the prevention of prostate cancer.

Männistö *et al.* (2004) assessed the relationship between dietary carotenoids and the risk of lung cancer from a pooled analysis of 7 cohort studies as part of the Pooling Project of Prospective Studies of Diet and Cancer. A random-effects model was used to combine the relative risks for developing lung cancer that were calculated for 7 cohort studies that were performed in North America and Europe, each of which determined dietary carotenoid intake at baseline through the use of a validated dietary questionnaire. During a follow-up of up to 7 to 16 years, a total of 3,155 incident cases of lung cancer were diagnosed among 399,765 participants of the cohort studies. The multivariate relative risk for the highest compared to the lowest quintile of lycopene intake was 0.91 (95% CI: 0.78-1.07) and the overall trend was not significant (p=0.42). No statistically significant associations between lycopene intake and lung cancer risk were found based on smoking status or lung cell type, although current smokers had a multivariate relative risk of 0.81 (95% CI: 0.70-0.94) for the highest *vs*. lowest lycopene intake quartile and an overall trend toward reduced cancer risk (p=0.06) (Männistö *et al.*, 2004).

Koushik *et al.* (2006) evaluated the intake of the major carotenoids and the risk of epithelial ovarian cancer in a pooled analysis of 10 cohort studies. Intakes were assessed using food frequency questionnaires administered at baseline in each of the 10 studies. During a follow-up of 7 to 22 years across studies, 2,012 cases of ovarian cancer occurred among the 521,911 subjects. Multivariate analyses revealed no association between lycopene intake and ovarian cancer, with a relative risk comparing the highest and lowest quintile of intake of 0.97 (95% CI:

0.84-1.12; p value for trend: 0.95), and there was no evidence of statistically significant heterogeneity between studies. Moreover, associations between lycopene intake and ovarian cancer risk did not vary significantly by histological type of ovarian cancer or by population subgroup. It was concluded that consumption of lycopene during adulthood was not associated with ovarian cancer risk (Koushik *et al.*, 2006).

More recently, Männistö *et al.* (2007) conducted a pooled analysis of 11 cohort studies carried out in North America and Europe that investigated dietary carotenoids and the risk of colorectal cancer. Baseline intakes of specific carotenoids were estimated using food frequency questionnaires, and the follow-up period for each study ranged from 6 to 20 years (between 1980 and 2003). A total of 7,885 incident cases of colorectal cancer were diagnosed in the 702,647 participants in the studies. The pooled multivariate relative risk of colorectal cancer comparing the highest and lowest quintile of lycopene intake was 1.04 (95% CI: 0.96-1.12; p value for trend: 0.60). No significant between-studies heterogeneity was reported for the 5th quintile of lycopene intake, and no significant association between lycopene intake and colorectal cancer at any specific subsite (colon, proximal colon, distal colon, or rectum) was observed. The authors concluded that the pooled data did not support a reduction in risk of colorectal cancer risk with increased lycopene intake (Männistö *et al.*, 2007).

3.3.3 Primary Research Articles on Lycopene and Cancer Risk

Pertinent data from primary research articles can be found in **Attachment I** to **Appendix C**. No intervention studies assessing lycopene and cancer risk were identified, although there were 2 intervention studies that examined the influence of lycopene on prostate specific antigen (PSA) levels in men (**Attachment I** to **Appendix C**). Bunker *et al.* (2007) conducted an unblinded, randomized, Phase I clinical trial in men with elevated prostate cancer risk (defined as men with high-grade prostatic intraepithelial neoplasia, atypical foci, or repeated non-cancerous biopsies). Men received 4 months intervention with 30 mg/day lycopene plus a multivitamin (38 men) or a multivitamin alone (39 men), after which serum lycopene and PSA levels were measured and compared to baseline. Measurements were also performed after 1 month of intervention. Combined treatment with lycopene and the multivitamin was found to increase serum lycopene concentrations at both 1 and 4 months compared to baseline whereas the multivitamin alone did not. However, no statistically significant effect of lycopene supplementation, either alone or in combination with the multivitamin, on serum PSA levels was observed at 1 or 4 months compared to baseline. Thus, lycopene supplementation increased circulating lycopene concentrations but did not alter serum PSA levels in men with high prostate cancer risk (Bunker *et al.*, 2007).

The second intervention trial (Schwarz *et al.,* 2008) included elderly men free of prostate cancer with histologically proven benign prostate hyperplasia and PSA levels >4 µg/L. Benign prostatic hyperplasia is characterized by hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large nodules in the periurethral region of the prostate, which results in the

compression of the urethra and an interference in the normal flow of urine. PSA levels are typically elevated in patients with benign prostatic hyperplasia because of increased organ volume and inflammation due to urinary tract infections; however, benign prostatic hyperplasia is not considered to be a premalignant lesion. The condition starts at approximately 30 years of age. By 50 years of age, about 50% of men have histologic evidence of BPH, and 75% by 80 years of age.

The men were supplemented for 6 months with either lycopene (15 mg/day) or placebo. Following the 6-month intervention period, prostate weight (as assessed by trans-rectal ultrasonography) increased significantly from baseline by 23.7% in the placebo group; however, there were no between-group differences. Prostate volume (as assessed by digital rectal examination) increased significantly from baseline in the placebo group by 26.8%; however, in a recent study involving 1688 men (the Krimpen Study; Bosch *et al.,* 2004), digital rectal examination was found to have limited value in the estimation of prostate volume, and was found to be accurate only in identifying very large prostates (>50 mL). Prostate volumes were below 50 mL at baseline in both groups. The placebo group (but not the treatment group) had significant reductions from baseline in energy intake, total cholesterol, and LDL cholesterol, suggesting that the groups differed with respect to various dietary and lifestyle factors, and that the study failed to control for these. A significant inverse association has been reported for HDL cholesterol and prostate weight (Hammarsten *et al.,* 1997; Nukui, 1997; Ozden *et al.,* 2007), and if HDL cholesterol was lowered in the placebo group, this may have resulted in an increase in prostate weight. Thus, although this study suggests that lycopene supplementation may attenuate the progression of benign prostatic hyperplasia, the study failed to account for several confounding variables, thereby limiting interpretation of study results.

A total of 32 observational studies (reported in 31 publications) were identified in which dietary intakes or circulating levels of lycopene were assessed and quantified (*i.e.*, tertiles, quartiles, or quintiles of intake or blood levels) and their possible relation to cancer risk determined.

Thirteen studies assessed the potential relationship between lycopene and prostate cancer risk (Goodman *et al.*, 2003; Huang *et al.*, 2003; Bosetti *et al.*, 2004; Wu *et al.*, 2004; Chang *et al.*, 2005; Jian *et al.*, 2005; McCann *et al.*, 2005; Kirsh *et al.*, 2006a; Kirsh *et al.*, 2006b; Key *et al.*, 2007; Jian *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a), 4 studies assessed breast cancer risk (Cho *et al.*, 2003; Sesso *et al.*, 2005; Tamimi *et al.*, 2005; Huang *et al.*, 2007), and 4 studies assessed colon, rectal, or colorectal cancer risk (Murtaugh *et al.*, 2004; Nkondjock and Ghadirian, 2004; Wakai *et al.*, 2005; Kune and Watson, 2006). The remaining 11 studies assessed associations with lung (Goodman *et al.*, 2003; Wright *et al.*, 2003; Yuan *et al.*, 2003), bladder (Hung *et al.*, 2006), esophagus (De Stefani *et al.*, 2006), ovarian (Zhang *et al.*, 2007b), pancreatic (Nkondjock *et al.*, 2005), uterine (Terry *et al.*, 2008), skin (Dorgan *et al.*, 2004), and gastric cancers (Jenab *et al.*, 2006; Larsson *et al.*, 2007). A summary of these studies is presented in Table 3.3.3-1.

Table 3.3.3-1 Summary of Studies Assessing Lycopene Intakes or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Prostate cancer					
Kirsh *et al.*, 2006a	Cohort	Dietary intake *via* FFQ at baseline only	NS	NS	NS
Kirsh *et al.*, 2006b	Cohort	Dietary intake *via* FFQ at baseline	NS	NS	NS
Chang *et al.*, 2005	Case-control	Plasma lycopene	NS	NR	NR
Goodman *et al.*, 2003	Nested case-control	Serum lycopene	NS	NS	0.47 (0.26-0.87)
Key *et al.*, 2007	Nested case-control	Plasma lycopene	NS for localized disease	NS	NS
			p=0.05 for advanced disease	0.40 (0.19-0.88)	NS
Bosetti *et al.*, 2004	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Huang *et al.*, 2003	Nested case-control	Serum lycopene	NS	NS	NS
Jian *et al.*, 2005	Case-control	Dietary intake *via* FFQ	↓ (p=0.009)	0.18 (0.08-0.41)	0.41 (0.21-0.77)
Jian *et al.*, 2007	Case-control	Dietary intake *via* FFQ	↓ (p NR)	0.17 (0.08-0.39)	0.40 (0.21-0.77)
McCann *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Peters *et al.*, 2007	Nested case-control	Serum lycopene	NS	NS	NS
Wu *et al.*, 2004	Nested case-control	Serum lycopene	NS	NS	NS
Zhang *et al.*, 2007a	Case-control	Plasma lycopene	NS	NS	NS
Breast cancer					
Cho *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline and 4 years later	NS	NS	NS
Sesso *et al.*, 2005	Cohort and nested case-control	Dietary intake *via* FFQ at baseline, and plasma lycopene at baseline	NS	NS	NS

Table 3.3.3-1 Summary of Studies Assessing Lycopene Intakes or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Huang *et al.*, 2007	Case-control	Dietary intake *via* FFQ	↓ (p<0.001)	0.26 (0.14-0.46)	0.17 (0.08-0.34)
Tamimi *et al.*, 2005	Nested case-control	Plasma lycopene	NS	NS	NS
Colon, rectal, or colorectal cancer					
Wakai *et al.*, 2005	Nested case-control	Serum lycopene	NS	NS	NS
Kune and Watson, 2006	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Murtaugh *et al.*, 2004	Case-control	Dietary intake *via* FFQ	NS for men	NS	NS
			↓ (p=0.01) for women	NS	NS
Nkondjock and Ghadirian, 2004	Case-control	Dietary intake *via* FFQ	p=0.05 for ever-smokers	0.63 (0.40-0.98)	NS
			NS for never-smokers	NS	NS
Lung cancer					
Goodman *et al.*, 2003	Nested case-control	Serum lycopene	NS	NS	NS
Yuan *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline	NS (p value not reported)	NS	NS
Wright *et al.*, 2003	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Skin cancer					
Dorgan *et al.*, 2004	Cohort	Serum lycopene	NS	NS	NS
Uterine cancer					
Terry *et al.*, 2008	Cohort	Dietary intake *via* FFQ at baseline	NS	NS	NS
Gastric cancer					
Jenab *et al.*, 2006	Nested case-control	Serum lycopene	NS	NS	NS
Larsson *et al.*, 2007	Cohort	Dietary intake *via* FFQ at baseline	NS	NS	NS
Bladder cancer					
Hung *et al.*, 2006	Case-control	Plasma lycopene	NS	NS	NS

Table 3.3.3-1 Summary of Studies Assessing Lycopene Intakes or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Esophageal cancer					
De Stefani *et al.*, 2006	Case-control	Dietary intake *via* FFQ	↓ (p<0.0001)	0.29 (0.18-0.49)	0.50 (0.32-0.77)
Ovarian cancer					
Zhang *et al.*, 2007b	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Pancreatic cancer					
Nkondjock *et al.*, 2005	Case-control	Dietary intake *via* FFQ	↓ (p=0.026) for men	0.69 (0.46-0.96)	NS
			NS for women	NS	NS

Abbreviations: ↓, decreased; FFQ, food frequency questionnaire; NR, not reported; NS, not significant

For prostate cancer risk, 2 of the 13 studies indicated a statistically significant trend for a protective effect of lycopene (determined by dietary intake). In 1 of these studies the statistical value for the trend was p=0.009 (Jian *et al.*, 2005). The statistical value of the trend was not provided in the other study although the relative risk of the highest *versus* the lowest quartile of lycopene intake was 0.17 (95% CI: 0.08-0.39) (Jian *et al.*, 2007). Two studies indicated trends for a protective effect of high circulating lycopene levels on advanced prostate cancer (Key *et al.*, 2007) or on prostate cancer in general (Zhang *et al.*, 2007a) that bordered on statistical significance (p=0.05 and 0.075, respectively). None of the other 9 studies provided evidence of a protective effect of high dietary intake (Bosetti *et al.*, 2004; McCann *et al.*, 2005; Kirsh *et al.*, 2006a; Kirsh *et al.*, 2006b) or high circulating levels (Goodman *et al.*, 2003; Huang *et al.*, 2003; Wu *et al.*, 2004; Chang *et al.*, 2005; Peters *et al.*, 2007) of lycopene on prostate cancer risk.

Of the 4 studies examining breast cancer risk, one indicated a statistically significant trend for a reduction in risk associated with high lycopene intake (Huang *et al.*, 2007) while the other 3 did not find similar effects for high intake (Cho *et al.*, 2003; Sesso *et al.*, 2005) or high circulating levels (Sesso *et al.*, 2005; Tamimi *et al.*, 2005) of lycopene. Potentially beneficial effects of high lycopene intake were reported for the risks of colon and rectal cancers in 2 of the 4 studies examining these relationships. Specifically, Nkondjock and Ghadirian (2004) found a borderline significant trend (p=0.05) for a reduced risk of colon cancer with higher lycopene intake levels, but only in subjects that had smoked at some time in their lives; the risk in never-smokers was not affected by lycopene intake. Moreover, high intake levels were also found to be associated with a reduced risk of rectal cancer in women (p=0.01) but not in men (Murtaugh *et al.*, 2004).

The other 2 studies did not find associations between colorectal cancer risk and serum levels (Wakai *et al.*, 2005) or intake levels (Kune and Watson, 2006) of lycopene.

The remaining 10 studies assessed the potential association between dietary intake or circulating levels of lycopene and the risks of lung, bladder, esophagus, ovarian, pancreatic, uterine, skin, and gastric cancers. Of these, beneficial effects of high lycopene intake were reported for the risk of esophageal cancer (De Stefani *et al.*, 2006) and for the risk of pancreatic cancer in men but not women (Nkondjock *et al.*, 2005). A protective effect of borderline statistical significance (p=0.059) was also reported for high circulating lycopene levels on the risk of bladder cancer (Hung *et al.*, 2006). None of the other studies reported any change in cancer risk associated with dietary intake (Wright *et al.*, 2003; Yuan *et al.*, 2003; Larsson *et al.*, 2007; Zhang *et al.*, 2007b; Terry *et al.*, 2008) or circulating levels (Goodman *et al.*, 2003; Dorgan *et al.*, 2004) of lycopene.

As can be seen from Table 3.3.3-2, of the 32 observational studies identified (in 31 publications), significant inverse associations between cancer risk and dietary intakes/circulating levels of lycopene were reported in 9 studies (*i.e.,* 4 for prostate cancer risk; 1 for breast cancer risk; 2 for colon, rectal, or colorectal cancer risk; 1 for esophageal cancer; and 1 for pancreatic cancer). All observational studies in which increased intakes of lycopene were associated with decreased risk of cancer were case-control studies. Case-control studies are of limited value in establishing causality, given that dietary intakes are assessed retrospectively and are subject to recall bias, which tends to drive associations *away from the null*. Furthermore, it is difficult to establish temporality (*i.e.,* that decreased intakes/circulating levels of lycopene preceded the development of cancer), given that cancer is associated with extensive cell death and apoptosis (*i.e.,* oxidative stress), and that it is possible that reduced circulating levels of lycopene are a *consequence*, as opposed to a *cause*, of the disease.

Table 3.3.3-2 Lycopene and Cancer Risk – A Summary of Findings by Study Type

Study Type	Exposure	Cancer Type[1]	Proportion of Studies Reporting Significant Risk Reduction[2,3]
Randomized controlled trial	Supplementation (30 mg/day with a multivitamin for 4 months)	Prostate[4]	0/1 (0%)
Cohort	Circulating Levels	Skin	0/1 (0%)
	Dietary Intake	Prostate (n=2), breast (n=2), lung, uterine, gastric	0/7 (0%)
Case-control	Circulating Levels	**Prostate** (n=7), breast (n=2), colon, rectal, or colorectal, lung, gastric, bladder	2/13 (15.4%)
	Dietary Intake	**Prostate** (n=4), **breast**, **colon, rectal, or colorectal** (n=3), lung, **esophageal**, ovarian, **pancreatic**	7/12 (58.3%)

[1] Bolded cancers are those for which significant reductions in risk with increased intake/circulating levels of lycopene.
[2] Significance was defined as P<0.05 between the treatment and placebo groups, or, for observational studies, as P<0.05 for the trend, the highest centile *versus* the lowest centile, or an intermediate centile *versus* the lowest centile.
[3] The study by Sesso *et al.* (2005) is counted both as a cohort dietary intake study and as a case-control circulating level study.
[4] Serum levels of prostate-specific antigen (PSA) were measured as a surrogate marker for prostate cancer in men at high risk of developing prostate cancer.

In summary, a review of the recent published scientific literature indicates that minimal evidence exists for a beneficial effect of lycopene on cancer risk, a finding consistent with all authoritative body recommendations and position statements.

4.0 β-CRYPTOXANTHIN

4.1 Introduction

β-Cryptoxanthin is a common carotenoid in the human diet and is found in a variety of foods including red peppers, mango, papaya, tangerines, and others (Holden *et al.*, 1999). As it can be converted to retinol, the active form of vitamin A, β-cryptoxanthin is considered a provitamin A carotenoid. β-Cryptoxanthin can be absorbed intact in the intestines or cleaved to form vitamin A prior to secretion into lymph (IOM, 2000). Distribution occurs *via* the circulation where β-cryptoxanthin is associated with lipoproteins, particularly the high-density lipoprotein (HDL) fraction (IOM, 2000), and storage of β-cryptoxanthin and other carotenoids occurs in many organs including adipose tissue, liver, kidney, and adrenal glands (IOM, 2006). As with other provitamin A carotenoids, the only known function of β-cryptoxanthin in humans is to serve as a source of vitamin A (IOM, 2000).

Although β-cryptoxanthin is a provitamin A carotenoid, olestra is enriched with sufficient pre-formed vitamin A to offset any effect on the absorption of β-cryptoxanthin.

4.2 Authoritative Body Statements and Opinions on β-Cryptoxanthin and Cancer Risk

No authoritative body statements specific to β-cryptoxanthin were identified in the published literature. Statements by the WCRF/AICR, IARC, the Food and Nutrition Board of the Institute of Medicine, and the American Cancer Society (Table 1.1-2) indicate that while beneficial health effects of foods containing carotenoids have been documented, it is not possible to discern whether the observed beneficial effects are due to a particular carotenoid such as β-cryptoxanthin, other nutrients in β-cryptoxanthin-containing products, lifestyle factors associated with consumption of β-cryptoxanthin-containing products, a combination of these, or other factors altogether.

A summary of the authoritative body position statements and recommendations regarding β-cryptoxanthin is provided in Table 1.1-2.

4.3 Review of Scientific Literature Pertaining to β-Cryptoxanthin and Cancer Risk

As some of the authoritative body statements and position documents described above are several years old, a literature search was conducted to identify articles that relate to the effects of β-cryptoxanthin on cancer risk that have been recently published in the scientific literature. Specifically, this search focused on identifying articles published in the last 5 years (*i.e.*, from 2003 to the present) and aimed to identify reviews, meta-analyses, and primary intervention and observational studies in humans. The search terms that were used included [(beta cryptoxanthin OR beta caroten-3-ol OR 472-70-8) AND (human OR humans OR subject OR subjects OR patient? OR clinical? OR volunteer? OR double OR blind OR double blind OR epidemiol OR case OR stud? OR control OR cohort? OR intervention? OR observation? OR meta OR analysis) AND (cancer? OR tumor? OR tumour? OR neoplas?)]. The search identified these terms in the title or abstract of articles contained in the following databases: Medline, ToxFile, AGRIS, Agricola, FSTA, Foodline, Biosis Previews, NTIS, and EMBASE. For the primary studies that were identified, a critical assessment of the methodologies and endpoints described in the publications was performed. The results of the literature search and the assessment of the data contained in the articles that were identified are described in the following sections.

4.3.1 Review Articles on β-Cryptoxanthin and Cancer Risk

No review articles specific to the potential effects of β-cryptoxanthin on cancer risk were identified. Two review articles in which β-cryptoxanthin was discussed as one of several carotenoids that may contribute to cancer risk reduction were identified and are described below.

Dagnelie *et al.* (2004) conducted a review of prospective cohort and intervention studies on potential dietary risk factors for prostate cancer that were published between 1966 and September 2003. The authors identified one cohort study in which serum levels of β-cryptoxanthin were measured and were found to not be associated with reduced risk (relative risk estimate =0.80) of prostate cancer. One cohort study was also identified in which dietary β-cryptoxanthin was estimated using a dietary questionnaire and which did not report any change in prostate cancer risk associated with higher intake levels. The authors did not provide any conclusion specific to the data for β-cryptoxanthin that were analyzed in their review (Dagnelie *et al.*, 2004).

Ruano-Ravina *et al.* (2006) evaluated articles published between 1994 and October 2003 that reported the results of cohort and case-control studies pertaining to β-cryptoxanthin and lung cancer, although case-control studies with less than 300 subjects were not assessed. The authors reviewed a total of 7 studies that included 5 cohort and 2 case-control studies. Three of the 5 cohort studies reported a significant protective effect of β-cryptoxanthin for subjects with the highest intake, while the 2 case-control studies reported risk ratios of 0.82 (non-significant) and 0.29 (significance not indicated). Apparent protective effects in smokers were reported in 2 cohort studies but not in a third that assessed data based on smoking status (Ruano-Ravina *et al.*, 2006).

4.3.2 Meta-Analyses and Pooled Analyses on β-Cryptoxanthin and Cancer Risk

No meta-analyses related to β-cryptoxanthin and cancer risk were identified. However, 3 pooled analyses related to β-cryptoxanthin and cancer risk were identified and are described briefly below.

Männistö *et al.* (2004) assessed the relationship between dietary carotenoids and the risk of lung cancer from a pooled analysis of 7 cohort studies as part of the Pooling Project of Prospective Studies of Diet and Cancer. A random-effects model was used to combine the relative risks for developing lung cancer that were calculated from 7 cohort studies that were performed in North America and Europe, each of which determined dietary carotenoid intake at baseline through the use of a validated dietary questionnaire. During a follow-up of up to 7 to 16 years, a total of 3,155 incident cases of lung cancer were diagnosed among 399,765 participants of the cohort studies. The multivariate relative risk for the highest compared to the lowest quintile of β-cryptoxanthin intake was 0.76 (95% CI: 0.67-0.86) and the overall trend was statistically significant ($p<0.001$). Moreover, a statistically significant inverse association between β-cryptoxanthin intake and lung cancer risk was identified for current smokers; the multivariate relative risk for the highest compared to the lowest quartile of β-cryptoxanthin intake in current smokers was 0.70 (95% CI: 0.60-0.81) and the overall trend was statistically significant ($p<0.001$). The risks of developing lung cell type-specific cancers were also reduced with increased β-cryptoxanthin intake. Specifically, the multivariate relative risks for the highest compared to the lowest quartile of β-cryptoxanthin intake for adenocarcinomas, small cell

carcinomas, and squamous cell carcinomas were 0.80 (95% CI: 0.68-0.93), 0.66 (95% CI: 0.51-0.87), and 0.67 (95% CI: 0.56-0.80), respectively, and statistically significant trends were observed for all (p=0.01, p=0.02, and p<0.001, respectively) (Männistö *et al.*, 2004).

Koushik *et al.* (2006) evaluated the intake of the major carotenoids and the risk of epithelial ovarian cancer in a pooled analysis of 10 cohort studies. Intakes were assessed using food frequency questionnaires administered at baseline in each of the 10 studies. During a follow-up of 7 to 22 years across studies, 2,012 cases of ovarian cancer occurred among the 521,911 subjects. Multivariate analyses revealed no association between β-cryptoxanthin intake and ovarian cancer, with a relative risk comparing the highest and lowest quintile of intake of 0.98 (95% CI: 0.85-1.13; p value for trend: 0.99), and there was no evidence of statistically significant heterogeneity between studies. Moreover, associations between β-cryptoxanthin intake and ovarian cancer risk did not vary significantly by histological type of ovarian cancer or by population subgroup. It was concluded that consumption of β-cryptoxanthin during adulthood was not associated with ovarian cancer risk (Koushik *et al.*, 2006).

More recently, Männistö *et al.* (2007) conducted a pooled analysis of 11 cohort studies carried out in North America and Europe that investigated dietary carotenoids and the risk of colorectal cancer. Baseline intakes of specific carotenoids were estimated using food frequency questionnaires, and the follow-up period for each study ranged from 6 to 20 years (between 1980 and 2003). A total of 7,885 incident cases of colorectal cancer were diagnosed in the 702,647 participants in the studies. The pooled multivariate relative risk of colorectal cancer comparing the highest and lowest quintile of β-cryptoxanthin intake was 0.99 (95% CI: 0.91-1.07; p value for trend: 0.51). No significant between-studies heterogeneity was reported for the 5th quintile of β-cryptoxanthin intake, and no significant association between β-cryptoxanthin intake and colorectal cancer at any specific subsite (colon, proximal colon, distal colon, or rectum) was observed. The authors concluded that the pooled data did not support an important association between β-cryptoxanthin intake and colorectal cancer risk (Männistö *et al.*, 2007).

4.3.3 Primary Research Articles on β-Cryptoxanthin and Cancer Risk

Pertinent data from primary research articles can be found in **Attachment I** to **Appendix C**. No intervention studies assessing β-cryptoxanthin and cancer risk were identified. A total of 30 observational studies were identified (in 29 publications) in which dietary intake or circulating levels of β-cryptoxanthin were assessed and quantified (*i.e.*, tertiles, quartiles, or quintiles of intake or blood levels) and their possible relation to cancer risk was determined (**Attachment I** to **Appendix C**). Eleven studies assessed the potential relationship between β-cryptoxanthin and prostate cancer risk (Goodman *et al.*, 2003; Huang *et al.*, 2003; Bosetti *et al.*, 2004; Wu *et al.*, 2004; Chang *et al.*, 2005; Jian *et al.*, 2005; McCann *et al.*, 2005; Kirsh *et al.*, 2006a; Key *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a), 4 studies assessed breast cancer risk (Cho *et al.*, 2003; Sesso *et al.*, 2005; Tamimi *et al.*, 2005; Huang *et al.*, 2007), and 4 studies

assessed lung cancer risk (Goodman *et al.*, 2003; Yuan *et al.*, 2003; Wright *et al.*, 2003; Stram *et al.*, 2007). The remaining 11 studies assessed the risks of colon (Nkondjock and Ghadirian, 2004), colorectal (Wakai *et al.*, 2005), bladder (Hung *et al.*, 2006), ovarian (Zhang *et al.*, 2007b), pancreatic (Nkondjock *et al.*, 2005), skin (Fung *et al.*, 2003; Dorgan *et al.*, 2004), and esophageal and/or gastric cancers (Abnet *et al.*, 2003; De Stefani *et al.*, 2006; Jenab *et al.*, 2006; Larsson *et al.*, 2007). A summary of these studies is presented in Table 4.3.3-1.

Table 4.3.3-1 Summary of Studies Assessing β-Cryptoxanthin Intake or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Prostate cancer					
Kirsh *et al.*, 2006a	Cohort	Dietary intake *via* FFQ at baseline only	NS	NS	NS
Chang *et al.*, 2005	Case-control	Plasma β-cryptoxanthin	NS	NR	NR
Goodman *et al.*, 2003	Nested case-control	Serum β-cryptoxanthin	NS	NS	NS
Jian *et al.*, 2005	Case-control	Dietary intake *via* FFQ	↓ (p<0.001)	0.15 (0.06-0.34)	0.29 (0.15-0.59)
Key *et al.*, 2007	Nested case-control	Plasma β-cryptoxanthin	NS	NS	NS
Bosetti *et al.*, 2004	Case-control	Dietary intake *via* FFQ	NS	NS	0.72 (0.55-0.93)
Huang *et al.*, 2003	Nested case-control	Serum β-cryptoxanthin	NS	NS	NS
McCann *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Peters *et al.*, 2007	Nested case-control	Serum β-cryptoxanthin	NS	NS	NS
Wu *et al.*, 2004	Nested case-control	Serum β-cryptoxanthin	NS	NS	NS
Zhang *et al.*, 2007a	Case-control	Plasma β-cryptoxanthin	NS	NS	NS
Breast cancer					
Cho *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline and 4 years later	NS	NS	NS
Sesso *et al.*, 2005	Cohort and nested case-control	Dietary intake *via* FFQ at baseline, and plasma β-cryptoxanthin at baseline	NS	NS	NS
Huang *et al.*, 2007	Case-control	Dietary intake *via* FFQ	↓ (p=0.03)	0.43 (0.23-0.82)	NS

Table 4.3.3-1 Summary of Studies Assessing β-Cryptoxanthin Intake or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Tamimi *et al.*, 2005	Nested case-control	Plasma β-cryptoxanthin	NS	NS	NS
Lung cancer					
Goodman *et al.*, 2003	Nested case-control	Serum β-cryptoxanthin	NS	NS	0.49 (0.29-0.85)
Yuan *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline	↓ (p=0.02)	0.73 (0.54-0.98)	NS
Stram *et al.*, 2007	Nested case-control	Serum β-cryptoxanthin	↓ (p=0.037)	NS	NS
Wright *et al.*, 2003	Case-control	Dietary intake *via* FFQ	NS for non- or former smokers	NS	0.45 (0.23-0.86)
			↓ (p=0.03) for current smokers	NS	NS
Colon, rectal, or colorectal cancer					
Wakai *et al.*, 2005	Nested case-control	Serum β-cryptoxanthin	NS	NS	NS
Nkondjock and Ghadirian, 2004	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Skin cancer					
Dorgan *et al.*, 2004	Cohort	Serum β-cryptoxanthin	NS	NS	NS
Fung *et al.*, 2003	Cohort	Dietary intake *via* FFQ	NS	NS	NS
Esophageal and/or gastric cancer					
Jenab *et al.*, 2006	Nested case-control	Serum β-cryptoxanthin	↓ (p=0.006)	0.53 (0.30-0.94)	0.56 (0.35-0.90)
Larsson *et al.*, 2007	Cohort	Dietary intake *via* FFQ at baseline	NS	NS	NS
Abnet *et al.*, 2003	Nested case-control	Serum β-cryptoxanthin at baseline	NS	NS	NS
De Stefani *et al.*, 2006	Case-control	Dietary intake *via* FFQ	↓ (p<0.0001)	0.34 (0.21-0.57)	0.48 (0.30-0.75)
Bladder cancer					
Hung *et al.*, 2006	Case-control	Plasma β-cryptoxanthin	↓ (p=0.031)	NS	NS

Table 4.3.3-1 Summary of Studies Assessing β-Cryptoxanthin Intake or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Ovarian cancer					
Zhang *et al.*, 2007b	Case-control	Dietary intake *via* FFQ	↓ (p<0.01)	0.51 (0.31-0.83)	0.49 (0.31-0.78)
Pancreatic cancer					
Nkondjock *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS

Abbreviations: ↓, decreased; FFQ, food frequency questionnaire; NS, not significant

For prostate cancer risk, only 1 of the 11 studies indicated a trend for a protective effect of β-cryptoxanthin (determined by dietary intake) that was of statistical significance (Jian *et al.*, 2005) while 1 study (Bosetti *et al.*, 2003) reported a significant difference between an intermediate centile and the control centile. None of the other 9 studies provided evidence of a protective effect of high dietary intake (McCann *et al.*, 2005; Kirsh *et al.*, 2006a) or high circulating levels (Goodman *et al.*, 2003; Huang *et al.*, 2003; Wu *et al.*, 2004; Chang *et al.*, 2005; Key *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a) of β-cryptoxanthin on prostate cancer risk. Of the 4 studies examining breast cancer risk, one reported a statistically significant trend for a reduction in risk associated with high intake of β-cryptoxanthin (Huang *et al.*, 2007) while the other 3 did not find similar effects for high intake (Cho *et al.*, 2003; Sesso *et al.*, 2005) or high circulating levels (Sesso *et al.*, 2005; Tamimi *et al.*, 2005) of β-cryptoxanthin. Three of the 4 studies examining lung cancer risk reported an inverse association between intake levels or circulating levels of β-cryptoxanthin that had a statistically significant trend, while the fourth reported a reduction in lung cancer risk only in an intermediate centile. Specifically, dietary intake was inversely associated with decreased risk in current but not in non- or former smokers in the study by Wright *et al.* (2003) and with decreased risk in all subjects in the study by Yuan *et al.* (2003). In addition, Stram *et al.* (2007) reported an inverse association between serum β-cryptoxanthin levels and lung cancer risk while this relationship was only noted in an intermediate centile level of serum β-cryptoxanthin in the study by Goodman *et al.* (2003).

The remaining 11 studies assessed the potential association between dietary intake or circulating levels of β-cryptoxanthin and the risks of colon, colorectal, bladder, ovarian, pancreatic, skin, and esophageal and/or gastric cancers. Of these, beneficial effects of high β-cryptoxanthin intake were reported for the risk of esophageal (De Stefani *et al.*, 2006; Jenab *et al.*, 2006) and ovarian (Zhang *et al.*, 2007b) cancers, while a beneficial effect of high plasma β-cryptoxanthin levels was reported for the risk of bladder cancer (Hung *et al.*, 2006). None of

the other studies reported any change in cancer risk associated with dietary intake (Fung *et al.*, 2003; Nkondjock and Ghadirian, 2004; Nkondjock *et al.*, 2005; Larsson *et al.*, 2007) or circulating levels (Abnet *et al.*, 2003; Dorgan *et al.*, 2004; Wakai *et al.*, 2005) of β-cryptoxanthin.

As summarized in Table 4.3.3-2, of the 30 observational studies identified (in 29 publications), significant reductions in cancer risk with increased dietary intakes/circulating levels of β-cryptoxanthin were reported for 10 studies, 9 of which were case-control studies. As already discussed, data from observational studies, in general, and case-control studies specifically cannot be used to demonstrate causality. Since dietary intakes are assessed retrospectively in case-control studies, subjects with the disease tend to report intakes with less accuracy (recall bias), which biases associations away from the null. Additionally, it is not possible to elucidate from case-control studies whether lowered intakes/circulating levels of β-cryptoxanthin are a *cause* or a *consequence* of the disease. Cumulatively, results of the studies described above indicate that high dietary intake or high circulating levels of β-cryptoxanthin have not been associated with a reduced risk of prostate and breast cancers, while inverse associations between dietary intake or circulating levels of β-cryptoxanthin have been reported for the risk of lung cancer. Thus, although individual observational studies have reported some potentially beneficial effects of high dietary intakes or high circulating levels of β-cryptoxanthin on certain types of cancer, causality cannot be established from these observational studies, given the inconsistent findings presented in these observational studies, and the absence of data from human intervention studies. Limitations associated with observational studies are discussed in more detail in Section 10.2.

Table 4.3.3-2 β-Cryptoxanthin and Cancer Risk – A Summary of Findings by Study Type

Study Type	Exposure	Cancer Type[1]	Proportion of Studies Reporting Significant Risk Reduction[2,3]
Randomized controlled trial	Not applicable	Not applicable	No intervention studies were identified
Cohort	Circulating Levels	Skin	0/1 (0%)
	Dietary Intake	Prostate, breast (n=2), **lung**, skin, esophageal and/or gastric	1/6 (16.7%)
Case-control	Circulating Levels	Prostate (n=7), breast (n=2), **lung** (n=2), colon, rectal, or colorectal, **esophageal and/or gastric** (n=2), **bladder**	3/15 (20%)
	Dietary Intake	**Prostate** (n=3), **breast**, **lung**, colon, rectal, or colorectal, **esophageal and/or gastric**, **ovarian**, pancreatic	6/9 (66.7%)

[1] Bolded cancers are those for which significant reductions in risk with increased intake/circulating levels of β-cryptoxanthin.
[2] Significance was defined as P<0.05 between the treatment and placebo groups, or, for observational studies, as P<0.05 for the trend, the highest centile *versus* the lowest centile, or an intermediate centile *versus* the lowest centile.
[3] The study by Sesso *et al.* (2005) is counted both as a cohort dietary intake study and as a case-control circulating level study.

5.0 α-CAROTENE

5.1 Introduction

α-Carotene is one of the most common carotenoids in the human diet and is found in a variety of foods including carrots, winter squash, pumpkin, and others (Holden *et al.*, 1999). As it can be converted to retinol, the active form of vitamin A, α-carotene is considered a provitamin A carotenoid. α-Carotene can be absorbed intact in the intestines or cleaved to form vitamin A prior to secretion into lymph (IOM, 2000). Distribution occurs *via* the circulation where α-carotene is associated with lipoproteins, particularly the LDL fraction (IOM, 2000), and storage of α-carotene and other carotenoids occurs in many organs including adipose tissue, liver, kidney, and adrenal glands (IOM, 2006). The only known function of α-carotene in humans is to serve as a source of vitamin A (IOM, 2000).

5.2 Authoritative Body Statements and Opinions on α-Carotene and Cancer Risk

No authoritative body statements specific to α-carotene were identified in the published literature. Statements by the WCRF/AICR, IARC, the Food and Nutrition Board of the Institute of Medicine, and the American Cancer Society (Table 4-2) indicate that while beneficial health effects of foods containing carotenoids have been documented, it is not possible to discern whether the observed beneficial effects are due to a particular carotenoid such as α-carotene, other nutrients in α-carotene-containing products, lifestyle factors associated with consumption of α-carotene-containing products, a combination of these, or other factors altogether.

A summary of the authoritative body position statements and recommendations regarding α-carotene is provided in Table 1.1-2.

5.3 Review of Scientific Literature Pertaining to α-Carotene and Cancer Risk

As some of the authoritative body statements and position documents described above are several years old, a literature search was conducted to identify articles that relate to the effects of α-carotene on cancer risk that have been published recently in the scientific literature. Specifically, this search focused on identifying articles published in the last 5 years (*i.e.*, from 2003 to the present) and aimed to identify reviews, meta-analyses, and primary intervention and observational studies in humans. The search terms that were used included [(alpha carotene OR 7488-99-5) AND (human OR humans OR subject OR subjects OR patient? OR clinical? OR volunteer? OR double OR blind OR double blind OR epidemiol OR case OR stud? OR control OR cohort? OR intervention? OR observation? OR meta OR analysis) AND (cancer? OR tumor? OR tumour? OR neoplas?)]. The search identified these terms in the title or abstract of articles contained in the following databases: Medline, ToxFile, AGRIS, Agricola, FSTA,

Foodline, Biosis Previews, NTIS, and EMBASE. For the primary studies that were identified, a critical assessment of the methodologies and endpoints described in the publications was performed. The results of the literature search and the assessment of the data contained in the articles that were identified are described in the following sections.

5.3.1 Review Articles on α-Carotene and Cancer Risk

No review articles specific to the potential effects of α-carotene on cancer risk were identified. Two review articles in which α-carotene was discussed as one of several carotenoids that may contribute to cancer risk reduction were identified and are described below.

Dagnelie *et al.* (2004) conducted a review of prospective cohort and intervention studies on potential dietary risk factors for prostate cancer that were published between 1966 and September 2003. The authors identified one cohort study in which serum levels of α-carotene were measured and were found to be inversely associated with a reduced risk (defined by Dagnelie *et al.* as a relative risk estimate <0.80) of prostate cancer. Two additional cohort studies in which dietary α-carotene was estimated using dietary questionnaires or interviews did not report any change in prostate cancer risk associated with higher intake levels. The authors did not provide any conclusion specific to the data for α-carotene that were analyzed in their review (Dagnelie *et al.*, 2004), likely due to the scarcity of data.

Ruano-Ravina *et al.* (2006) evaluated articles published between 1994 and October 2003 that reported the results of cohort and case-control studies pertaining to α-carotene and lung cancer, although case-control studies with less than 300 subjects were not assessed. The authors indicated that none of the 7 studies that were reviewed (5 cohort and 2 case-control) reported a statistically significant association for the highest intake of α-carotene. One of the cohort studies that the authors assessed reported a risk level of 0.6 while one of the case-control studies reported a risk level of 0.48, although neither of these made reference to the significance of these findings (Ruano-Ravina *et al.*, 2006).

5.3.2 Meta-Analyses and Pooled Analyses on α-Carotene and Cancer Risk

No meta-analyses related to α-carotene and cancer risk were identified. However, 3 pooled analyses related to α-carotene and cancer risk were identified and are described briefly below.

Männistö *et al.* (2004) assessed the relationship between dietary carotenoids and the risk of lung cancer from a pooled analysis of 7 cohort studies as part of the Pooling Project of Prospective Studies of Diet and Cancer. A random-effects model was used to combine the relative risks for developing lung cancer that were calculated from 7 cohort studies that were performed in North America and Europe, each of which determined dietary carotenoid intake at baseline through the use of a validated dietary questionnaire. During a follow-up of up to 7 to 16 years, a total of 3,155 incident cases of lung cancer were diagnosed among 399,765

participants of the cohort studies. The multivariate relative risk for the highest compared to the lowest quintile of α-carotene intake was 0.93 (95% CI: 0.82-1.06) and the overall trend was not significant (p=0.47). Moreover, no statistically significant associations between α-carotene intake and lung cancer risk were found based on smoking status or lung cell type (Männistö *et al.*, 2004).

Koushik *et al.* (2006) evaluated the intake of the major carotenoids and the risk of epithelial ovarian cancer in a pooled analysis of 10 cohort studies. Intakes were assessed using food frequency questionnaires administered at baseline in each of the 10 studies. During a follow-up of 7 to 22 years across studies, 2,012 cases of ovarian cancer occurred among the 521,911 subjects. Multivariate analyses revealed no association between α-carotene intake and ovarian cancer, with a relative risk comparing the highest and lowest quintile of intake of 1.00 (95% CI: 0.85-1.18; p value for trend: 0.58), and there was no evidence of statistically significant heterogeneity between studies. Moreover, associations between α-carotene intake and ovarian cancer risk did not vary significantly by histological type of ovarian cancer or by population subgroup. It was concluded that consumption of α-carotene during adulthood was not associated with ovarian cancer risk (Koushik *et al.*, 2006).

More recently, Männistö *et al.* (2007) conducted a pooled analysis of 11 cohort studies carried out in North America and Europe that investigated dietary carotenoids and the risk of colorectal cancer. Baseline intakes of specific carotenoids were estimated using food frequency questionnaires, and the follow-up period for each study ranged from 6 to 20 years (between 1980 and 2003). A total of 7,885 incident cases of colorectal cancer were diagnosed in the 702,647 participants in the studies. The pooled multivariate relative risk of colorectal cancer comparing the highest and lowest quintile of α-carotene intake was 1.01 (95% CI: 0.93-1.09; p value for trend: 0.75). No significant between-studies heterogeneity was reported for the 5th quintile of α-carotene intake, and no significant association between α-carotene intake and colorectal cancer at any specific subsite (colon, proximal colon, distal colon, or rectum) was observed. The authors concluded that the pooled data did not support an important association between α-carotene intake and colorectal cancer risk (Männistö *et al.*, 2007).

5.3.3 Primary Research Articles on α-Carotene and Cancer Risk

Pertinent data from primary research articles can be found in **Attachment I** to **Appendix C**. No intervention studies assessing α-carotene and cancer risk were identified. A total of 28 observational studies (in 27 publications) were identified in which dietary intakes or circulating levels of α-carotene were assessed and quantified (*i.e.*, tertiles, quartiles, or quintiles of intake or blood levels) and their possible relation to cancer risk determined. Eleven studies assessed the potential relationship between α-carotene and prostate cancer risk (Goodman *et al.*, 2003; Huang *et al.*, 2003; Bosetti *et al.*, 2004; Wu *et al.*, 2004; Chang *et al.*, 2005; Jian *et al.*, 2005; McCann *et al.*, 2005; Kirsh *et al.*, 2006a; Key *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a) and 4 studies assessed breast cancer risk (Cho *et al.*, 2003; Sesso *et al.*, 2005; Tamimi

et al., 2005; Huang *et al.*, 2007). The remaining 13 studies assessed the risks of colon (Nkondjock and Ghadirian, 2004), colorectal (Wakai *et al.*, 2005), lung (Goodman *et al.*, 2003; Wright *et al.*, 2003; Yuan *et al.*, 2003), bladder (Hung *et al.*, 2006), esophageal (De Stefani *et al.*, 2006), ovarian (Zhang *et al.*, 2007b), pancreatic (Nkondjock *et al.*, 2005), skin (Fung *et al.*, 2003; Dorgan *et al.*, 2004), and gastric cancers (Jenab *et al.*, 2006; Larsson *et al.*, 2007). A summary of these studies is presented in Table 5.3.3-1.

Table 5.3.3-1 Summary of Studies Assessing α-Carotene Intake or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Prostate cancer					
Kirsh *et al.*, 2006a	Cohort	Dietary intake *via* FFQ at baseline only	NS	NS	NS
Chang *et al.*, 2005	Case-control	Plasma α-carotene	↓ (p value NR)	NR	NR
Goodman *et al.*, 2003	Nested case-control	Serum α-carotene	NS	NS	NS
Jian *et al.*, 2005	Case-control	Dietary intake *via* FFQ	↓ (p<0.043)	0.43 (0.21-0.85)	NS
Key *et al.*, 2007	Nested case-control	Plasma α-carotene	NS	NS	NS
Bosetti *et al.*, 2004	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Huang *et al.*, 2003	Nested case-control	Serum α-carotene	NS	NS	NS
McCann *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Peters *et al.*, 2007	Nested case-control	Serum α-carotene	NS	NS	NS
Wu *et al.*, 2004	Nested case-control	Serum α-carotene	NS	NS	NS
Zhang *et al.*, 2007a	Case-control	Plasma α-carotene	NS	NS	NS
Breast cancer					
Cho *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline and 4 years later	NS	NS	NS

Table 5.3.3-1 Summary of Studies Assessing α-Carotene Intake or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Sesso *et al.*, 2005	Cohort and nested case-control	Dietary intake *via* FFQ at baseline, and plasma α-carotene at baseline	NS	NS	NS
Huang *et al.*, 2007	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Tamimi *et al.*, 2005	Nested case-control	Plasma α-carotene	↓ (p=0.01)	0.64 (0.47-0.88)	NS
Colon, rectal, or colorectal cancer					
Wakai *et al.*, 2005	Nested case-control	Serum α-carotene	NS for men	NS	NS
			↑ (p=0.007) for women	4.72 (1.29-17.3)	NS
Nkondjock and Ghadirian, 2004	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Lung cancer					
Goodman *et al.*, 2003	Nested case-control	Serum α-carotene	NS	NS	NS
Yuan *et al.*, 2003	Cohort	Dietary intake *via* FFQ at baseline	NS (p value not reported)	NS	NS
Wright *et al.*, 2003	Case-control	Dietary intake *via* FFQ	NS	NS	NS
Skin cancer					
Dorgan *et al.*, 2004	Cohort	Serum α-carotene	NS for basal cell carcinoma	NS	NS
			↑ (p=0.04) for squamous cell carcinoma	NS	NS
Fung *et al.*, 2003	Cohort	Dietary intake *via* FFQ	NS	NS	NS
Gastric cancer					
Jenab *et al.*, 2006	Nested case-control	Serum α-carotene	NS	NS	NS
Larsson *et al.*, 2007	Cohort	Dietary intake *via* FFQ at baseline	↓ (p=0.03)	0.50 (0.30-0.83)	0.61 (0.38-0.98)
Bladder cancer					
Hung *et al.*, 2006	Case-control	Plasma α-carotene	↓ (p=0.0321)	0.12 (0.02-0.95)	NS

Table 5.3.3-1 Summary of Studies Assessing α-Carotene Intake or Circulating Levels with Cancer Risk

Reference	Study Type	Biomarker of Exposure	Direction of Association and Statistical Significance		
			P for trend	Highest *vs.* Lowest Centile (OR or RR and 95% CI)	Intermediate *vs.* Lowest Centile (OR or RR and 95% CI)
Esophageal cancer					
De Stefani *et al.*, 2006	Case-control	Dietary intake *via* FFQ	↓ (p<0.0001)	0.28 (0.16-0.47)	0.52 (0.34-0.81)
Ovarian cancer					
Zhang *et al.*, 2007b	Case-control	Dietary intake *via* FFQ	↓ (p<0.001)	0.39 (0.23-0.66)	0.57 (0.36-0.90)
Pancreatic cancer					
Nkondjock *et al.*, 2005	Case-control	Dietary intake *via* FFQ	NS for men	NS	0.68 (0.46-0.98)
			NS for women	NS	NS

Abbreviations: ↓, decreased; ↑, increased; FFQ, food frequency questionnaire; NS, not significant

For prostate cancer risk, only 2 of the 11 studies indicated a statistically significant trend for a protective effect of α-carotene. Jian *et al.* (2005) reported a significantly reduced risk associated with increased dietary intake and Chang *et al.* (2005) reported a reduced risk with elevated circulating levels, although the statistical value of the effect was not reported in the latter study. Another study measuring dietary intake reported an inverse association that was of borderline statistical significance (p=0.062) (Bosetti *et al.*, 2004). None of the other 8 studies provided evidence of a protective effect of high dietary intake (McCann *et al.*, 2005; Kirsh *et al.*, 2006a) or high circulating levels (Goodman *et al.*, 2003; Huang *et al.*, 2003; Wu *et al.*, 2004; Key *et al.*, 2007; Peters *et al.*, 2007; Zhang *et al.*, 2007a) of α-carotene on prostate cancer risk. Of the 4 studies examining breast cancer risk, 1 indicated a statistically significant trend for a reduction in risk associated with high plasma levels of α-carotene (Tamimi *et al.*, 2005) while the other 3 did not find similar effects for high intake (Cho *et al.*, 2003; Sesso *et al.*, 2005; Huang *et al.*, 2007) or high circulating levels (Sesso *et al.*, 2005) of α-carotene.

The remaining 13 studies assessed the potential association between dietary intake or circulating levels of α-carotene and the risks of colon, colorectal, lung, bladder, esophageal, ovarian, pancreatic, skin, and gastric cancers. Of these, beneficial effects (*i.e.*, statistically significant trends) of high α-carotene intake were reported for the risk of esophageal (De Stefani *et al.*, 2006), ovarian (Zhang *et al.*, 2007b), and gastric cancers (Larsson *et al.*, 2007), while a beneficial effect was noted in a study of pancreatic cancer risk but only in men in an intermediate centile of α-carotene intake (Nkondjock *et al.*, 2005). A beneficial effect of high plasma α-carotene levels was reported for the risk of bladder cancer (Hung *et al.*, 2006). Conversely, Wakai *et al.* (2005) reported an increased risk of colorectal cancer associated with high serum α-carotene levels in females but not in males, while Dorgan *et al.* (2004) reported an

increased risk of squamous cell carcinoma (but not basal cell carcinoma) associated with high serum α-carotene levels. None of the other studies reported any change in cancer risk associated with dietary intake of α-carotene (Fung *et al.*, 2003; Goodman *et al.*, 2003; Wright *et al.*, 2003; Yuan *et al.*, 2003; Nkondjock and Ghadirian, 2004; Jenab *et al.*, 2006).

Results of the studies described above indicate that high dietary intake or high circulating levels of α-carotene have not generally been associated with a reduced risk of the most commonly studied cancer endpoints, namely prostate and breast cancer. Moreover, the majority of studies related to other cancer types have similarly not reported beneficial effects of α-carotene. As summarized in Table 5.3.3-2, of the 28 observational studies identified (in 27 publications), significant reductions in cancer risk with increased dietary intakes/circulating levels of α-carotene were reported for 8 studies, 7 of which were case-control studies. While individual observational studies have reported some potentially beneficial effects of high dietary intake or high circulating levels of α-carotene on certain types of cancer, firm conclusions cannot be drawn from these observational studies, particularly in the absence of randomized and controlled human experimental studies.

Table 5.3.3-2 α-Carotene and Cancer Risk – A Summary of Findings by Study Type

Study Type	Exposure	Cancer Type[1]	Proportion of Studies Reporting Significant Risk Reduction[2,3]
Randomized controlled trial	Not applicable	Not applicable	No intervention studies were identified
Cohort	Circulating Levels	Skin	0/1 (0%)
	Dietary Intake	Prostate, breast (n=2), lung, skin, **gastric**	1/6 (16.7%)
Case-control	Circulating Levels	**Prostate** (n=7), **breast** (n=2), colon, rectal, or colorectal, lung, gastric, **bladder**	3/13 (23%)
	Dietary Intake	**Prostate** (n=3), breast, colon, rectal, or colorectal, lung, **esophageal**, **ovarian**, **pancreatic**	4/9 (44.4%)

[1] Bolded cancers are those for which significant reductions in risk with increased intake/circulating levels of α-carotene.
[2] Significance was defined as P<0.05 between the treatment and placebo groups, or, for observational studies, as P<0.05 for the trend, the highest centile *versus* the lowest centile, or an intermediate centile *versus* the lowest centile.
[3] The study by Sesso *et al.* (2005) is counted both as a cohort dietary intake study and as a case-control circulating level study.

In summary, this review of the recent published scientific literature indicates that minimal evidence exists for a beneficial effect of α-carotene on cancer risk, a finding consistent with all authoritative body recommendations and position statements.

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ATTACHMENT I TO APPENDIX C:

TABULAR SUMMARY FROM HUMAN INTERVENTION AND OBSERVATIONAL STUDIES ASSESSING THE HEALTH EFFECTS OF β-CAROTENE, LYCOPENE, β-CRYPTOXANTHIN, AND α-CAROTENE

January 18, 2010

ATTACHMENT I TO APPENDIX C: TABULAR SUMMARY FROM HUMAN INTERVENTION AND OBSERVATIONAL STUDIES ASSESSING THE HEALTH EFFECTS OF β-CAROTENE, LYCOPENE, β-CRYPTOXANTHIN, AND α-CAROTENE

Table of Contents

Table C-1	Tabulation of Data from Human Intervention Studies of β-Carotene (Cancer)	I-1
Table C-2	Tabulation of Data from Observational Studies of β-Carotene (Cancer)	I-2
Table C-3	Tabulation of Data from Human Intervention Studies of β-Carotene (CVD)	I-42
Table C-4	Tabulation of Data from Observational Studies of β-Carotene (CVD)	I-43
Table C-5	Tabulation of Data from Human Intervention Studies of Lycopene (Cancer)	I-48
Table C-6	Tabulation of Data from Human Observational Studies of Lycopene (Cancer)	I-50
Table C-7	Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)	I-70
Table C-8	Tabulation of Data from Observational Studies of α-Carotene (Cancer)	I-87

Table C-1 Tabulation of Data from Human Intervention Studies of β-Carotene (Cancer)

Reference	Daily Dose	Duration	Population and Final Sample Size	Endpoint(s)	Incidence (treatment *versus* placebo)	Significance/ Risk Ratios (between groups)		
						RR	95% CI	P-value for trend
Wright *et al.*, 2007	20 mg	5 to 8 years (median 6.1 years)	29,133 male smokers, aged 50 to 69 years and cancer-free at baseline	Cancers of oral cavity/pharynx	Cases: 15 *vs.* 18 Deaths: 4 *vs.* 2	0.84 2.01	0.42 – 1.66 0.37 – 10.95	NR but NS
				Cancers of esophagus	Cases: 6 *vs.* 7 Deaths: 4 *vs.* 6	0.86 0.67	0.29 – 2.56 0.19 – 2.37	NR but NS
				Cancers of larynx	Cases: 12 *vs.* 17 Deaths: 3 *vs.* 3	0.71 1.00	0.34 – 1.48 0.20 – 4.96	NR but NS

Abbreviation: NR = not reported; NS = non-significant

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES – PROSTATE CANCER											
Kirsh *et al.*, 2006a	Cohort (up to 8 years follow-up)	29,361 men aged 55 – 74 years (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial)	1st quintile of intake (µg/day)	2,180 (median)	Prostate Cancer	227			1.00	NA	0.40
			2nd quintile of intake (µg/day)	3,191 (median)		274			1.09	0.91 – 1.30	
			3rd quintile of intake (µg/day)	4,119 (median)		258			0.96	0.80 – 1.15	
			4th quintile of intake (µg/day)	5,338 (median)		288			1.01	0.85 – 1.21	
			5th quintile of intake (µg/day)	7,744 (median)		291			0.96	0.80 – 1.15	
			Category 1 supplement use (µg/day)	0	Prostate cancer	801			1.00	NA	0.55
			Category 2 supplement use (µg/day)	>0 - <750		57			0.91	0.70 – 1.20	
			Category 3 supplement use (µg/day)	750 - <1,500		352			1.00	0.88 – 1.14	
			Category 4 supplement use (µg/day)	1,500 – <2,000		47			1.15	0.85 – 1.54	
			Category 5 supplement use (µg/day)	≥2,000		81			0.82	0.65 – 1.04	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE-CONTROL STUDIES-PROSTATE CANCER											
Bosetti *et al*., 2004	Case-control	Cases: 1,294 incident, histologically prostate cancer cases in men <75 years of age Controls: 1,451 healthy men <75 years of age	1st quintile of mean intake (µg/day)	NR. Average intake in controls was reported to be 4,515.1 µg/day; average intake in cases was not reported.	Prostate cancer	251 cases and 290 controls		1.00		NA	0.017
			2nd quintile of mean intake (µg/day)			252 cases and 290 controls		0.90		0.70 - 1.16	
			3rd quintile of mean intake (µg/day)			263 cases and 290 controls		0.86		0.66 - 1.11	
			4th quintile of mean intake (µg/day)			278 cases and 291 controls		0.83		0.64 - 1.07	
			5th quintile of mean intake (µg/day)			250 cases and 290 controls		0.72		0.55 - 0.94	
Chang, *et al*., 2005	Case-control	Cases: 118 non-hispanic caucasian men Controls: 52 men from same area	Median Plasma Level	Controls: 0.34 Cases: 0.25	Prostate cancer	118 cases and 52 controls		0.46		0.21 - 0.98	NA

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Goodman *et al*., 2003	Case-control (nested in β-Carotene and Retinol Efficacy Trial [CARET])	Cases: 174 men and 102 women with lung cancer Controls: 174 male and 102 female cancer-free subjects matched for high-risk population, study centre location, age, sex, smoking, and year of randomization	1st quartile of serum β-carotene (ng/mL)	<87	Lung cancer	NR		1.0		NA	0.73
			2nd quartile of serum β-carotene (ng/mL)	87-158				1.43		0.88 – 2.32	
			3rd quartile of serum β-carotene (ng/mL)	158-255				0.85		0.49 – 1.45	
			4th quartile of serum β-carotene (ng/mL)	>255				1.07		0.63 – 1.83	
		Cases: 174 men with lung cancer Controls: 174 cancer-free men, matched as described above	1st quartile of serum β-carotene (ng/mL)	<87	Lung cancer	NR		1.0		NA	0.42
			2nd quartile of serum β-carotene (ng/mL)	87-158				1.29		0.72 – 2.32	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd quartile of serum β-carotene (ng/mL)	158-255				1.11		0.57 – 2.15	
			4th quartile of serum β-carotene (ng/mL)	>255				1.40		0.71 – 2.74	
		Cases: 102 women with lung cancer Controls: 102 cancer-free women, matched as described above	1st quartile of serum β-carotene (ng/mL)	<87	Lung cancer	NR		1.0		NA	0.11
			2nd quartile of serum β-carotene (ng/mL)	87-158				1.71		0.71 – 4.17	
			3rd quartile of serum β-carotene (ng/mL)	158-255				0.53		0.21 – 1.35	
			4th quartile of serum β-carotene (ng/mL)	>255				0.72		0.30 – 1.75	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		Cases: 205 men with prostate cancer Controls: 205 cancer-free men, matched as described above	1st quartile of serum β-carotene (ng/mL)	<94	Prostate cancer	NR		1.0		NA	0.69
			2nd quartile of serum β-carotene (ng/mL)	94-139				0.94		0.55 – 1.62	
			3rd quartile of serum β-carotene (ng/mL)	139-219				1.06		0.61 – 1.83	
			4th quartile of serum β-carotene (ng/mL)	>219				0.85		0.49 – 1.49	
		Cases: 174 men and 102 women with lung cancer	Mean serum β-carotene (ng/mL)	141	Lung cancer	276					0.23
		Controls: 174 male and 102 female cancer-free subjects matched as described above	Mean serum β-carotene (ng/mL)	152		0					

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		Cases: 102 women with lung cancer	Mean serum β-carotene (ng/mL)	169	Lung cancer	102					0.20
		Controls: 102 cancer-free women, matched as described above	Mean serum β-carotene (ng/mL)	194		0					
		Cases: 174 men with lung cancer	Mean serum β-carotene (ng/mL)	126	Lung cancer	174					0.57
		Controls: 174 cancer-free men, matched as described above	Mean serum β-carotene (ng/mL)	132		0					
		Cases: 205 men with prostate cancer	Mean serum β-carotene (ng/mL)	135	Prostate cancer	205					0.49
		Controls: 205 cancer-free men, matched as described above	Mean serum β-carotene (ng/mL)	142		0					

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Huang *et al.*, 2003	Case-control (nested in the CLUE 1 and CLUE 2 studies)	CLUE 1 (blood collected in 1974) Case: 182 men (mean age of 54 years) diagnosed with prostate cancer Control: 364 men (mean age of 54 years) without prostate cancer	1st quintile of serum β-carotene (µg/dL)	≤4.4	Prostate cancer	33 cases and 70 controls		1.00		NA	0.59
			2nd quintile of serum β-carotene (µg/dL)	>4.4 – 7.0		50 cases and 74 controls		1.47		0.84 – 2.55	
			3rd quintile of serum β-carotene (µg/dL)	>7.0 – 9.8		23 cases and 73 controls		0.66		0.34 – 1.27	
			4th quintile of serum β-carotene (µg/dL)	>9.8 – <15.6		43 cases and 72 controls		1.19		0.65 – 2.19	
			5th quintile of serum β-carotene (µg/dL)	≥15.6		33 cases and 74 controls		0.94		0.50 – 1.77	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		CLUE 2 (blood collected in 1989) Case: 142 men (mean age of 66 years) diagnosed with prostate cancer Control: 284 men (mean age of 66 years) without prostate cancer	1st quintile of serum β-carotene (µg/dL)	≤4.2	Prostate cancer	22 cases and 57 controls		1.00		NA	0.60
			2nd quintile of serum β-carotene (µg/dL)	>4.2 – 6.7		29 cases and 59 controls		1.32		0.65 – 2.68	
			3rd quintile of serum β-carotene (µg/dL)	>6.7 – 10.3		36 cases and 52 controls		1.92		0.96 – 3.85	
			4th quintile of serum β-carotene (µg/dL)	>10.3 - <15.8		24 cases and 59 controls		1.05		0.51 – 2.18	
			5th quintile of serum β-carotene (µg/dL)	≥15.8		31 cases and 57 controls		1.47		0.74 – 2.92	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Jian *et al*., 2005	Case-control	Cases: 130 Chinese men with prostate cancer, aged ~72.7 years Controls: 274 Chinese men with no malignant disease, aged ~71.4 years	1st quartile of intake (µg β-carotene/day)	<1962.0	Prostate cancer	50		1.00		NA	0.253
			2nd quartile of intake (µg β-carotene/day)	1962.0 – 4076.3		36		0.72		0.40 – 1.31	
			3rd quartile of intake (µg β-carotene/day)	4076.3 – 7490.6		24		0.42		0.21 – 0.83	
			4th quartile of intake (µg β-carotene/day)	>7490.6		20		0.34		0.17 – 0.69	
		Cases: 130 Chinese men with prostate cancer, aged ~72.7 years	Intake of β-carotene (µg/day) [median (range)]	2633.6 (1275.0 – 5327.3)	Prostate cancer	130					**0.002**
		Controls: 274 Chinese men with no malignant disease, aged ~71.4 years	Intake of β-carotene (µg/day) [median (range)]	4076 (1962.0 – 7490.6)		274					

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Key *et al*., 2007	Case-control nested within The European Prospective Investigation into Cancer and Nutrition cohort study	137,001 men approximately 60 years of age and free of prostate cancer at baseline; nested case-control consisted of 966 cases and 1,064 matched controls	1st quintile of plasma β-carotene (mean µg/dL)	<8.21	Prostate cancer	179 Cases and 213 controls			1.00	NA	0.24
			2nd quintile of plasma β-carotene (mean µg/dL)	8.21 – <13.12		209 Cases and 213 controls			1.17	0.87 - 1.56	
			3rd quintile of plasma β-carotene (mean µg/dL)	13.12 – <18.52		207 Cases and 213 controls			1.14	0.84 – 1.54	
			4th quintile of plasma β-carotene (mean µg/dL)	18.52 - <27.28		198 Cases and 213 controls			1.06	0.77 – 1.45	
			5th quintile of plasma β-carotene (mean µg/dL)	≥27.28		173 Cases and 212 controls			0.92	0.66 – 2.28	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
McCann *et al*., 2005	Case-control	Cases: 433 men with primary, histologically confirmed prostate cancer Controls: 538 population-based healthy men	1st quartile of intake (µg/day)	≤3,833	Prostate cancer	141 cases and 135 controls		1.00		NA	0.40
			2nd quartile of intake (µg/day)	3,833 – 5,455		108 cases and 134 controls		0.82		0.57 – 1.17	
			3rd quartile of intake (µg/day)	5,455 – 8,040		104 cases and 135 controls		0.81		0.56 – 1.19	
			4th quartile of intake (µg/day)	>8,040		80 cases and 134 controls		0.72		0.43 – 1.19	
Peters *et al*., 2007	Case-control	Cases: 692 incident prostate cancer cases in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Controls: 844 healthy individuals from the same trial	1st quintile of serum β-carotene (µg/dL)	6.1	Prostate cancer	117 cases and 168 controls		1.00		NA	0.16
			2nd quintile of serum β-carotene (µg/dL)	10.3		122 cases and 169 controls		1.03		0.73 – 1.45	
			3rd quintile of serum β-carotene (µg/dL)	15.2		156 cases and 168 controls		1.36		0.97 – 1.90	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quintile of serum β-carotene (µg/dL)	22.0		136 cases and 169 controls		1.14		0.81 – 1.61	
			5th quintile of serum β-carotene (µg/dL)	38.7		160 cases and 168 controls		1.30		0.93 – 1.82	
Wu *et al.*, 2004	Case-control (nested in the Health Professionals Follow-up Study)	Case: 450 male health professionals diagnosed with prostate cancer (aged 40-75 years) Control: 450 male health professionals without prostate cancer (aged 40-75 years)	1st quintile of plasma β-carotene	NR. Median plasma β-carotene was reported as 1,582.7 nmol/L in cases and 1,625.5 nmol/L in controls	Prostate cancer	96 cases and 84 controls			1.00	NA	0.49
			2nd quintile of plasma β-carotene			91 cases and 89 controls			0.86	0.55 – 1.35	
			3rd quintile of plasma β-carotene			81 cases and 99 controls			0.69	0.45 – 1.08	
			4th quintile of plasma β-carotene			92 cases and 88 controls			0.92	0.57 – 1.47	
			5th quintile of plasma β-carotene			90 cases and 90 controls			0.78	0.48 – 1.25	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Zhang *et al.*, 2007a	Case-control	Cases: 193 men diagnosed with prostate cancer in 3 major hospitals Controls: 197 healthy men without prostate cancer	1st quartile of plasma β-carotene (µg/L)	34.7	Prostate cancer	37 cases and 49 controls		1.00		NA	0.64
			2nd quartile of plasma β-carotene (µg/L)	72.5		42 cases and 49 controls		1.31		0.68 – 2.54	
			3rd quartile of plasma β-carotene (µg/L)	126.9		64 cases and 50 controls		1.97		1.00 – 3.91	
			4th quartile of plasma β-carotene (µg/L)	283.5		50 cases and 49 controls		1.48		0.67 – 3.29	
CASE-CONTROL STUDIES-COLON, RECTAL OR COLORECTAL CANCERS											
Chiu *et al.*, 2003	Case-control	Cases: 469 women from Shanghai, China, aged 30-74, and newly diagnosed with colon cancer Controls: 701 healthy women from Shanghai, China aged 30-74	1st quartile of intake (mg carotene/day)	≤465.9	Colon cancer	NR		1.00		NA	**0.02**
			2nd quartile of intake (mg carotene/day)	466.0 – 638.1				0.7		0.5-0.9	
			3rd quartile of intake (mg carotene/day)	638.2 – 1039.2				0.8		0.5-1.1	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quartile of intake (mg carotene/day)	≥1039.3				0.6		0.4-0.9	
		Cases: 462 men from Shanghai, China, aged 30-74, and newly diagnosed with colon cancer Controls: 851 healthy men from Shanghai, China aged 30-74	1st quartile of intake (mg carotene/day)	≤447.3				1.00		NA	**<0.01**
			2nd quartile of intake (mg carotene/day)	447.4 – 676.3				0.8		0.6-1.2	
			3rd quartile of intake (mg carotene/day)	676.4 – 1040.2				0.6		0.5-0.9	
			4th quartile of intake (mg carotene/day)	≥1040.3				0.5		0.3-0.7	
Erhardt *et al*., 2003	Case-control	Case: 41 male and 32 female white subjects with colorectal adenomas, aged 30-80 Control: 25 male and 38 female white subjects with no colonic polyps, aged 30-80	Median plasma β-carotene (μg/L)	Case: 0.38 Control: 0.51	Colorectal adenoma	73 cases and 63 controls					NS

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		Case: 14 male and 15 female white subjects with colonic hyperplastic polyps, aged 30-80 Control: 25 male and 38 female white subjects with no colonic polyps, aged 30-80	Median plasma β-carotene (µg/L; ALL)	Case: 0.35 Control: 0.51	Colonic hyperplastic polyp	29 cases and 63 controls					NS
Murtaugh *et al*., 2004	Case-control	Cases: 952 men and women with rectal cancer Controls: 1,205 healthy individuals	1st quintile of mean intake (µg/day)	M: ≤2,137 F: ≤2,308	Rectal cancer	M: 119 cases and 135 controls F: 89 cases and 107 controls		M: 0.9 F: 1.1		M: 0.5–1.4 F: 0.6 – 1.9	M: 0.96 F: 0.10
			2nd quintile of mean intake (µg/day)	M: >2,137 – 3,252 F: >2,308 – 3,483		M: 100 cases and 134 controls F: 88 cases and 105 controls		M: 0.8 F: 1.2		M: 0.5–1.2 F: 0.7–1.9	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd quintile of mean intake (µg/day)	M: >3,252 – 4,894 F: >3,483 – 4,876		M: 131 cases and 134 controls F: 78 cases and 106 controls		M: 1.0 F: 1.0		M: 0.7–1.6 F: 0.6 – 1.6	
			4th quintile of mean intake (µg/day)	M: <4,894 – 7,493 F: >4,876 – 7,294		M: 105 cases and 136 controls F: 65 cases and 108 controls		M: 0.9 F: 0.8		M: 0.6 – 1.3 F: 0.5–1.3	
			5th quintile of mean intake (µg/day)	M: >7,493 F: >7,294		M: 104 cases and 134 controls F: 73 cases and 106 controls		M: 1.0 F: 1.0		M: NA F: NA	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Nkondjock and Ghadirian, 2004	Case-control	Cases: 402 men and women with colorectal cancer Controls: 688 population-based healthy individuals	1st quartile of intake (µg/day)	ES: 2,239 NS: 2,471	Colon cancer	ES: 81 cases and 126 controls NS: 30 cases and 41 controls		ES: 1.00 NS: 1.00		ES: NA NS: NA	ES: 0.72 NS: 0.02
			2nd quartile of intake (µg/day)	ES: 5,086 NS: 4,246		ES: 78 cases and 111 controls NS: 43 cases and 56 controls		ES: 0.85 NS: 1.10		ES: 0.56 – 1.29 NS: 0.56 – 2.17	
			3rd quartile of intake (µg/day)	ES: 8,605 NS: 8,074		ES: 61 cases and 97 controls NS: 26 cases and 70 controls		ES: 0.89 NS: 0.57		ES: 0.57 – 1.39 NS: 0.28 – 1.16	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quartile of intake (µg/day)	ES: 15,914 NS: 15,903		ES: 53 cases and 103 controls NS: 30 cases and 64 controls		ES: 1.11 NS: 0.44		ES: 0.69 – 1.78 NS: 0.21 – 0.92	
Satia-Abouta *et al.*, 2003	Case-control	Cases: 337 caucasians (56% men and 44% women), aged 40-80, with a first diagnosis of invasive adenocarcinoma of the colon Controls: 596 cancer-free Caucasians (55% men and 45% women), and matched for age, sex, and race	1st quartile of intake (µg β-carotene/day) (median)	1403	Colon cancer	133		1.0		NA	**0.05**
			2nd quartile of intake (µg β-carotene/day) (median)	2672		88		0.8		0.5 – 1.1	
			3rd quartile of intake (µg β-carotene/day) (median)	4087		84		0.8		0.5 – 1.3	
			4th quartile of intake (µg β-carotene/day) (median)	7396		51		0.5		0.3 – 0.9	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		Cases: 276 African-Americans (48% men and 52% women), aged 40-80, with a first diagnosis of invasive adenocarcinoma of the colon	1st quartile of intake (µg β-carotene/day) (median)	1385	Colon cancer	85		1.0		NA	**0.009**
			2nd quartile of intake (µg β-carotene/day) (median)	2978		67		0.7		0.4 – 1.1	
		Controls: 400 African-Americans (44% men and 56% women), aged 40-80, and matched for age, sex, and race	3rd quartile of intake (µg β-carotene/day) (median)	4286		58		0.4		0.3 – 0.7	
			4th quartile of intake (µg β-carotene/day) (median)	7545		66		0.6		0.3 – 0.9	
		Caucasian cases (n=337)	Mean intake of β-carotene (µg/day)	3453	Colon cancer	337					**0.0001**
		Caucasian controls (n=596)	Mean intake of β-carotene (µg/day)	4657		0					
		African-American cases (n=276)	Mean intake of β-carotene (µg/day)	4188	Colon cancer	276					**0.35**

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		African-American controls (n=400)	Mean intake of β-carotene (µg/day)	4433		0					
Senesse *et al.*, 2005	Case-control	Case: 214 men and 148 women, aged 60.7 ± 10.7 years, with colorectal adenoma(s). Control: 182 men and 245 women, aged 54.1 ± 14.1 years, polyp-free.	1st quartile of intake (µg/day)	<3,353.0	Colorectal adenoma	NR		1.0		NA	0.61
			2nd quartile of intake (µg/day)	3,353.0 - <5,109.0				1.1		0.8 – 1.7	
			3rd quartile of intake (µg/day)	5,109.0 – <6,887.3				1.3		0.8 -1.9	
			4th quartile of intake (µg/day)	≥6,887.3				0.8		0.5 – 1.3	
Wakai *et al.*, 2005	Case-control (nested in the Japan Collaborative Cohort Study)	23,454 men and women aged 40 to 79 years and free of cancer at baseline; nested case-control consisted of 116 cases and 298 matched controls	1st tertile of serum β-carotene (mean µmol/L)	M: <0.21 F: <0.50	Colorectal cancer	M: 21 F: 20		M: 1.00 F: 1.00		NA	M: 0.10 F: 0.040
			2nd tertile of serum β-carotene (mean µmol/L)	M: 0.21 – 0.53 F: 0.50 – 0.75		M: 20 F: 8		M: 0.69 F: 0.24		M: 0.25 – 1.90 F: 0.06 – 0.89	
			3rd tertile of serum β-carotene (mean µmol/L)	M: >0.54 F: >0.76		M: 13 F: 34		M: 0.39 F: 2.00		M: 0.12 – 1.23 F: 0.70 – 5.73	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES - BREAST CANCER											
Cho *et al.*, 2003	Cohort (8 years follow-up)	90,655 women aged 26 to 46 years and free of cancer (except nonmelanoma skin cancer) at baseline	1st quintile of intake (µg/day)	1,675	Breast cancer	NR			1.00	NA	0.97
			2nd quintile of intake (µg/day)	2,769		NR			1.00	0.79 - 1.27	
			3rd quintile of intake (µg/day)	3,739		NR			0.83	0.65 - 1.06	
			4th quintile of intake (µg/day)	4,993		NR			1.04	0.82 - 1.32	
			5th quintile of intake (µg/day)	7,701		NR			0.96	0.75 - 1.22	
Sesso *et al.*, 2005	Cohort (9.9 years follow-up) with nested case-control	39,876 women aged ≥45 years and free of cardiovascular disease and cancer at baseline; nested case-control consisted of 508 cases and 508 matched controls	1st quartile of plasma β-carotene (µg/dL)	8.3	Breast cancer	NR			1.00	NA	0.36
			2nd quartile of plasma β-carotene (µg/dL)	15.0		NR			1.24	0.75 – 2.05	
			3rd quartile of plasma β-carotene (µg/dL)	24.3		NR			1.20	0.71 – 2.02	
			4th quartile of plasma β-carotene (µg/dL)	45.6		NR			1.36	0.79 – 2.33	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE-CONTROL STUDIES – BREAST CANCER											
Huang *et al*., 2007	Case-control	Cases: 122 females with histologically confirmed breast cancer Controls: 632 healthy females recruited from outpatient clinics	1st quartile of mean intake (µg/day)	<2,415.8	Breast cancer	46 cases and 158 controls		1.00		NA	0.01
			2nd quartile of mean intake (µg/day)	2,415.9 – 3,491.5		34 cases and 158 controls		0.63		0.37 – 1.09	
			3rd quartile of mean intake (µg/day)	3,419.6 – 4,686.9		21 cases and 158 controls		0.36		0.20 – 0.66	
			4th quartile of mean intake (µg/day)	>4,687		21 cases and 158 controls		0.38		0.21 – 0.71	
Tamimi *et al.*, 2005	Nested case-control	Cases: 969 female nurses diagnosed with breast cancer (aged 43 to 70 years) Controls: 969 female nurses without breast cancer (aged 43 to 70 years)	1st quintile of plasma β-carotene (µmol/L)	0.18	Breast cancer	NR		1.00		NA	0.01
			2nd quintile of plasma β-carotene (µmol/L)	0.31		NR		1.07		0.80 - 1.43	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd quintile of plasma β-carotene (µmol/L)	0.45		NR		1.19		0.88 – 1.60	
			4th quintile of plasma β-carotene (µmol/L)	0.67		NR		0.99		0.73 - 1.35	
			5th quintile of plasma β-carotene (µmol/L)	1.15		NR		0.73		0.53 - 1.02	
COHORT STUDIES – GASTRIC CANCER											
Abnet *et al*., 2003	Cohort (5.25 year of follow-up)	2,125 healthy adults aged 40-69 years (selected from the General Population Trial of Linxian [China])	1st quartile of serum β-carotene (µg/dL)	<2.4	Esophageal (E), gastric cardia (GC), or gastric non-cardia (GN) cancer	E: 590 GC: 295 GN: 87			E: 1 GC: 1 GN: 1	NA NA NA	0.72 0.54 0.25
			2nd quartile of serum β-carotene (µg/dL)	2.4 – 4.3					E: 1.1 GC: 0.89 GN: 1.9	0.82 – 1.5 0.64 – 1.2 1.0 – 3.6	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd quartile of serum β-carotene (µg/dL)	>4.3 – 7.3					E: 0.89 GC: 0.76 GN: 1.3	0.66 – 1.2 0.54 – 1.1 0.66 – 2.6	
			4th quartile of serum β-carotene (µg/dL)	>7.3					E: 1.0 GC: 0.95 GN: 1.9	0.74 – 1.4 0.67 – 1.4 0.89 – 3.9	
Larsson *et al*., 2007	Cohort (average 7.2 years follow-up)	82,002 men and women aged 48-83 years and free of cancer at baseline	1st quartile of intake (µg/day)	1,107	Gastric cancer	47			1.00	NA	0.07
			2nd quartile of intake (µg/day)	1,974		27			0.63	0.39 – 1.02	
			3rd quartile of intake (µg/day)	3,065		38			0.81	0.81 – 1.27	
			4th quartile of intake (µg/day)	5,210		27			0.55	0.32 – 0.94	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE-CONTROL – GASTRIC CANCER											
Jenab *et al.*, 2006	Case-control (nested in EPIC study)	Cases: 137 men and 107 women aged 43-72 with gastric cancer Controls: 349 men and 296 women, cancer-free (except non-melanoma skin cancer) aged 42-72 Cases: 137 men and 107 women aged 43-72 with gastric cancer	1st quartile of serum β-carotene (µg/dl)	<12.0	Gastric cancer	NR		1.00		NA	0.539 0.51
			2nd quartile of serum β-carotene (µg/dl)	≥12.0 - <17.8				0.96		0.60 – 1.79	
			3rd quartile of serum β-carotene (µg/dl)	≥17.8 - <26.5				1.09		0.67 – 1.79	
			4th quartile of serum β-carotene (µg/dl)	≥26.5				1.13		0.69 – 1.86	
			Mean serum β-carotene (µg/dl) (95%CI)	19.0 (5.6 – 53.6)		244					
		Controls: 349 men and 296 women, cancer-free (except non-melanoma skin cancer) aged 42-72	Mean serum β-carotene (µg/dl) (95%CI)	19.0 (5.5 – 52.8)		0					

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES – LUNG CANCER											
Yuan *et al*., 2003	Cohort (average 5.3 years follow-up)	62,392 men and women aged 45 to 74 years and free of cancer at baseline	1st quintile of intake (µg/1,000 kcal)	583	Lung cancer	147			1.00	NA	0.97
			2nd quintile of intake (µg/1,000 kcal)	936		94			0.86	0.66 - 1.11	
			3rd quintile of intake (µg/1,000 kcal)	1235		87			0.95	0.73 – 1.24	
			4th quintile of intake (µg/1,000 kcal)	1637		90			1.17	0.89 – 1.52	
			5th quintile of intake (µg/1,000 kcal)	2473		64			1.00	0.74 - 1.35	
CASE-CONTROL STUDIES – LUNG CANCER											
Goodman *et al*., 2003	Case-control (nested in β-Carotene and Retinol Efficacy Trial [CARET])	Cases: 174 men and 102 women with lung cancer Controls: 174 male and 102 female cancer-free subjects matched for high-risk population, study centre	1st quartile of serum β-carotene (ng/mL)	<87	Lung cancer	NR		1.0		NA	0.73
			2nd quartile of serum β-carotene (ng/mL)	87-158				1.43		0.88 – 2.32	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		location, age, sex, smoking, and year of randomization	3rd quartile of serum β-carotene (ng/mL)	158-255				0.85		0.49 – 1.45	
			4th quartile of serum β-carotene (ng/mL)	>255				1.07		0.63 – 1.83	
		Cases: 174 men with lung cancer Controls: 174 cancer-free men, matched as described above	1st quartile of serum β-carotene (ng/mL)	<87	Lung cancer	NR		1.0		NA	0.42
			2nd quartile of serum β-carotene (ng/mL)	87-158				1.29		0.72 – 2.32	
			3rd quartile of serum β-carotene (ng/mL)	158-255				1.11		0.57 – 2.15	
			4th quartile of serum β-carotene (ng/mL)	>255				1.40		0.71 – 2.74	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		Cases: 102 women with lung cancer Controls: 102 cancer-free women, matched as described above	1st quartile of serum β-carotene (ng/mL)	<87	Lung cancer	NR		1.0		NA	0.11
			2nd quartile of serum β-carotene (ng/mL)	87-158				1.71		0.71 – 4.17	
			3rd quartile of serum β-carotene (ng/mL)	158-255				0.53		0.21 – 1.35	
			4th quartile of serum β-carotene (ng/mL)	>255				0.72		0.30 – 1.75	
		Cases: 205 men with prostate cancer Controls: 205 cancer-free men, matched as described above	1st quartile of serum β-carotene (ng/mL)	<94	Prostate cancer	NR		1.0		NA	0.69
			2nd quartile of serum β-carotene (ng/mL)	94-139				0.94		0.55 – 1.62	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd quartile of serum β-carotene (ng/mL)	139-219				1.06		0.61 – 1.83	
			4th quartile of serum β-carotene (ng/mL)	>219				0.85		0.49 – 1.49	
		Cases: 174 men and 102 women with lung cancer	Mean serum β-carotene (ng/mL)	141	Lung cancer	276					0.23
		Controls: 174 male and 102 female cancer-free subjects matched as described above	Mean serum β-carotene (ng/mL)	152		0					
		Cases: 102 women with lung cancer	Mean serum β-carotene (ng/mL)	169	Lung cancer	102					0.20
		Controls: 102 cancer-free women, matched as described above	Mean serum β-carotene (ng/mL)	194		0					

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		Cases: 174 men with lung cancer	Mean serum β-carotene (ng/mL)	126	Lung cancer	174					0.57
		Controls: 174 cancer-free men, matched as described above	Mean serum β-carotene (ng/mL)	132		0					
		Cases: 205 men with prostate cancer	Mean serum β-carotene (ng/mL)	135	Prostate cancer	205					0.49
		Controls: 205 cancer-free men, matched as described above	Mean serum β-carotene (ng/mL)	142		0					
Wright *et al.*, 2003	Case-control	Cases: 587 women with incident primary lung cancer Controls: 624 population-matched women without lung cancer	1st quintile of intake (µg/day)	<823.58	Lung cancer	NS/FS: 53 cases and 48 controls CS: 113 cases and 76 controls		NS/FS: 1.00 CS: 1.00		NA	NS/FS: 0.51 CS: 0.02

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			2nd quintile of intake (µg/day)	823.58 - 1145.95		NS/FS: 33 cases and 56 controls CS: 82 cases and 69 controls		NS/FS: 0.55 CS: 0.79		NS/FS: 0.29 - 1.0 CS: 0.50 - 1.3	
			3rd quintile of intake (µg/day)	1145.96 - 1526.06		NS/FS: 35 cases and 52 controls CS: 65 cases and 73 controls		NS/FS: 0.55 CS: 0.59		NS/FS: 0.29 - 1.1 CS: 0.37 - 0.95	
			4th quintile of intake (µg/day)	1526.07 - 2323.54		NS/FS: 41 cases and 50 controls CS: 69 cases and 75 controls		NS/FS: 0.76 CS: 0.67		NS/FS: 0.40 - 1.4 CS: 0.41 - 1.1	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			5th quintile of intake (µg/day)	>2323.54		NS/FS: 39 cases and 58 controls CS: 57 cases and 67 controls		NS/FS: 0.62 CS: 0.54		NS/FS: 0.33 - 1.2 CS: 0.32 - 0.90	
COHORT STUDIES - SKIN CANCER											
Dorgan *et al*., 2004	Cohort (5 years follow-up)	302 men and women aged 40 to 75 years (the Isotretinoin Basal Cell Carcinoma Prevention Trial)	1st tertile of serum β-carotene (mean µg/dL)	Not Reported	Basal cell carcinoma (NMSC)	77			1.00	NA	0.94
			2nd tertile of serum β-carotene (mean µg/dL)	NR		69			0.77	0.55 – 1.09	
			3rd tertile of serum β-carotene (mean µg/dL)	NR		75			1.01	0.71 – 1.44	
			1st tertile of serum β-carotene (mean µg/dL)	NR	Squamous cell carcinoma (NMSC)	26			1.00	NA	0.06

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			2nd tertile of serum β-carotene (mean µg/dL)	NR		30			1.09	0.62 – 1.93	
			3rd tertile of serum β-carotene (mean µg/dL)	NR		29			1.47	0.81 – 2.68	
Fung *et al*., 2003	Cohort (10 year of follow-up for men and 14 years for women)	84,944 female nurses aged 30-55 in 1976 and 43,867 male physicians aged 40-75 in 1986	1st quintile of intake (µg/day; median)	2009 µg/day (women) 2186 µg/day (men)	Squamous cell carcinoma (skin)	NR			1.00	NA	Men: 0.88 Women: 0.31 Pooled: 0.43
			2nd quintile of intake (µg/day)	NR					Men:1.90 Women: 0.87 Pooled: 1.28	Men: 1.28 – 2.83 Women: 0.62 – 1.24 Pooled: 0.60 – 2.74	
			3rd quintile of intake (µg/day)	NR					Men: 1.63 Women: 1.01 Pooled: 1.26	Men: 1.09 – 2.45 Women: 0.72 – 1.41 Pooled: 0.79 – 2.03	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quintile of intake (µg/day)	NR					Men: 1.52 Women: 0.99 Pooled: 1.21	Men: 1.01 – 2.30 Women: 0.71 – 1.39 Pooled: 0.80 – 1.83	
			5th quintile of intake (µg/day; median)	7277 µg/day (women) 8750 µg/day (men)					Men: 1.42 Women: 1.10 Pooled: 1.21	Men: 0.93 – 2.16 Women: 0.79 – 1.54 Pooled: 0.94 – 1.58	
CASE-CONTROL STDUIES – SKIN CANCERS											
Schaumberg *et al.*, 2004	Case-control (nested in the Physicians' Health Study)	Case: 1,338 men aged 40-84 years at baseline who developed a NMSC during 12 years of follow-up. Control: 1,338 men aged 40-84 years who	1st quartile of plasma β-carotene (µg/dL)	≤7.28	NMSC	305 cases and 334 controls		1.00		NA	0.84
			2nd quartile of plasma β-carotene (µg/dL)	>7.28 – 13.14		330 cases and 335 controls		1.06		0.77 – 1.45	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		remained NMSC-free during follow-up.	3rd quartile of plasma β-carotene (µg/dL)	>13.14 – 23.28		351 cases and 335 controls		1.04		0.75 – 1.44	
			4th quartile of plasma β-carotene (µg/dL)	>23.28		352 cases and 334 controls		0.97		0.69 – 1.37	
COHORT STUDIES – ESOPHAGEAL/UPPER AERODIGESTIVE TRACT CANCER											
Abnet *et al*., 2003	Cohort (5.25 year of follow-up)	2,125 healthy adults aged 40-69 years (selected from the General Population Trial of Linxian [China])	1st quartile of serum β-carotene (µg/dL)	<2.4	Esophageal (E), gastric cardia (GC), or gastric non-cardia (GN) cancer	E: 590 GC: 295 GN: 87			E: 1 GC: 1 GN: 1	NA NA NA	0.72 0.54 0.25
			2nd quartile of serum β-carotene (µg/dL)	2.4 – 4.3					E: 1.1 GC: 0.89 GN: 1.9	0.82 – 1.5 0.64 – 1.2 1.0 – 3.6	
			3rd quartile of serum β-carotene (µg/dL)	>4.3 – 7.3					E: 0.89 GC: 0.76 GN: 1.3	0.66 – 1.2 0.54 – 1.1 0.66 – 2.6	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quartile of serum β-carotene (µg/dL)	>7.3					E: 1.0 GC: 0.95 GN: 1.9	0.74 – 1.4 0.67 – 1.4 0.89 – 3.9	
De Stefani *et al*., 2006	Case-control	Cases: 234 men and women with squamous cell carcinoma of the esophagus Controls: 936 hospital-based controls without neoplastic disease	1st quartile of mean intake (units NR)	<2,535.9	Squamous cell carcinoma of the esophagus	NR		NR		NR	0.48
			2nd quartile of mean intake (units NR)	2,535.9 – 4,573.2		70 cases (controls NR)		0.67		0.42 – 1.07	
			3rd quartile of mean intake (units NR)	4,573.2 – 7,420.3		61 cases (controls NR)		0.87		0.55 – 1.38	
			4th quartile of mean intake (units NR)	>7,420.3		59 cases (controls NR)		0.78		0.49 – 1.24	
Wright *et al*., 2007	Cohort (5 to 8 years of follow-up as part of an intervention trial [See Table C.1-1])	29,133 male smokers, aged 50-69 years and cancer-free at baseline	Tertiles of serum β-carotene	Individual tertiles of serum β-carotene were NR	Cancers of oral cavity/pharynx	NR		NR		NR	NR, but NS
					Cancers of esophagus	NR		0.07[2]		0.009 – 0.59	0.008
					Cancers of larynx	NR		0.81		0.39 – 1.69	0.61

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES – CANCER MORTALITY AND TOBACCO RELATED CANCERS											
Buijsse *et al*., 2005 [plasma carotene, not specific to β-carotene]	Cohort (10 years of follow-up)	1,168 elderly men and women aged 70-75 years between December 1988 and March 1989 (the Survey in Europe on Nutrition and the Elderly, a Concerted Action [SENECA])	1st tertile of plasma carotene (µmol/L)	0.22	Cancer mortality	96			0.59 for a 1-SD change of 0.39 µmol/L for plasma carotene	0.44 – 0.79	NA
			2nd tertile of plasma carotene (µmol/L)	0.54							
			3rd tertile of plasma carotene (µmol/L)	1.12							
Touvier *et al.*, 2005	Cohort (median 7.4 years follow-up)	59,910 women aged 40-65 years in 1990 (French component of the European Prospective Investigation into Cancer and Nutrition)	1st tertile of intake (µg/day)	2,285.6	Tobacco-related cancers	NS: 163 ES: 71	1.00 1.00			NA NA	NS: 0.03 ES: 0.09
			2nd tertile of intake (µg/day)	3,731.8		NS: 128 ES: 93	0.72 1.43			0.57 – 0.92 1.05 – 1.96	
			3rd tertile of intake (µg/day)	5,929.9		NS: 147 ES: 81	0.80 1.20			0.64 – 1.01 0.86 – 1.67	
			Supplement use (µg/day)	4,207.2		NS: 5 ES: 12	0.44 2.14			0.18 – 1.07 1.16 – 3.97	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE-CONTROL STUDIES – BLADDER, PANCREATIC AND OVARIAN CANCER STUDIES											
Hung *et al*., 2006	Case-control	Cases: 84 patients at a cancer center with bladder cancer Controls: 173 healthy individuals without bladder cancer	1st quartile of plasma β-carotene (0.1 µmol/L)	Cases: 0.97 Controls: 1.34	Bladder cancer	31 cases and 43 controls		1.00		NA	0.047
			2nd quartile of plasma β-carotene (0.1 µmol/L)	NR		21 cases and 44 controls		0.15		0.03 – 0.83	
			3rd quartile of plasma β-carotene (0.1 µmol/L)	Cases: 3.19 Controls: 4.22		18 cases and 42 controls		0.30		0.05 – 1.72	
			4th quartile of plasma β-carotene (0.1 µmol/L)	NR		14 cases and 44 controls		0.11		0.04 – 0.80	
Nkondjock *et al*., 2005	Case-control	Cases: 258 men and 204 women with histologically confirmed prostate cancer Controls: 2,331 population-based healthy men and 2,594	1st quartile of mean intake (µg/day)	M: 6,215 F: 5,953	Pancreatic cancer	M: 69 cases and 634 controls F: 40 cases and 505 controls		M: 1.00 F: 1.00		M: NA F: NA	M: 0.58 F: 0.40

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		population-based healthy women	2nd quartile of mean intake (µg/day)	M: 10,621 F: 9,803		M: 64 cases and 532 controls F: 39 cases and 607 controls		M: 0.93 F: 1.30		M: 0.63 – 1.38 F: 0.80 – 2.12	
			3rd quartile of mean intake (µg/day)	M: 15,788 F: 14,935		M: 69 cases and 565 controls F: 61 cases and 574 controls		M: 0.89 F: 0.83		M: 0.61 – 1.30 F: 0.53 – 1.30	
			4th quartile of mean intake (µg/day)	M: 25,763 F: 22,059		M: 46 cases and 531 controls F: 56 cases and 608 controls		M: 1.22 F: 0.96		M: 0.80 – 1.87 F: 0.60 – 1.51	

Table C-2 Tabulation of Data from Observational Studies of β-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Zhang *et al*., 2007b	Case-control	Cases: 254 patients with histologically confirmed epithelial ovarian cancer Controls: 652 age-matched healthy individuals	1st quartile of mean intake (µg/day)	<3,104	Ovarian cancer	87 cases and 163 controls		1.00		NA	<0.01
			2nd quartile of mean intake (µg/day)	3,104 – 4,859		82 cases and 163 controls		0.94		0.62 – 1.41	
			3rd quartile of mean intake (µg/day)	4,860 – 8,068		42 cases and 163 controls		0.46		0.29 – 0.73	
			4th quartile of mean intake (µg/day)	>8,069		39 cases and 163 controls		0.51		0.31 – 0.84	

Abbreviations: CI = confidence interval; CS = current smokers; ES = ever smokers; FS = former smokers; HR = hazard ratio; NA = not applicable; NMSC = nonmelanoma skin cancer; NS = never smokers; OR = odds ratio; RR = relative risk
[1] Mean values are presented unless otherwise noted.
[2] Relative risk for highest *versus* lowest tertile.

Table C-3 Tabulation of Data from Human Intervention Studies of β-Carotene (CVD)

Reference	Daily Dose	Duration	Population and Final Sample Size	Endpoint(s)	Incidence (treatment *versus* placebo)	Significance/ Risk Ratios (between groups)		
						RR	95% CI	P-value for trend
Cook *et al.*, 2007	50 mg (alternate days)	Mean follow-up period of 9.4 years	8,171 female health professionals, 40 years or older, with a reported history of CVD or at least 3 cardiac risk factors	Major CVD[1]	731 *vs.* 719	1.02	0.92 – 1.13	0.71
				Myocardial infarction	135 *vs.* 139	0.97	0.77 – 1.23	0.82
				Revascularization	438 *vs.* 451	0.98	0.86 – 1.11	0.71
				Stroke	161 *vs.* 137	1.17	0.93 – 1.47	0.17
				Transient ischemic attack	201 *vs.* 220	0.91	0.75 – 1.10	0.35
				CVD death	211 *vs.* 184	1.14	0.94 – 1.39	0.65

Abbreviations: CVD = cardiovascular disease
[1] Major CVD includes myocardial infarction, stroke, revascularization procedure or death due to cardiovascular disease.

Table C-4 Tabulation of Data from Observational Studies of β-Carotene (CVD)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE CONTROL STUDIES – MYOCARDIAL INFARCTION											
Hak *et al.*, 2003	Case-control (nested in the Physicians' Health Study)	Case: 531 male physicians diagnosed with MI (age 58.1 ± 8.6 years) Control: 531 paired control subjects free from MI (age 57.9 ± 8.5 years)	1st quintile of plasma β-carotene (ng/mL)	111.1 (median)	MI	NR			1	NA	0.23
			2nd quintile of plasma β-carotene (ng/mL)	165.9 (median)					0.79	0.49 – 1.27	
			3rd quintile of plasma β-carotene (ng/mL)	210.9 (median)					0.71	0.44 – 1.17	
			4th quintile of plasma β-carotene (ng/mL)	290.3 (median)					0.60	0.36 – 0.98	
			5th quintile of plasma β-carotene (ng/mL)	476.8 (median)					0.74	0.44 – 1.26	

Table C-4 Tabulation of Data from Observational Studies of β-Carotene (CVD)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Kabagambe *et al.*, 2005	Case-control	Subjects from Costa Rica. Case: 1,456 men and women with a first acute MI, aged 58 ± 11 years. Control: 1,456 men and women without MI, aged 58 ± 11 years.	1st quintile of adipose tissue β-carotene (μmol/kg)	0.08 (median)	Non-fatal acute MI	NR		1.00		NA	0.02
			2nd quintile of adipose tissue β-carotene (μmol/kg)	0.35 (median)				0.89		0.68 – 1.15	
			3rd quintile of adipose tissue β-carotene (μmol/kg)	0.67 (median)				1.01		0.77 – 1.32	
			4th quintile of adipose tissue β-carotene (μmol/kg)	1.13 (median)				0.74		0.55 – 0.99	
			5th quintile of adipose tissue β-carotene (μmol/kg)	2.26 (median)				0.70		0.51 – 0.96	

Table C-4 Tabulation of Data from Observational Studies of β-Carotene (CVD)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Tavani *et al.*, 2006	Case-control	Subjects from Milan, Italy Case: 580 men and 180 women, median age 61, range 19 to 79 years, with non-fatal acute MI. Control: 439 mean and 243 women, median age 59, range 18 to 79 years, admitted to hospital for unrelated conditions.	1st quartile of intake (µg/day)	Mean intake of 7,185.7 (individual quartiles NR)	Acute MI	241 cases and 171 controls		1		NA	0.037
			2nd quartile of intake (µg/day)			199 cases and 170 controls		0.85		0.62 – 1.18	
			3rd quartile of intake (µg/day)			167 cases and 171 controls		0.74		0.53 – 1.04	
			4th quartile of intake (µg/day)			153 cases and 170 controls		0.71		0.50 – 1.01	

Table C-4 Tabulation of Data from Observational Studies of β-Carotene (CVD)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES – CVD MORTALITY											
Buijsse *et al.*, 2008	Cohort (15 years of follow-up)	559 Dutch men, aged 71.8 ± 5.2 years in 1985 (the Zutphen Elderly Study)	Tertiles of dietary intake (µg/day)	Mean value of 2,766 ± 1,474 at baseline (individual tertiles NR)	Cardiovascular mortality	197			0.80[3]	0.6 – 0.97	NA
Ito *et al.*, 2006	Cohort (11.9 years of follow-up)	1,190 males and 1,871 females, aged 39 to 80 years from rural Japan	Not classified	Plasma β-carotene levels were measured but NR	Cardiovascular disease mortality (includes heart disease and stroke)	80	0.64[2]			0.47 – 0.89	0.007
					Heart disease mortality	40	0.84[2]			0.53 – 1.34	0.465
					Stroke mortality	37	0.48[2]			0.31 – 0.76	0.253

Table C-4 Tabulation of Data from Observational Studies of β-Carotene (CVD)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES – CORONARY ARTERY DISEASE											
Osganian *et al.*, 2003	Cohort (12 years of follow-up)	73,286 female nurses in the U.S., aged 30 to 55 years in 1976 (the Nurses' Health Study)	1st quintile of intake (µg/day)	1,720 (median)	Total CAD (non-fatal MI and fatal CAD)	231			1.0	NA	0.05
			2nd quintile of intake (µg/day)	2,633 (median)		208			0.89	0.73 – 1.08	
			3rd quintile of intake (µg/day)	3,528 (median)		165			0.69	0.56 – 0.85	
			4th quintile of intake (µg/day)	4,843 (median)		216			0.89	0.73 – 1.10	
			5th quintile of intake (µg/day)	7,639 (median)		178			0.74	0.59 – 0.93	

Abbreviations: CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; NR = not reported
[1] Mean values are presented unless otherwise noted.
[2] Hazard ratio per each logarithmically transformed value of serum β-carotene levels (µmol/L)
[3] Relative risk for a 1-SD increase in β-carotene intake

Table C-5 Tabulation of Data from Human Intervention Studies of Lycopene (Cancer)

Reference	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
					Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
Bunker *et al.*, 2007	30 mg lycopene plus a multivitamin	Capsules	4 months	38 male subjects (aged 40-79 years) with at least one prostate cancer risk factor at baseline	Prostate-Specific Antigen (ng/mL)				NS	NS	Not reported
					5.31	5.74	0.43	0.35			
	Multivitamin only			39 male subjects (aged 40-79 years) with at least one prostate cancer risk factor at baseline	Prostate-Specific Antigen (ng/mL)				NS		
					5.31	5.39	0.08	Not applicable			
Schwarz *et al.*, 2008	30 mg lycopene	Capsules	6 months	19 male subjects (aged 45 to 70 years) with histologically confirmed benign prostate hyperplasia	Prostate-Specific Antigen (ng/mL)				P<0.05	NS	NS
					6.56	5.82	-0.74	-0.70			
					Prostate volume (mL; estimated by digital rectal examination)				NS	NS	NS
					47.4	49.7	2.5	-9.2			
					Prostate weight (g; estimated by trans-rectal ultrasonography)				NS	NS	NS

Table C-5 Tabulation of Data from Human Intervention Studies of Lycopene (Cancer)

Reference	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
					Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
					42.2	43.4	1.2	-8.4			
					International prostate symptom score (points)				P<0.01	NS	NS
					12.0	10.3	-1.7	0.6			
	Placebo			18 male subjects (aged 45 to 70 years) with histologically confirmed benign prostate hyperplasia	Prostate-Specific Antigen (ng/mL)				NS	NS	NS
					6.85	6.81	-0.04	Not applicable			
					Prostate volume (mL; estimated by digital rectal examination)				P<0.01	NS	NS
					43.6	55.3	11.7	Not applicable			
					Prostate weight (g; estimated by trans-rectal ultrasonography)				P<0.05	NS	NS
					40.5	50.1	9.6	Not applicable			
					International prostate symptom score (points)				P<0.05	NS	NS
					12.4	10.1	-2.3	Not applicable			

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES											
Key *et al.*, 2007	Case-control nested in a cohort (average 6 years follow-up)	137,001 men approximately 60 years of age and free of prostate cancer at baseline; nested case-control consisted of 966 cases and 1,064 matched controls	1st quintile of plasma lycopene (mean µg/dL)	<15.04	Prostate cancer (localized disease)	77			1.00	NA	0.50
			2nd quintile of plasma lycopene (mean µg/dL)	15.04 – <24.32		113			1.31	0.87 – 1.97	
			3rd quintile of plasma lycopene (mean µg/dL)	24.32 – <34.75		115			1.36	0.90 – 2.05	
			4th quintile of plasma lycopene (mean µg/dL)	34.75 - <49.37		83			1.05	0.69 – 1.59	
			5th quintile of plasma lycopene (mean µg/dL)	>49.37		95			1.40	0.89 – 2.21	
			1st quintile of plasma lycopene (mean µg/dL)	<15.04	Prostate cancer (advanced disease)	48			1.00	NA	0.05
			2nd quintile of plasma lycopene (mean µg/dL)	15.04 – <24.32		45			1.35	0.67 – 2.74	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd quintile of plasma lycopene (mean µg/dL)	24.32 – <34.75		44			1.19	0.62 – 2.29	
			4th quintile of plasma lycopene (mean µg/dL)	34.75 - <49.37		43			0.93	0.47 – 1.85	
			5th quintile of plasma lycopene (mean µg/dL)	>49.37		25			0.40	0.19 – 0.88	
Kirsh *et al.*, 2006b	Cohort (up to 8 years follow-up)	29,631 men aged 55 to 74 years with no history of prostate, lung, or colon cancer (the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial)	1st quintile of intake (µg/day)	5,052	Prostate Cancer	269			1.00	NA	0.33
			2nd quintile of intake (µg/day)	7,555		287			1.10	0.93 – 1.30	
			3rd quintile of intake (µg/day)	9,650		268			1.06	0.89 – 1.25	
			4th quintile of intake (µg/day)	12,271		271			1.07	0.90 – 1.27	
			5th quintile of intake (µg/day)	17,593		243			0.95	0.79 – 1.13	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE-CONTROL STUDIES											
Bosetti *et al.*, 2004	Case-control	Cases: 1,294 incident, histologically prostate cancer cases in men <75 years of age Controls: 1,451 healthy men <75 years of age	1st quintile of mean intake (µg/day)	NR. Average intake in controls was reported to be 7,486.8 µg/day; average intake in cases was not reported.	Prostate cancer	243 cases and 290 controls		1.00		NA	0.93
			2nd quintile of mean intake (µg/day)			262 cases and 290 controls		1.06		0.82 – 1.37	
			3rd quintile of mean intake (µg/day)			246 cases and 290 controls		0.99		0.76 – 1.28	
			4th quintile of mean intake (µg/day)			300 cases and 291 controls		1.15		0.89 – 1.49	
			5th quintile of mean intake (µg/day)			243 cases and 290 controls		0.94		0.72 – 1.23	
Huang *et al.*, 2003	Case-control	CLUE 1 (blood collected in 1974) Cases: 182 men (mean age of 54 years) diagnosed with prostate cancer Controls: 364 men (mean age of 54	1st quintile of serum lycopene (µg/dL)	≤21.7	Prostate cancer	41 cases and 71 controls		1.00		NA	0.72
			2nd quintile of serum lycopene (µg/dL)	>21.7 – 31.1		36 cases and 73 controls		0.86		0.51 – 1.47	
			3rd quintile of serum lycopene (µg/dL)	>31.1 – 41.1		31 cases and 73 controls		0.74		0.41 – 1.33	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
		years) without prostate cancer	4th quintile of serum lycopene (µg/dL)	>41.1 – <54.9		39 cases and 71 controls		0.96		0.55 – 1.67	
			5th quintile of serum lycopene (µg/dL)	≥54.9		35 cases and 73 controls		0.83		0.46 – 1.48	
		CLUE 2 (blood collected in 1989) Cases: 142 men (mean age of 66 years) diagnosed with prostate cancer Controls: 284 men (mean age of 66 years) without prostate cancer	1st quintile of serum lycopene (µg/dL)	≤24.3	Prostate cancer	33 cases and 57 controls		1.00		NA	0.49
			2nd quintile of serum lycopene (µg/dL)	>24.3 – 35.2		29 cases and 56 controls		0.88		0.45 – 1.70	
			3rd quintile of serum lycopene (µg/dL)	>35.2 – 48.8		26 cases and 58 controls		0.77		0.40 – 1.47	
			4th quintile of serum lycopene (µg/dL)	>48.8 - <62.8		28 cases and 57 controls		0.83		0.42 – 1.62	
			5th quintile of serum lycopene (µg/dL)	≥62.8		26 cases and 56 controls		0.79		0.41 – 1.54	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Jian *et al.*, 2007	Case-control	Cases: 130 men with prostate cancer Controls: 274 men recruited from the same hospitals and without evidence or history of any type of cancer	1st quartile of mean intake (µg/day)	<1,609	Prostate cancer	55 cases and 68 controls		1.00		NA	NR
			2nd quartile of mean intake (µg/day)	1,609 – 3,081		32 cases and 69 controls		0.47		0.25 – 0.86	
			3rd quartile of mean intake (µg/day)	3,081 – 4,917		30 cases and 69 controls		0.40		0.21 – 0.77	
			4th quartile of mean intake (µg/day)	>4,917		13 cases and 68 controls		0.17		0.08 – 0.39	
McCann *et al.*, 2005	Case-control	Cases: 433 men with primary, histologically confirmed prostate cancer Controls: 538 population-based healthy men	1st quartile of intake (µg/day)	≤3,902	Prostate cancer	139 cases and 135 controls		1.00		NA	0.95
			2nd quartile of intake (µg/day)	3,902 – 5,796		92 cases and 134 controls		0.71		0.49 – 1.02	
			3rd quartile of intake (µg/day)	5,796 – 8,863		113 cases and 135 controls		0.96		0.66 – 1.39	
			4th quartile of intake (µg/day)	>8,863		89 cases and 134 controls		0.87		0.55 – 1.38	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Peters *et al.*, 2007	Case-control	Cases: 692 incident prostate cancer cases in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Controls: 844 healthy individuals from the same trial	1st quintile of serum lycopene (µg/dL)	30.5	Prostate cancer	136 cases and 168 controls		1.00		NA	0.28
			2nd quintile of serum lycopene (µg/dL)	46.8		130 cases and 169 controls		1.00		0.72 – 1.40	
			3rd quintile of serum lycopene (µg/dL)	62.2		121 cases and 168 controls		0.93		0.66 – 1.31	
			4th quintile of serum lycopene (µg/dL)	78.5		154 cases and 169 controls		1.16		0.84 – 1.61	
			5th quintile of serum lycopene (µg/dL)	108.4		151 cases and 168 controls		1.14		0.82 – 1.58	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Wu *et al.*, 2004	Case-control nested in a cohort (7-11 years follow-up)	Cases: 450 male health professionals diagnosed with prostate cancer (aged 40 – 75 years) Controls: 450 male health professionals without prostate cancer (aged 40 – 75 years)	1st quintile of plasma lycopene	NR. Median plasma lycopene was reported as 698.3 nmol/L in cases and 726.0 nmol/L in controls.	Prostate cancer	101 cases and 79 controls		1.00		NA	0.33
			2nd quintile of plasma lycopene			88 cases and 92 controls		0.72		0.45 – 1.15	
			3rd quintile of plasma lycopene			82 cases and 98 controls		0.56		0.34 – 0.93	
			4th quintile of plasma lycopene			91 cases and 89 controls		0.73		0.44 – 1.19	
			5th quintile of plasma lycopene			88 cases and 92 controls		0.66		0.38 – 1.13	
Zhang *et al.*, 2007a	Case-control	Cases: 193 men diagnosed with prostate cancer in 3 major hospitals Controls: 197 healthy men without prostate cancer	1st quartile of plasma lycopene (µg/L)	140.5	Prostate cancer	68 cases and 49 controls		1.00		NA	0.075
			2nd quartile of plasma lycopene (µg/L)	230.4		42 cases and 49 controls		0.75		0.42 – 1.36	
			3rd quartile of plasma lycopene (µg/L)	333.3		59 cases and 50 controls		1.02		0.57 – 1.84	
			4th quartile of plasma lycopene (µg/L)	513.7		24 cases and 49 controls		0.46		0.22 – 0.94	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES											
Cho *et al.*, 2003	Cohort (8 years follow-up)	90,655 women aged 26 to 46 years and free of cancer (except nonmelanoma skin cancer) at baseline	1st quintile of intake (µg/day)	3,570	Breast cancer	NR			1.00	NA	0.06
			2nd quintile of intake (µg/day)	5,527		NR			1.01	0.79 – 1.30	
			3rd quintile of intake (µg/day)	7,637		NR			0.91	0.71 – 1.18	
			4th quintile of intake (µg/day)	10,494		NR			1.19	0.94 – 1.50	
			5th quintile of intake (µg/day)	15,745		NR			1.17	0.92 – 1.49	
Sesso *et al.*, 2005	Cohort (9.9 years follow-up) with nested case-control	39,876 women aged ≥ 45 years and free of cardiovascular disease and cancer at baseline; nested case-control consisted of 508 cases and 508 matched controls	1st quintile of intake (µg/day)	3,326	Breast cancer	208			1.00	NA	0.71
			2nd quintile of intake (µg/day)	5,427		213			0.95	0.77 – 1.18	
			3rd quintile of intake (µg/day)	7,683		215			1.00	0.80 – 1.24	
			4th quintile of intake (µg/day)	10,813		237			1.10	0.89 – 1.36	
			5th quintile of intake (µg/day)	16,741		203			1.00	0.80 – 1.25	
			1st quartile of plasma lycopene (µg/dL)	5.6	Breast cancer	NR			1.00	NA	0.86

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			2nd quartile of plasma lycopene (µg/dL)	8.5		NR			0.95	0.59 – 1.55	
			3rd quartile of plasma lycopene (µg/dL)	11.2		NR			1.15	0.69 – 1.90	
			4th quartile of plasma lycopene (µg/dL)	15.9		NR			0.93	0.56 – 1.52	
CASE-CONTROL STUDIES											
Huang *et al.*, 2007	Case-control	Cases: 122 females with histologically confirmed breast cancer Controls: 632 healthy females recruited from outpatient clinics	1st quartile of mean intake (µg/day)	<4,243.1	Breast cancer	59 cases and 158 controls		1.00		NA	<0.001
			2nd quartile of mean intake (µg/day)	4,243.1 – 8,522.8		29 cases and 159 controls		0.42		0.25 – 0.73	
			3rd quartile of mean intake (µg/day)	8,522.9 – 12,670.9		12 cases and 156 controls		0.17		0.08 – 0.34	
			4th quartile of mean intake (µg/day)	>12,671		22 cases and 159 controls		0.26		0.14 – 0.46	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Tamimi *et al.*, 2005	Case-control nested in a cohort (up to 22 years follow-up)	Cases: 969 female nurses diagnosed with breast cancer (aged 43 to 70 years) Controls: 969 female nurses without breast cancer (aged 43 to 70 years)	1st quintile of plasma lycopene (µmol/L)	0.39	Breast cancer	NR		1.00		0.96 – 1.76	0.53
			2nd quintile of plasma lycopene (µmol/L)	0.59		NR		1.30		0.74 - 1.38	
			3rd quintile of plasma lycopene (µmol/L)	0.76		NR		1.01		0.76 – 1.42	
			4th quintile of plasma lycopene (µmol/L)	0.94		NR		1.04		0.76 - 1.42	
			5th quintile of plasma lycopene (µmol/L)	1.26		NR		1.01		0.73 - 1.39	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
COHORT STUDIES											
Wakai *et al.*, 2005	Case-control nested in a cohort (8 years follow-up)	23,454 men and women aged 40 to 79 years and free of cancer at baseline; nested case-control consisted of 116 cases and 298 matched controls	1st tertile of serum lycopene (mean µmol/L)	M: <0.09 F: <0.13	Colorectal cancer	M: 20 F: 23		M: 1.00 F: 1.00		NA	M: 0.32 F: 0.93
			2nd tertile of serum lycopene (mean µmol/L)	M: 0.09 – 0.20 F: 0.13 – 0.34		M:17 F: 16		M: 0.77 F: 0.71		M: 0.28 – 2.16 F: 0.34 – 1.71	
			3rd tertile of serum lycopene (mean µmol/L)	M: >0.21 F: >0.35		M: 17 F: 23		M: 0.57 F: 1.12		M: 0.19 – 1.71 F: 0.46 – 3.32	
CASE-CONTROL STUDIES											
Kune and Watson, 2006	Case-control	Cases: 715 men and women with colorectal cancer (the Melbourne Colorectal Cancer Study) Controls: 727 community-based controls	1st quintile of intake	NR	Colorectal cancer	NR		1.00		NA	NR (but not significant)
			2nd quintile of intake	NR		NR		1.03		0.73 – 1.44	
			3rd quintile of intake	NR		NR		1.00		0.71 – 1.40	
			4th quintile of intake	NR		NR		0.89		0.63 – 1.26	
			5th quintile of intake	NR		NR		0.86		0.61 – 1.21	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Murtaugh *et al.*, 2004	Case-control	Cases: 952 men and women with rectal cancer Controls: 1,205 healthy individuals	1st quintile of mean intake (µg/day)	M: ≤3,673 F: ≤3,136	Rectal cancer	M: 112 cases and 134 controls F: 99 cases and 107 controls		M: 0.9 F: 1.7		M: 0.6 – 1.4 F: 1.0 – 2.8	0.01
			2nd quintile of mean intake (µg/day)	M: >3,673 – 6,489 F: >3,136 – 5,714		M: 105 cases and 135 controls F: 90 cases and 106 controls		M: 0.9 F: 1.5		M: 0.6 – 1.3 F: 0.9 – 2.3	
			3rd quintile of mean intake (µg/day)	M: >6,489 – 10,111 F: >5,714 – 8,869		M: 114 cases and 135 controls F: 63 cases and 107 controls		M: 0.9 F: 1.0		M: 0.6 – 1.4 F: 0.6 – 1.6	
			4th quintile of mean intake (µg/day)	M: <10,111 – 16,806 F: >8,869 – 14,208		M: 110 cases and 135 controls F: 65 cases and 106 controls		M: 0.9 F: 0.9		M: 0.6 – 1.3 F: 0.6 – 1.4	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			5th quintile of mean intake (µg/day)	M: >16,806 F: >14,208		M: 118 cases and 134 controls F: 76 cases and 106 controls		M: 1.0 F: 1.0		M: NA F: NA	
Nkondjock and Ghadirian, 2004	Case-control	Cases: 402 men and women with colorectal cancer Controls: 688 population-based healthy individuals	1st quartile of intake (µg/day)	ES: 770 NS: 560	Colon cancer	ES: 67 cases and 128 controls NS: 28 cases and 44 controls		ES: 1.00 NS: 1.00		ES: NA NS: NA	ES: 0.05 NS: 0.65
			2nd quartile of intake (µg/day)	ES: 2,774 NS: 2,386		ES: 65 cases and 103 controls NS: 37 cases and 62 controls		ES: 0.73 NS: 0.96		ES: 0.46 – 1.13 NS: 0.49 – 1.87	
			3rd quartile of intake (µg/day)	ES: 5,941 NS: 5,474		ES: 65 cases and 101 controls NS: 31 cases and 71 controls		ES: 0.73 NS: 1.50		ES: 0.47 – 1.15 NS: 0.76 – 2.93	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quartile of intake (µg/day)	ES: 14,131 NS: 12,674		ES: 76 cases and 105 controls NS: 33 cases and 53 controls		ES: 0.63 NS: 1.00		ES: 0.40 – 0.98 NS: 0.50 – 1.98	
COHORT STUDIES											
Yuan *et al.*, 2003	Cohort (average 5.3 years follow-up)	62,392 men and women aged 45 to 74 years and free of cancer at baseline	1st quintile of intake (µg/1,000 kcal)	70	Lung cancer	138			1.00	NA	NR
			2nd quintile of intake (µg/1,000 kcal)	238		128			1.11	0.88 – 1.43	
			3rd quintile of intake (µg/1,000 kcal)	452		77			0.77	0.58 – 1.02	
			4th quintile of intake (µg/1,000 kcal)	755		80			0.89	0.67 – 1.18	
			5th quintile of intake (µg/1,000 kcal)	1,490		59			0.89	0.65 – 1.21	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
CASE-CONTROL STUDIES											
Wright *et al.*, 2003	Case-control	Cases: 587 women with incident primary lung cancer Controls: 624 population-matched women without lung cancer	1st quintile of intake (µg/day)	<175.80	Lung cancer	NS/FS: 48 cases and 54 controls CS: 79 cases and 70 controls		NS/FS: 1.00 CS: 1.00		NA	NS/FS: 0.38 CS: 0.19
			2nd quintile of intake (µg/day)	175.80 – 314.30		NS/FS: 39 cases and 52 controls CS: 73 cases and 73 controls		NS/FS: 0.92 CS: 0.98		NS/FS: 0.49 – 1.7 CS: 0.60 – 1.6	
			3rd quintile of intake (µg/day)	314.31 – 552.26		NS/FS: 47 cases and 61 controls CS: 84 cases and 64 controls		NS/FS: 0.91 CS: 1.2		NS/FS: 0.50 – 1.7 CS: 0.73 – 2.0	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			4th quintile of intake (µg/day)	552.27 – 962.27		NS/FS: 40 cases and 51 controls CS: 84 cases and 74 controls		NS/FS: 0.79 CS: 1.1		NS/FS: 0.41 – 1.5 CS: 0.67 – 1.8	
			5th quintile of intake (µg/day)	>962.27		NS/FS: 27 cases and 46 controls CS: 66 cases and 79 controls		NS/FS: 0.74 CS: 0.74		NS/FS: 0.36 – 1.5 CS: 0.43 – 1.3	
Hung *et al.*, 2006	Case-control	Cases: 84 patients at a cancer center with bladder cancer Controls: 173 healthy individuals without bladder cancer	1st quartile of plasma lycopene (0.1 µmol/L)	Cases: 1.04 Controls: 1.92	Bladder cancer	49 cases and 43 controls		1.00		NA	0.059
			2nd quartile of plasma lycopene (0.1 µmol/L)	NR		23 cases and 43 controls		0.77		0.18 – 3.24	
			3rd quartile of plasma lycopene (0.1 µmol/L)	Cases: 2.56 Controls: 4.01		9 cases and 43 controls		0.58		0.13 – 2.63	
			4th quartile of plasma lycopene (0.1 µmol/L)	NR		3 cases and 44 controls		0.05		0.002 – 1.14	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
De Stefani *et al.*, 2006	Case-control	Cases: 234 men and women with squamous cell carcinoma of the esophagus Controls: 936 hospital-based controls without neoplastic disease	1st quartile of mean intake (units NR)	<1,702.3	Squamous cell carcinoma of the esophagus	NR		NR		NR	<0.0001
			2nd quartile of mean intake (units NR)	1,702.3 – 2,522.2		101 cases (controls NR)		0.59		0.38 – 0.90	
			3rd quartile of mean intake (units NR)	2,522.2 – 3,528.7		50 cases (controls NR)		0.50		0.32 – 0.77	
			4th quartile of mean intake (units NR)	>3,528.7		29 cases (controls NR)		0.29		0.18 – 0.49	
Zhang *et al.*, 2007b	Case-control	Cases: 254 patients with histologically confirmed epithelial ovarian cancer Controls: 652 age-matched healthy individuals	1st quartile of mean intake (µg/day)	<2,509	Ovarian cancer	61 cases and 162 controls		1.00		NA	>0.05
			2nd quartile of mean intake (µg/day)	2,509 – 6,220		77 cases and 164 controls		1.39		0.89 – 2.15	
			3rd quartile of mean intake (µg/day)	6,221 – 11,856		54 cases and 157 controls		1.02		0.63 – 1.65	
			4th quartile of mean intake (µg/day)	>11,857		58 cases and 169 controls		1.01		0.62 – 1.64	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Nkondjock *et al.*, 2005	Case-control	Cases: 462 men with histologically confirmed prostate cancer Controls: 4,721 population-based healthy men	1st quartile of mean intake (µg/day)	M: 898 F: 837	Pancreatic cancer	M: 56 cases and 651 controls F: 42 cases and 487 controls		M: 1.00 F: 1.00		M: NA F: NA	M: 0.026 F: 0.27
			2nd quartile of mean intake (µg/day)	M: 1,215 F: 1,139		M: 58 cases and 536 controls F: 41 cases and 604 controls		M: 0.78 F: 1.38		M: 0.51 – 1.19 F: 0.84 – 2.56	
			3rd quartile of mean intake (µg/day)	M: 2,106 F: 1,951		M: 63 cases and 518 controls F: 48 cases and 621 controls		M: 0.76 F: 1.05		M: 0.49 – 1.16 F: 0.65 – 1.70	
			4th quartile of mean intake (µg/day)	M: 7,585 F: 7,234		M: 71 cases and 557 controls F: 65 cases and 582 controls		M: 0.69 F: 0.91		M: 0.46 – 0.96 F: 0.56 – 1.43	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
Terry *et al.*, 2008	Cohort (10 years follow-up)	82,512 women aged 26 to 46 years and free of cancer at baseline	1st quintile of intake (µg/day)	3,283	Uterine leiomyome	1,276	1.00			NA	0.18
			2nd quintile of intake (µg/day)	4,742		1,215	0.92			0.88 – 1.03	
			3rd quintile of intake (µg/day)	6,064		1,277	0.96			0.91 – 1.06	
			4th quintile of intake (µg/day)	8,143		1,307	1.00			0.93 – 1.09	
			5th quintile of intake (µg/day)	12,511		1,227	0.93			0.86 – 1.00	
Dorgan *et al.*, 2004	Cohort (5 years follow-up)	302 men and women aged 40 to 75 years (the Isotretinoin Basal Cell Carcinoma Prevention Trial)	1st tertile of serum lycopene (mean µg/dL)	M: <30.88 F: <34.87	Basal cell carcinoma	79			1.00	NA	0.56
			2nd tertile of serum lycopene (mean µg/dL)	M: 30.88 – 49.60 F: 34.87 – 54.40		66			0.72	0.50 – 1.03	
			3rd tertile of serum lycopene (mean µg/dL)	M: >49.61 F: >54.41		74			1.01	0.70 – 1.45	
			1st tertile of serum lycopene (mean µg/dL)	M: <30.88 F: <34.87	Squamous cell carcinoma	31			1.00	NA	0.74
			2nd tertile of serum lycopene (mean µg/dL)	M: 30.88 – 49.60 F: 34.87 – 54.40		29			0.99	0.59 – 1.89	

Table C-6 Tabulation of Data from Human Observational Studies of Lycopene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	Lycopene Intake/ Supplement Dose or Plasma/ Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)				
							HR	OR	RR	95% CI	P for trend
			3rd tertile of serum lycopene (mean µg/dL)	M: >49.61 F: >54.41		23			1.06	0.58 – 2.01	
Larsson *et al.*, 2007	Cohort (average 7.2 years follow-up)	82,002 men and women aged 48 to 83 years and free of cancer at baseline	1st quartile of intake (µg/day)	739	Gastric cancer	47			1.00	NA	0.93
			2nd quartile of intake (µg/day)	1,502		35			0.97	0.62 – 1.52	
			3rd quartile of intake (µg/day)	2,257		34			1.15	0.72 – 1.82	
			4th quartile of intake (µg/day)	3,541		23			0.92	0.53 – 1.58	

Abbreviations: CI = confidence interval; CS = current smokers F = females; FS = former smokers; HR = hazard ratio; M = males, NA = not applicable; NR = not reported; NS = never smokers; OR = odds ratio; RR = relative risk.
[1] Median values are presented unless otherwise noted.

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
COHORT STUDIES										
Key *et al.*, 2007	Case-control nested in a cohort (average 6 years follow-up)	137,001 men approximately 60 years of age and free of prostate cancer at baseline; nested case-control consisted of 966 cases and 1,064 matched controls	1st quintile of plasma β-cryptoxanthin (mean µg/dL)	<2.99	Prostate cancer	180		1.0	NA	0.79
			2nd quintile of plasma β-cryptoxanthin (mean µg/dL)	2.99 – <5.23		202		1.09	0.81-1.47	
			3rd quintile of plasma β-cryptoxanthin (mean µg/dL)	5.23 – <8.24		197		1.04	0.76-1.42	
			4th quintile of plasma β-cryptoxanthin (mean µg/dL)	8.24 - <13.04		188		0.95	0.69-1.31	
			5th quintile of plasma β-cryptoxanthin (mean µg/dL)	≥13.04		199		1.02	0.73-1.44	
CASE-CONTROL STUDIES										
Bosetti *et al.*, 2004	Case-control	Cases: 1,294 incident, histologically prostate cancer cases in men <75 years of age	1st quintile of mean intake (µg/day)	NR. Average intake in controls was reported to be 277.1 µg/day; average intake in cases was not reported.	Prostate cancer	260 cases and 290 controls	1.00		NA	0.013

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
		Controls: 1,451 healthy men <75 years of age	2nd quintile of mean intake (µg/day)			309 cases and 290 controls	1.21		0.94 – 1.54	
			3rd quintile of mean intake (µg/day)			258 cases and 288 controls	0.96		0.74 – 1.23	
			4th quintile of mean intake (µg/day)			212 cases and 293 controls	0.72		0.55 – 0.93	
			5th quintile of mean intake (µg/day)			255 cases and 290 controls	0.90		0.69 – 1.16	
Huang *et al.*, 2003	Case-control	CLUE 1 (blood collected in 1974) Cases: 182 men (mean age of 54 years) diagnosed with prostate cancer Controls: 364 men (mean age of 54 years) without prostate cancer	1st quintile of serum β-cryptoxanthin (µg/dL)	≤2.6	Prostate cancer	29 cases and 74 controls	1.00		NA	0.93
			2nd quintile of serum β-cryptoxanthin (µg/dL)	>2.6 – 4.1		36 cases and 71 controls	1.39		0.76 – 2.57	
			3rd quintile of serum β-cryptoxanthin (µg/dL)	>4.1 – 7.7		46 cases and 74 controls	1.71		0.93 – 3.14	
			4th quintile of serum β-cryptoxanthin (µg/dL)	>7.7 – <12.6		38 cases and 68 controls	1.55		0.83 – 2.90	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			5th quintile of serum β-cryptoxanthin (µg/dL)	≥12.6		33 cases and 72 controls	1.25		0.65 – 2.38	
		CLUE 2 (blood collected in 1989) Cases: 142 men (mean age of 66 years) diagnosed with prostate cancer	1st quintile of serum β-cryptoxanthin (µg/dL)	≤3.3	Prostate cancer	34 cases and 59 controls	1.00		NA	0.82
			2nd quintile of serum β-cryptoxanthin (µg/dL)	>3.3 – 5.6		22 cases and 55 controls	0.69		0.36 – 1.33	
		Controls: 284 men (mean age of 66 years) without prostate cancer	3rd quintile of serum β-cryptoxanthin (µg/dL)	>5.6 – 8.5		33 cases and 54 controls	1.03		0.55 – 1.90	
			4th quintile of serum β-cryptoxanthin (µg/dL)	>8.5 - <12.1		21 cases and 58 controls	0.62		0.32 – 1.21	
			5th quintile of serum β-cryptoxanthin (µg/dL)	≥12.1		31 cases and 58 controls	0.90		0.48 – 1.70	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
McCann *et al.*, 2005	Case-control	Cases: 433 men with primary, histologically confirmed prostate cancer Controls: 538 population-based healthy men	1st quartile of intake (µg/day)	≤36	Prostate cancer	121 cases and 135 controls	1.00		NA	0.90
			2nd quartile of intake (µg/day)	36 – 99		114 cases and 134 controls	0.97		0.68 – 1.38	
			3rd quartile of intake (µg/day)	99– 201		98 cases and 135 controls	0.85		0.59 – 1.22	
			4th quartile of intake (µg/day)	>201		100 cases and 134 controls	0.92		0.64 – 1.33	
Peters *et al.*, 2007	Case-control	Cases: 692 incident prostate cancer cases in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Controls: 844 healthy individuals from the same trial	1st quintile of serum β-cryptoxanthin (µg/dL)	2.9	Prostate cancer	139 cases and 168 controls	1.00		NA	0.50
			2nd quintile of serum β-cryptoxanthin (µg/dL)	5.0		139 cases and 169 controls	0.98		0.71 – 1.36	
			3rd quintile of serum β-cryptoxanthin (µg/dL)	6.8		123 cases and 168 controls	0.87		0.62 – 1.22	
			4th quintile of serum β-cryptoxanthin (µg/dL)	9.5		132 cases and 169 controls	0.89		0.64 – 1.25	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			5th quintile of serum β-cryptoxanthin (µg/dL)	16.8		158 cases and 168 controls	1.09		0.78 – 1.52	
Wu *et al.*, 2004	Case-control nested in a cohort (7-11 years follow-up)	Cases: 450 male health professionals diagnosed with prostate cancer (aged 40 – 75 years) Controls: 450 male health professionals without prostate cancer (aged 40 – 75 years)	1st quintile of plasma β-cryptoxanthin	NR. Median plasma β-cryptoxanthin was reported as 114.1 nmol/L in cases and 116.3 nmol/L in controls.	Prostate cancer	98 cases and 82 controls	1.00		NA	0.94
			2nd quintile of plasma β-cryptoxanthin			79 cases and 101 controls	0.71		0.46 – 1.10	
			3rd quintile of plasma β-cryptoxanthin			94 cases and 86 controls	0.85		0.53 – 1.37	
			4th quintile of plasma β-cryptoxanthin			86 cases and 94 controls	0.81		0.51 – 1.29	
			5th quintile of plasma β-cryptoxanthin			93 cases and 87 controls	0.94		0.56 – 1.58	
Zhang *et al.*, 2007a	Case-control	Cases: 193 men diagnosed with prostate cancer in 3 major hospitals Controls: 197 healthy men without prostate cancer	1st quartile of plasma β-cryptoxanthin (µg/L)	32.2	Prostate cancer	59 cases and 49 controls	1.00		NA	0.13
			2nd quartile of plasma β-cryptoxanthin (µg/L)	58.7		54 cases and 49 controls	1.01		0.56 – 1.83	
			3rd quartile of plasma β-cryptoxanthin (µg/L)	86.0		42 cases and 50 controls	0.76		0.39 – 1.46	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			4th quartile of plasma β-cryptoxanthin (µg/L)	137.0		38 cases and 49 controls	0.60		0.28 – 1.27	
COHORT STUDIES										
Cho *et al.*, 2003	Cohort (8 years follow-up)	90,655 women aged 26 to 46 years and free of cancer (except nonmelanoma skin cancer) at baseline	1st quintile of intake (µg/day)	8	Breast cancer	NR		1.00	NA	0.11
			2nd quintile of intake (µg/day)	23		NR		1.07	0.83 – 1.37	
			3rd quintile of intake (µg/day)	37		NR		1.11	0.87 – 1.43	
			4th quintile of intake (µg/day)	58		NR		1.26	0.99 – 1.60	
			5th quintile of intake (µg/day)	104		NR		1.20	0.94 – 1.54	
Sesso *et al.*, 2005	Case-control nested in a cohort (9.9 years follow-up)	39,876 women aged ≥ 45 years and free of cardiovascular disease and cancer at baseline; nested case-control consisted of 508 cases and 508 matched controls	1st quartile of plasma β-cryptoxanthin (µg/dL)	3.5	Breast cancer	NR		1.00	NA	0.21
			2nd quartile of plasma β-cryptoxanthin (µg/dL)	6.7		NR		1.31	0.79 – 2.17	
			3rd quartile of plasma β-cryptoxanthin (µg/dL)	11.2		NR		0.83	0.49 – 1.43	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			4th quartile of plasma β-cryptoxanthin (µg/dL)	20.6		NR		0.82	0.46 – 1.44	
CASE-CONTROL STUDIES										
Huang *et al.*, 2007	Case-control	Cases: 122 females with histologically confirmed breast cancer Controls: 632 healthy females recruited from outpatient clinics	1st quartile of mean intake (µg/day)	<232.4	Breast cancer	36 cases and 158 controls	1.00		NA	0.03
			2nd quartile of mean intake (µg/day)	232.5 – 422.9		34 cases and 158 controls	0.80		0.46 – 1.41	
			3rd quartile of mean intake (µg/day)	423.0 – 674.9		31 cases and 158 controls	0.73		0.41– 1.30	
			4th quartile of mean intake (µg/day)	≥675.0		21 cases and 158 controls	0.43		0.23 – 0.82	
Tamimi *et al.*, 2005	Case-control nested in a cohort (up to 22 years follow-up)	Cases: 969 female nurses diagnosed with breast cancer (aged 43 to 70 years) Controls: 969 female nurses without breast cancer (aged 43 to 70 years)	1st quintile of plasma β-cryptoxanthin (µmol/L)	0.05	Breast cancer	NR	1.00		0.96 – 1.76	0.08
			2nd quintile of plasma β-cryptoxanthin (µmol/L)	0.09		NR	1.43		1.06 – 1.92	
			3rd quintile of plasma β-cryptoxanthin (µmol/L)	0.12		NR	1.23		0.90 – 1.69	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			4th quintile of plasma β-cryptoxanthin (μmol/L)	0.16		NR	0.88		0.64 – 1.22	
			5th quintile of plasma β-cryptoxanthin (μmol/L)	0.22		NR	0.95		0.69 – 1.31	
COHORT STUDIES										
Stram *et al.*, 2007	Case-control nested in a cohort (9-12 years follow-up)	18,244 men between 45 and 60 years of age and free of lung cancer at baseline; nested case-control consisted of 152 cases and 444 matched controls	1st quartile of serum β-cryptoxanthin (μg/dL)	<1.81	Lung cancer	NR	1.0		NA	0.037
			2nd quartile of serum β-cryptoxanthin (μg/dL)	1.81 – 3.00		NR	0.86		0.41 – 1.79	
			3rd quartile of serum β-cryptoxanthin (μg/dL)	3.01 – 4.53		NR	0.47		0.21 – 1.07	
			4th quartile of serum β-cryptoxanthin (μg/dL)	>4.53		NR	0.47		0.20 – 1.08	
Yuan *et al.*, 2003	Cohort (average 5.3 years follow-up)	62,392 men and women aged 45 to 74 years and free of cancer at baseline	1st quintile of intake (μg/1,000 kcal)	5	Lung cancer	142		1.00	NA	NR
			2nd quintile of intake (μg/1,000 kcal)	55		100		0.92	0.71 – 1.19	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			3rd quintile of intake (µg/1,000 kcal)	103		99		1.02	0.78 – 1.33	
			4th quintile of intake (µg/1,000 kcal)	174		66		0.75	0.56 – 1.02	
			5th quintile of intake (µg/1,000 kcal)	371		73		0.73	0.54 – 0.98	
CASE-CONTROL STUDIES										
Wright *et al.*, 2003	Case-control	Cases: 587 women with incident primary lung cancer Controls: 624 population-matched women without lung cancer	1st quintile of intake (µg/day)	<30.92	Lung cancer	NS/FS: 44 cases and 38 controls CS: 98 cases and 86 controls	NS/FS: 1.00 CS: 1.00		NA	NS/FS: 0.07 CS: 0.03
			2nd quintile of intake (µg/day)	30.92 – 59.74		NS/FS: 47 cases and 52 controls CS: 104 cases and 73 controls	NS/FS: 0.77 CS: 1.2		NS/FS: 0.41 – 1.4 CS: 0.77 – 1.9	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			3rd quintile of intake (µg/day)	59.75 – 89.77		NS/FS: 48 cases and 57 controls CS: 89 cases and 68 controls	NS/FS: 0.73 CS: 1.2		NS/FS: 0.40 – 1.4 CS: 0.75 – 1.9	
			4th quintile of intake (µg/day)	89.78 – 115.38		NS/FS: 32 cases and 66 controls CS: 41 cases and 59 controls	NS/FS: 0.45 CS: 0.71		NS/FS: 0.23 – 0.86 CS: 0.42 – 1.2	
			5th quintile of intake (µg/day)	>115.38		NS/FS: 30 cases and 51 controls CS: 54 cases and 74 controls	NS/FS: 0.62 CS: 0.65		NS/FS: 0.32 – 1.2 CS: 0.40– 1.1	
Nkondjock and Ghadirian, 2004	Case-control	Cases: 402 men and women with colorectal cancer Controls: 688 population-based healthy individuals	1st quartile of intake (µg/day)	ES: 2.32 NS: 2.15	Colon cancer	ES: 88 cases and 125 controls NS: 22 cases and 32 controls	ES: 1.00 NS: 1.00		ES: NA NS: NA	ES: 0.49 NS: 0.98

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			2nd quartile of intake (µg/day)	ES: 26.10 NS: 25.06		ES: 70 cases and 100 controls NS: 35 cases and 63 controls	ES: 0.86 NS: 0.83		ES: 0.56 – 1.32 NS: 0.40 – 1.72	
			3rd quartile of intake (µg/day)	ES: 91.41 NS: 90.15		ES: 48 cases and 114 controls NS: 36 cases and 70 controls	ES: 1.49 NS: 0.74		ES: 0.95 – 2.33 NS: 0.36 – 1.52	
			4th quartile of intake (µg/day)	ES: 213.49 NS: 201.65		ES: 67 cases and 98 controls NS: 36 cases and 66 controls	ES: 0.91 NS: 0.89		ES: 0.59 – 1.41 NS: 0.43 – 1.86	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
Wakai *et al.*, 2005	Case-control nested in a cohort (8 years follow-up)	23,454 men and women aged 40 to 79 years and free of cancer at baseline; nested case-control consisted of 116 cases and 298 matched controls	1st tertile of serum β-cryptoxanthin (mean µmol/L)	M: <0.11 F: <0.28	Colorectal cancer	M: 17 F: 26	M: 1.00 F: 1.00		NA	M: 0.93 F: 0.24
			2nd tertile of serum β-cryptoxanthin (mean µmol/L)	M: 0.11 – 0.32 F: 0.28 – 0.46		M: 20 F: 16	M: 1.02 F: 0.43		M: 0.34 – 3.03 F: 0.15–1.22	
			3rd tertile of serum β-cryptoxanthin (mean µmol/L)	M: >0.32 F: >0.46		M: 17 F: 20	M: 0.95 F: 0.50		M: 0.28 – 3.23 F: 0.18 – 1.44	
Hung *et al.*, 2006	Case-control	Cases: 84 patients at a cancer center with bladder cancer Controls: 173 healthy individuals without bladder cancer	1st quartile of plasma β-cryptoxanthin (0.1 µmol/L)	Cases: 0.32 Controls: 0.51	Bladder cancer	45 cases and 43 controls	1.00		NA	0.031
			2nd quartile of plasma β-cryptoxanthin (0.1 µmol/L)	NR		21 cases and 43 controls	1.43		0.32 - 6.31	
			3rd quartile of plasma β-cryptoxanthin (0.1 µmol/L)	Cases: 0.71 Controls: 1.64		13 cases and 43 controls	0.31		0.06 – 1.70	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			4th quartile of plasma β-cryptoxanthin (0.1 µmol/L)	NR		5 cases and 44 controls	0.11		0.01 - 1.03	
Zhang *et al.*, 2007b	Case-control	Cases: 254 patients with histologically confirmed epithelial ovarian cancer Controls: 652 age-matched healthy individuals	1st quartile of mean intake (µg/day)	<253	Ovarian cancer	82 cases and 163 controls	1.00		NA	<0.01
			2nd quartile of mean intake (µg/day)	253 – 654		75 cases and 163 controls	0.93		0.61 – 1.41	
			3rd quartile of mean intake (µg/day)	655 – 987		50 cases and 163 controls	0.49		0.31 – 0.78	
			4th quartile of mean intake (µg/day)	≥988		43 cases and 163 controls	0.51		0.31 – 0.83	
Nkondjock *et al.*, 2005	Case-control	Cases: 462 men with histologically confirmed prostate cancer Controls: 4,721 population-based healthy men	1st quartile of mean intake (µg/day)	M: 77 F: 837	Pancreatic cancer	M: 75 cases and 676 controls F: 52 cases and 462 controls	M: 1.00 F: 1.00		M: NA F: NA	M: 0.46 F: 0.27
			2nd quartile of mean intake (µg/day)	M: 162 F: 1,139		M: 75 cases and 565 controls F: 37 cases and 575 controls	M: 0.73 F: 1.50		M: 0.51 – 1.05 F: 0.95 – 2.38	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			3rd quartile of mean intake (µg/day)	M: 267 F: 1,951		M: 51 cases and 524 controls F: 52 cases and 615 controls	M: 1.02 F: 1.26		M: 0.68 – 1.53 F: 0.82 – 1.94	
			4th quartile of mean intake (µg/day)	M: 598 F: 7,234		M: 45 cases and 497 controls F: 55 cases and 642 controls	M: 1.09 F: 1.23		M: 0.72– 1.62 F: 0.80 – 1.87	
Dorgan *et al.*, 2004	Cohort (5 years follow-up)	302 men and women aged 40 to 75 years (the Isotretinoin Basal Cell Carcinoma Prevention Trial)	1st tertile of serum β-cryptoxanthin (mean µg/dL)	M: <4.42 F: <5.26	Basal cell carcinoma	78		1.00	NA	0.42
			2nd tertile of serum β-cryptoxanthin (mean µg/dL)	M: 4.42-7.34 F: 5.26-9.50		68		0.84	0.59-1.19	
			3rd tertile of serum β-cryptoxanthin (mean µg/dL)	M: >7.34 F: >9.50		75		1.06	0.75-1.50	
			1st tertile of serum β-cryptoxanthin (mean µg/dL)	M: <4.42 F: <5.26	Squamous cell carcinoma	25		1.00	NA	0.09

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			2nd tertile of serum β-cryptoxanthin (mean µg/dL)	M: 4.42-7.34 F: 5.26-9.50		26		1.45	0.80-2.65	
			3rd tertile of serum β-cryptoxanthin (mean µg/dL)	M: >7.34 F: >9.50		34		2.15	1.21 – 3.83	
COHORT										
Abnet *et al.*, 2003	Case-control nested in a cohort (5.25 years follow-up)	2,125 healthy adults aged 40 – 69 years (selected from the General Population Trial of Linxian [China]); nested case-control consisted of 1,072 cases and 1,053 matched controls	1st quartile of serum β-cryptoxanthin (µg/dL)	<2.0	Esophageal (E), gastric cardia (GC), or gastric non-cardia (GN) cancer	E: 590 GC: 295 GN: 87		E: 1 GC: 1 GN: 1	NA NA NA	E: 0.24 GC: 0.15 GN: 0.50
			2nd quartile of serum β-cryptoxanthin (µg/dL)	2.0 – 3.5				E: 1.2 GC: 0.97 GN: 1.6	E: 0.91 – 1.6 GC: 0.69 – 1.4 GN: 0.87 – 2.8	
			3rd quartile of serum β-cryptoxanthin (µg/dL)	>3.5 – 6.6				E: 1.1 GC: 1.2 GN: 1.6	E: 0.82 – 1.5 GC: 0.90 – 1.7 GN: 0.88 – 2.8	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			4th quartile of serum β-cryptoxanthin (µg/dL)	>6.6				E: 1.3 GC: 1.2 GN: 0.54	E: 0.93 – 1.7 GC: 0.85 – 1.7 GN: 0.23 – 1.3	
Larsson *et al.*, 2005	Cohort (average 7.2 years follow-up)	82,002 men and women aged 48 to 83 years and free of cancer at baseline	1st quartile of intake (µg/day)	27	Gastric cancer	43		1.00	NA	0.18
			2nd quartile of intake (µg/day)	121		24		0.72	0.44 – 1.20	
			3rd quartile of intake (µg/day)	284		41		1.46	0.93 – 2.29	
			4th quartile of intake (µg/day)	634		31		1.21	0.73 – 2.01	
CASE-CONTROL STUDIES										
De Stefani *et al.*, 2006	Case-control	Cases: 234 men and women with squamous cell carcinoma of the esophagus Controls: 936 hospital-based controls without neoplastic disease	1st quartile of mean intake (units NR)	<292.7	Squamous cell carcinoma of the esophagus	NR	NR		NR	<0.0001
			2nd quartile of mean intake (units NR)	292.7 – 585.4		93 cases (controls NR)	0.69		0.45 – 1.06	
			3rd quartile of mean intake (units NR)	585.4 – 864.0		48 cases (controls NR)	0.48		0.30 – 0.75	

Table C-7 Tabulation of Data from Observational Studies of β-Cryptoxanthin (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	β-Cryptoxanthin Intake/Supplement Dose or Plasma/ Serum/Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR	95% CI	P for trend
			4th quartile of mean intake (units NR)	>864.0		29 cases (controls NR)	0.34		0.21 – 0.57	

Abbreviations: CI = confidence interval; CS = current smokers F = females; FS = former smokers; HR = hazard ratio; M = males, NA = not applicable; NR = not reported; NS = never smokers; OR = odds ratio; RR = relative risk
[1] Median values are presented unless otherwise noted.

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
Key *et al.*, 2007	Case-control nested in a cohort (average 6 years follow-up)	137,001 men approximately 60 years of age and free of prostate cancer at baseline; nested case-control consisted of 966 cases and 1,064 matched controls	1st quintile of plasma α-carotene (mean µg/dL)	<2.59	Prostate cancer	156	NA	1.0	NA	0.89
			2nd quintile of plasma α-carotene (mean µg/dL)	2.59 – <4.43		211	NA	1.34	1.00-1.79	
			3rd quintile of plasma α-carotene (mean µg/dL)	4.43 – <6.70		214	NA	1.29	0.96-1.75	
			4th quintile of plasma α-carotene (mean µg/dL)	6.70 - <10.51		193	NA	1.21	0.88-1.66	
			5th quintile of plasma α-carotene (mean µg/dL)	≥10.51		192	NA	1.20	0.87-1.66	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
Bosetti *et al.*, 2004	Case-control	Cases: 1,294 incident, histologically confirmed prostate cancer cases in men <75 years of age Controls: 1,451 healthy men <75 years of age	1st quintile of mean intake (µg/day)	NR. Average intake in controls was reported to be 697.4 µg/day; average intake in cases was not reported.	Prostate cancer	243 cases and 291 controls	1.00		NA	0.062
			2nd quintile of mean intake (µg/day)			283 cases and 290 controls	1.07		0.83 – 1.38	
			3rd quintile of mean intake (µg/day)			257 cases and 289 controls	0.94		0.73 – 1.21	
			4th quintile of mean intake (µg/day)			246 cases and 291 controls	0.85		0.66 – 1.11	
			5th quintile of mean intake (µg/day)			265 cases and 290 controls	0.85		0.66 – 1.11	
Huang *et al.*, 2003	Case-control	CLUE 1 (blood collected in 1974) Cases: 182 men (mean age of 54 years) diagnosed with prostate cancer Controls: 364 men (mean age of 54	1st quintile of serum α-carotene (µg/dL)	≤1.4	Prostate cancer	41 cases and 77 controls	1.00		NA	0.61
			2nd quintile of serum α-carotene (µg/dL)	>1.4 – 1.9		29 cases and 56 controls	1.04		0.54 – 1.98	
			3rd quintile of serum α-carotene (µg/dL)	>1.9 – 2.7		30 cases and 51 controls	1.20		0.63 – 2.32	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
		years) without prostate cancer	4th quintile of serum α-carotene (μg/dL)	>2.7 – <3.9		29 cases and 60 controls	0.93		0.49 – 1.77	
			5th quintile of serum α-carotene (μg/dL)	≥3.9		30 cases and 63 controls	0.93		0.49 – 1.78	
		CLUE 2 (blood collected in 1989) Cases: 142 men (mean age of 66 years) diagnosed with prostate cancer Controls: 284 men (mean age of 66 years) without prostate cancer	1st quintile of serum α-carotene (μg/dL)	≤1.2	Prostate cancer	20 cases and 47 controls	1.00		NA	0.98
			2nd quintile of serum α-carotene (μg/dL)	>1.2 – 2.0		29 cases and 51 controls	1.32		0.64 – 2.73	
			3rd quintile of serum α-carotene (μg/dL)	>2.0 – 3.0		23 cases and 56 controls	0.97		0.45 – 2.09	
			4th quintile of serum α-carotene (μg/dL)	>3.0 - <5.5		34 cases and 58 controls	1.27		0.63 – 2.54	
			5th quintile of serum α-carotene (μg/dL)	≥5.5		23 cases and 54 controls	1.11		0.52 – 2.36	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
McCann *et al.*, 2005	Case-control	Cases: 433 men with primary, histologically confirmed prostate cancer Controls: 538 population-based healthy men	1st quartile of intake (µg/day)	≤626	Prostate cancer	143 cases and 135 controls	1.00		NA	0.54
			2nd quartile of intake (µg/day)	626 – 977		95 cases and 134 controls	0.73		0.51 – 1.05	
			3rd quartile of intake (µg/day)	977 – 1,488		97 cases and 135 controls	0.78		0.54 – 1.13	
			4th quartile of intake (µg/day)	>1,488		98 cases and 134 controls	0.91		0.59 – 1.39	
Peters *et al.*, 2007	Case-control	Cases: 692 incident prostate cancer cases in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Controls: 844 healthy individuals from the same trial	1st quintile of serum α-carotene (µg/dL)	2.6	Prostate cancer	136 cases and 168 controls	1.00	NA	NA	0.17
			2nd quintile of serum α-carotene (µg/dL)	4.7		115 cases and 168 controls	0.89	NA	0.63 – 1.25	
			3rd quintile of serum α-carotene (µg/dL)	6.9		145 cases and 169 controls	1.06	NA	0.76 – 1.48	
			4th quintile of serum α-carotene (µg/dL)	10.3		136 cases and 168 controls	1.04	NA	0.74 – 1.46	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			5th quintile of serum α-carotene (μg/dL)	16.6		160 cases and 168 controls	1.18	NA	0.85 – 1.64	
Wu *et al.*, 2004	Case-control nested in a cohort (7-11 years follow-up)	Cases: 450 male health professionals diagnosed with prostate cancer (aged 40 – 75 years) Controls: 450 male health professionals without prostate cancer (aged 40 – 75 years)	1st quintile of plasma α-carotene	NR. Median plasma α-carotene was reported as 105.3 nmol/L in cases and 107.0 nmol/L in controls.	Prostate cancer	99 cases and 81 controls	1.00	NA	NA	0.39
			2nd quintile of plasma α-carotene			83 cases and 97 controls	0.62	NA	0.38 – 0.99	
			3rd quintile of plasma α-carotene			87 cases and 93 controls	0.69	NA	0.43 – 1.10	
			4th quintile of plasma α-carotene			96 cases and 84 controls	0.89	NA	0.54 – 1.47	
			5th quintile of plasma α-carotene			85 cases and 95 controls	0.67	NA	0.40 – 1.09	
Zhang *et al.*, 2007a	Case-control	Cases: 193 men diagnosed with prostate cancer in 3 major hospitals Controls: 197 healthy men without prostate cancer	1st quartile of plasma α-carotene (μg/L)	7.1	Prostate cancer	43 cases and 49 controls	1.00	NA	NA	0.77
			2nd quartile of plasma α-carotene (μg/L)	14.6		55 cases and 49 controls	1.69	NA	0.91 – 3.14	
			3rd quartile of plasma α-carotene (μg/L)	24.4		56 cases and 50 controls	1.94	NA	0.98 – 3.90	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			4th quartile of plasma α-carotene (μg/L)	60.8		39 cases and 49 controls	1.29	NA	0.58 – 2.88	
Cho *et al.*, 2003	Cohort (8 years follow-up)	90,655 women aged 26 to 46 years and free of cancer (except nonmelanoma skin cancer) at baseline	1st quintile of intake (μg/day)	183	Breast cancer	NR	NA	1.00	NA	0.35
			2nd quintile of intake (μg/day)	405		NR	NA	0.83	0.65 – 1.05	
			3rd quintile of intake (μg/day)	606		NR	NA	0.90	0.71 – 1.13	
			4th quintile of intake (μg/day)	883		NR	NA	0.85	0.67 – 1.07	
			5th quintile of intake (μg/day)	1,537		NR	NA	0.85	0.67 – 1.08	
Huang *et al.*, 2007	Case-control	Cases: 122 females with histologically confirmed breast cancer Controls: 632 healthy females recruited from outpatient clinics	1st quartile of mean intake (μg/day)	<88.2	Breast cancer	26 cases and 158 controls	1.00		NA	0.62
			2nd quartile of mean intake (μg/day)	88.2 – 155.8		33 cases and 158 controls	1.21		0.67 – 2.20	
			3rd quartile of mean intake (μg/day)	155.9 – 266.2		29 cases and 158 controls	0.98		0.53 – 1.82	
			4th quartile of mean intake (μg/day)	≥266.3		34 cases and 158 controls	0.90		0.49 – 1.67	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
Sesso *et al.*, 2005	Case-control nested in a cohort (9.9 years follow-up)	39,876 women aged ≥ 45 years and free of cardiovascular disease and cancer at baseline; nested case-control consisted of 508 cases and 508 matched controls	1st quartile of plasma α-carotene (μg/dL)	2.2	Breast cancer	NR	NA	1.00	NA	0.85
			2nd quartile of plasma α-carotene (μg/dL)	4.3		NR	NA	1.04	0.60–1.81	
			3rd quartile of plasma α-carotene (μg/dL)	7.9		NR	NA	0.89	0.52 – 1.53	
			4th quartile of plasma α-carotene (μg/dL)	15.9		NR	NA	1.06	0.61 – 1.84	
Tamimi *et al.*, 2005	Case-control nested in a cohort (up to 22 years follow-up)	Cases: 969 female nurses diagnosed with breast cancer (aged 43 to 70 years) Controls: 969 female nurses without breast cancer (aged 43 to 70 years)	1st quintile of plasma α-carotene (μmol/L)	0.05	Breast cancer	NR	1.00	NA	NA	0.01
			2nd quintile of plasma α-carotene (μmol/L)	0.08		NR	0.83	NA	0.62 – 1.11	
			3rd quintile of plasma α-carotene (μmol/L)	0.11		NR	0.90	NA	0.67 - 1.21	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			4th quintile of plasma α-carotene (μmol/L)	0.16		NR	0.83	NA	0.62 – 1.13	
			5th quintile of plasma α-carotene (μmol/L)	0.26		NR	0.64	NA	0.47 – 0.88	
Nkondjock and Ghadirian, 2004	Case-control	Cases: 402 men and women with colorectal cancer Controls: 688 population-based healthy individuals	1st quartile of intake (μg/day)	ES: 249 NS: 242	Colon cancer	ES: 79 cases and 118 controls NS: 29 cases and 49 controls	ES: 1.00 NS: 1.00		ES: NA NS: NA	ES: 0.99 NS: 0.92
			2nd quartile of intake (μg/day)	ES: 754 NS: 735		ES: 61 cases and 107 controls NS: 28 cases and 60 controls	ES: 1.01 NS: 0.76		ES: 0.65 – 1.57 NS: 0.39 – 1.51	
			3rd quartile of intake (μg/day)	ES: 1,573 NS: 1,478		ES: 79 cases and 108 controls NS: 34 cases and 59 controls	ES: 0.79 NS: 0.86		ES: 0.52 – 1.21 NS: 0.44 – 1.67	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			4th quartile of intake (µg/day)	ES: 3,158 NS: 3,191		ES: 54 cases and 104 controls NS: 38 cases and 63 controls	ES: 1.12 NS: 0.91		ES: 0.70 – 1.78 NS: 0.47 – 1.77	
Wakai *et al.*, 2005	Case-control nested in a cohort (8 years follow-up)	23,454 men and women aged 40-79 years and free of cancer at baseline; nested case-control consisted of 116 cases and 298 matched controls	1st tertile of serum α-carotene (mean µmol/L)	M: <0.038 F: <0.070	Colorectal cancer	M: 16 F: 17	M: 1.00 F: 1.00	NA	NA	M: 0.54 F: 0.007
			2nd tertile of serum α-carotene (mean µmol/L)	M: 0.038 – 0.079 F: 0.070 – 0.102		M: 24 F: 14	M: 1.10 F: 1.36	NA	M: 0.41 – 2.93 F: 0.38 – 4.87	
			3rd tertile of serum α-carotene (mean µmol/L)	M: >0.079 F: >0.102		M: 14 F: 31	M: 0.73 F: 4.72	NA	M: 0.24 – 2.20 F: 1.29 – 17.3	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
Wright *et al.*, 2003	Case-control	Cases: 587 women with incident primary lung cancer Controls: 624 population-matched women without lung cancer	1st quintile of intake (µg/day)	<58.90	Lung cancer	NS/FS: 40 cases and 47 controls CS: 92 cases and 77 controls	NS/FS: 1.00 CS: 1.00		NA	NS/FS: 0.41 CS: 0.23
			2nd quintile of intake (µg/day)	58.90 – 102.04		NS/FS: 40 cases and 44 controls CS: 79 cases and 81 controls	NS/FS: 1.2 CS: 0.85		NS/FS: 0.63 – 2.3 CS: 0.54 – 1.3	
			3rd quintile of intake (µg/day)	102.05 – 156.63		NS/FS: 43 cases and 51 controls CS: 98 cases and 74 controls	NS/FS: 1.2 CS: 1.1		NS/FS: 0.63 – 2.3 CS: 0.72 – 1.8	
			4th quintile of intake (µg/day)	156.64 – 242.68		NS/FS: 36 cases and 60 controls CS: 67 cases and 65 controls	NS/FS: 0.96 CS: 0.79		NS/FS: 0.50 – 1.8 CS: 0.49 – 1.3	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			5th quintile of intake (µg/day)	≥242.68		NS/FS: 42 cases and 62 controls CS: 50 cases and 63 controls	NS/FS: 0.89 CS: 0.74		NS/FS: 0.47 – 1.7 CS: 0.44 – 1.2	
Yuan *et al.*, 2003	Cohort (average 5.3 years follow-up)	62,392 men and women aged 45 to 74 years and free of cancer at baseline	1st quintile of intake (µg/1,000 kcal)	23	Lung cancer	128	NA	1.00	NA	NR
			2nd quintile of intake (µg/1,000 kcal)	70		107	NA	0.98	0.76 – 1.27	
			3rd quintile of intake (µg/1,000 kcal)	114		94	NA	0.99	0.75 – 1.29	
			4th quintile of intake (µg/1,000 kcal)	186		82	NA	0.97	0.73 – 1.29	
			5th quintile of intake (µg/1,000 kcal)	376		71	NA	1.06	0.79 – 1.42	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
Hung *et al.*, 2006	Case-control	Cases: 84 patients at a cancer center with bladder cancer Controls: 173 healthy individuals without bladder cancer	1st quartile of plasma α-carotene (0.1 µmol/L)	Cases: 0.33 Controls: 0.39	Bladder cancer	32 cases and 43 controls	1.00	NA	NA	0.0321
			2nd quartile of plasma α-carotene (0.1 µmol/L)	NR		28 cases and 43 controls	0.49	NA	0.11 – 2.34	
			3rd quartile of plasma α-carotene (0.1 µmol/L)	Cases: 0.75 Controls: 1.18		14 cases and 43 controls	0.30	NA	0.06 – 1.48	
			4th quartile of plasma α-carotene (0.1 µmol/L)	NR		10 cases and 44 controls	0.12	NA	0.02 – 0.95	
De Stefani *et al.*, 2006	Case-control	Cases: 234 men and women with squamous cell carcinoma of the esophagus Controls: 936 hospital-based controls without neoplastic disease	1st quartile of mean intake (units NR)	<1,022.7	Squamous cell carcinoma of the esophagus	NR	NR	NA	NR	<0.0001
			2nd quartile of mean intake (units NR)	1,022.7– 2,045.4		99 cases (controls NR)	0.55	NA	0.36 – 0.85	
			3rd quartile of mean intake (units NR)	2,045.4– 3,068.1		50 cases (controls NR)	0.52	NA	0.34 – 0.81	
			4th quartile of mean intake (units NR)	>3,068.1		27 cases (controls NR)	0.28	NA	0.16 – 0.47	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
Zhang *et al.*, 2007b	Case-control	Cases: 254 patients with histologically confirmed epithelial ovarian cancer Controls: 652 age-matched healthy individuals	1st quartile of mean intake (µg/day)	<113	Ovarian cancer	78 cases and 163 controls	1.00		NA	<0.001
			2nd quartile of mean intake (µg/day)	113 – 218		82 cases and 163 controls	1.02		0.67 – 1.53	
			3rd quartile of mean intake (µg/day)	219 – 377		54 cases and 163 controls	0.57		0.36 – 0.90	
			4th quartile of mean intake (µg/day)	≥378		36 cases and 163 controls	0.39		0.23 – 0.66	
Nkondjock *et al.*, 2005	Case-control	Cases: 462 men with histologically confirmed prostate cancer Controls: 4,721 population-based healthy men	1st quartile of mean intake (µg/day)	M: 358 F: 341	Pancreatic cancer	M: 68 cases and 696 controls F: 45 cases and 443 controls	M: 1.00 F: 1.00		M: NA F: NA	M: 0.90 F: 0.13
			2nd quartile of mean intake (µg/day)	M: 694 F: 651		M: 77 cases and 549 controls F: 42 cases and 590 controls	M: 0.68 F: 1.65		M: 0.46 – 0.98 F: 1.04 – 2.61	

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			3rd quartile of mean intake (µg/day)	M: 1,501 F: 1,013		M: 58 cases and 516 controls F: 58 cases and 623 controls	M: 0.80 F: 1.31		M: 0.54–1.19 F: 0.84 – 2.04	
			4th quartile of mean intake (µg/day)	M: 2,060 F: 2,059		M: 45 cases and 501 controls F: 51 cases and 638 controls	M: 1.01 F: 1.56		M: 0.67 – 1.53 F: 0.98 – 2.42	
Dorgan *et al.*, 2004	Cohort (5 years follow-up)	302 men and women aged 40-75 years (the Isotretinoin Basal Cell Carcinoma Prevention Trial)	1st tertile of serum α-carotene (mean µg/dL)	M: <1.81 F: <3.23	Basal cell carcinoma	74		1.00	NA	0.56
			2nd tertile serum α-carotene (mean µg/dL)	M: 1.81-3.51 F: 3.23-6.08		76		1.21	0.87-1.70	
			3rd tertile serum α-carotene (mean µg/dL)	M: >3.52 F: >6.08		71		1.06	0.74-1.51	
			1st tertile serum α-carotene (mean µg/dL)	M: <1.81 F: <3.23	Squamous cell carcinoma	27		1.00	NA	0.04

Table C-8 Tabulation of Data from Observational Studies of α-Carotene (Cancer)

Reference	Study Design	Population and Final Sample Size	Subject Classification[1]	α-Carotene Intake/ Supplement Dose or Plasma/Serum/ Adipose Tissue Levels	Event Recorded	Event Incidence	Significance/ Risk Ratios (between groups)			
							OR	RR/HR	95% CI	P for trend
			2nd tertile serum α-carotene (mean µg/dL)	M: 1.81-3.51 F: 3.23-6.08		31		1.48	0.85-2.56	
			3rd tertile serum α-carotene (mean µg/dL)	M: >3.52 F: >6.08		27		1.45	0.92-3.06	
Larsson *et al.*, 2005	Cohort (average 7.2 years follow-up)	82,002 men and women aged 48 to 83 years and free of cancer at baseline	1st quartile of intake (µg/day)	166	Gastric cancer	44		1.00	NA	0.03
			2nd quartile of intake (µg/day)	458		29		0.61	0.38 – 0.98	
			3rd quartile of intake (µg/day)	858		39		0.80	0.51 – 1.25	
			4th quartile of intake (µg/day)	1,882		37		0.50	0.30 – 0.83	

Abbreviations: CI, confidence interval; CS, current smokers; ES, ever smokers; F, females; FS, former smokers; HR, hazard ratio; M, males; NA, not applicable; NR, not reported; NS, never smokers; OR, odds ratio; RR, relative risk
[1] Median values are presented unless otherwise noted.

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OLESTRA AMENDMENT GRAS NOTICE

APPENDIX D:

INFLUENCE OF OBSERVATIONAL STUDY DESIGN ON THE INTERPRETATION OF CANCER RISK REDUCTION BY CAROTENOIDS

December 17, 2009

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OLESTRA AMENDMENT GRAS NOTICE

APPENDIX E:

LUTEIN AND ZEAXANTHIN

January 18, 2010

APPENDIX E:

LUTEIN AND ZEAXANTHIN

Table of Contents

Page

1.0 LUTEIN AND ZEAXANTHIN E-4
1.1 Background on Lutein and Zeaxanthin E-4
1.1.1 Introduction E-4
1.1.2 Distribution of Lutein and Zeaxanthin in the Lens and Retinal Tissue E-4
1.1.3 Proposed Functions of Macular Pigment E-6
1.2 Background on Age-Related Eye Diseases E-8
1.2.1 Introduction E-8
1.2.2 Age-Related Cataract E-8
1.2.3 Age-related Macular Degeneration (ARMD) E-9
1.3 Objective of Scientific Assessment E-10
1.4 Method of Scientific Assessment E-10
1.5 Characterization of Biomarkers (Step 1) E-11
1.5.1 Biomarkers of Exposure E-11
1.5.2 Biomarkers of Outcome E-15
1.6 Literature Search (Step 2) E-17
1.7 Filtration of Identified Literature (Step 3) E-17
1.8 Assessment of Study Methodological Quality E-18
1.9 Evaluation of Totality of Evidence – Overview E-36
1.10 Evaluation of Totality of Evidence – Age-Related Cataract E-36
1.10.1 Overview E-36
1.10.2 Consistency E-42
1.10.3 Magnitude of Effect and Statistical Significance E-43
1.10.4 Opposing/Neutral Evidence E-45
1.10.5 Dose-response E-48
1.10.6 Temporality E-51
1.10.7 Effect of Dechallenge E-52
1.10.8 Specificity of Effect and Alternative Explanations E-52
1.10.9 Conclusions on Totality of Evidence – Age-Related Cataract E-57
1.11 Evaluation of Totality of Evidence – ARMD E-58
1.11.1 Overview E-58
1.11.2 Consistency E-67
1.11.3 Magnitude of Effect and Statistical Significance E-68
1.11.4 Opposing/Neutral Evidence E-68
1.11.5 Dose-response E-72
1.11.6 Temporality E-75
1.11.7 Effect of Dechallenge E-75
1.11.8 Specificity of Effect and Alternative Explanations E-75
1.11.9 Conclusions on Totality of Evidence – ARM, ARMD E-80
1.12 Evaluation of Totality of Evidence – Visual Performance E-82
1.12.1 Consistency E-82

1.12.2 Magnitude of Effect and Statistical Significance E-82
1.12.3 Opposing/Neutral Evidence E-86
1.12.4 Dose-response E-86
1.12.5 Temporality E-86
1.12.6 Effect of Dechallenge E-86
1.12.7 Specificity of Effect and Alternative Explanations E-86
1.12.8 Conclusion on Totality of Evidence – Visual Performance E-86

List of Attachments

Attachment I — Biomarkers of Age-related Cataract, age-related maculopathy, age-related macular degeneration

Attachment II — Excluded Studies

Attachment III — Tubular Summaries (Age-related Cataract, age-related macular degeneration, Visual Performance)

List of Figures and Tables

Figure 1.1.2-1 — Illustration of the Eye E-6
Figure 1.10.3-1 — Pooled Estimate of Risk of Cataract/Cataract Extraction for Lutein and Zeaxanthin Intakes (A) or Circulating Levels (B) in the Highest *vs.* Lowest Categories E-44
Figure 1.10.5.1-1 — Risk of Cataract as a Function of Lutein and Zeaxanthin Intakes E-50
Figure 1.10.5.1-2 — Risk of Cataract as a Function of Circulating Levels of Lutein and/or Zeaxanthin E-51
Figure 1.11.5.2-1 — Risk of ARMD as a Function of Lutein and Zeaxanthin Intakes E-74
Figure 1.11.5.2-2 — Risk of ARMD as a Function of Circulating Levels of Lutein and Zeaxanthin E-74

Table 1.4-1 — Method of Scientific Assessment E-11
Table 1.5.2-1 — Biomarkers of Visual Performance E-16
Table 1.7-1 — Inclusion and Exclusion Criteria Used to Filter Pertinent Identified Literature E-17
Table 1.8-1 — Quality Scores for Studies Assessing Cataract Risk as an Outcome E-19
Table 1.8-2 — Quality Scores for Studies Assessing ARM/ARMD as an Outcome E-25
Table 1.8-3 — Quality Scores for Studies Assessing Visual Performance as an Outcome E-33
Table 1.9-1 — Causality Criteria E-36
Table 1.10.1-1 — Studies Assessing the Relationship Between Lutein/Zeaxanthin and Risk of Cataract E-38
Table 1.10.4.1-1 — Characteristics of Supporting and Non-supporting Studies Assessing Dietary Intake as the Biomarker of Exposure E-45
Table 1.10.4.2-1 — Characteristics of Supporting and Non-supporting Studies Assessing Serum/Plasma as the Biomarker of Exposure E-47

Table 1.10.8.1-1 Carotenoid Composition Databases Used in Cataract Observational Studies E-54
Table 1.10.9-1 Summary of Evidence Regarding Causality E-57
Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD E-61
Table 1.11.4.1-1 Characteristics of Supporting and Non-supporting Studies Assessing Dietary Intakes as the Biomarker of Exposure E-69
Table 1.11.4.2-1 Characteristics of Supporting and Non-supporting Studies Assessing Serum/Plasma as the Biomarker of Exposure E-70
Table 1.11.4.2-2 Risk of ARM/ARMD as a Function of Circulating Levels of Lutein, Zeaxanthin, or Lutein+Zeaxanthin E-72
Table 1.11.8.1-1 Carotenoid Composition Databases Used in ARMD Observational Studies E-77
Table 1.11.9-1 Summary of Evidence Regarding Causality E-81
Table 1.12.1-1 Intervention Studies Assessing the Relationship Between Lutein and Zeaxanthin and Visual Performance E-84
Table 1.12.8-1 Summary of Evidence Regarding Causality E-87

1.0 LUTEIN AND ZEAXANTHIN

1.1 Background on Lutein and Zeaxanthin

1.1.1 Introduction

Lutein and its structural isomer zeaxanthin are hydroxylated carotenoids, each consisting of 40 carbons and 11 conjugated double bonds. Lutein and zeaxanthin are most concentrated in egg yolk and corn; as well, several fruits and vegetables contain varying levels of lutein and zeaxanthin (Sommerburg *et al.,* 1998). Although the principal natural form of zeaxanthin is the (*3R, 3'R*) form, 2 other stereoisomeric forms can result from configurations at its 2 chiral centers: (3R, *3'S* or meso-zeaxanthin) and (3S, 3'S). Both the (*3R, 3'R*) and the (3R, *3'S*) forms of zeaxanthin are present in the retina (Bone *et al.,* 1993; Landrum and Bone, 2001); however, the (*3R, 3'R*) form is, by far, the major natural form of zeaxanthin in foods, with meso-zeaxanthin being a very minor component of the human diet. Recently, conversion of lutein to meso-zeaxanthin was demonstrated in non-human primates (Johnson *et al.,* 2005). Given the limited intake of meso-zeaxanthin in the diet and its relative prominence in retinal tissue, it has been suggested that the conversion of lutein to meso-zeaxanthin may be of biological significance (Bone *et al.,* 1997; Khachik *et al.,* 2002).

1.1.2 Distribution of Lutein and Zeaxanthin in the Lens and Retinal Tissue

Lipoproteins are associated with carotenoid transport and tissue distribution in blood. While most carotenoids appear to be transported by LDL, HDL seems to be the predominant carrier of lutein and zeaxanthin (Clevidence and Bieri, 1993). Thus, low HDL levels, or a high ratio of LDL:HDL may reduce tissue transport of lutein and zeaxanthin.

Recently, Bhosale *et al.* (2004) purified a xanthophyll-binding protein from human macula. The protein was identified as a Pi isoform of human glutathione S-transferase (GSTP1), and had the highest affinity for dietary zeaxanthin (*3R, 3'R*) followed by its stereoisomer meso-zeaxanthin (*3R*, *3'S*). Lutein did not display any high-affinity binding to GSTP1.

Although 15 different dietary carotenoids can be measured in human plasma/serum, lutein and zeaxanthin are the only ones found in substantial amounts throughout the tissues of the visual system (Mares-Perlman *et al.*, 2002; Ribaya-Mercado and Blumberg, 2004; Smidt and Burke, 2004; Zhao *et al.*, 2006).

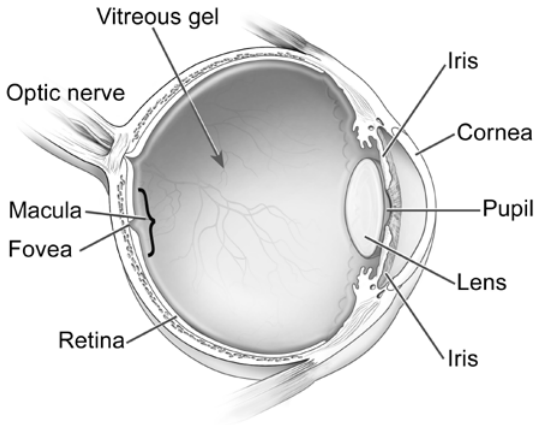
The human lens contains several antioxidant molecules that serve to protect it from oxidative damage including α-tocopherol, γ-tocopherol, retinol, ascorbic acid, and lutein and zeaxanthin (Garland, 1991; Yeum *et al.*, 1995, 1999). While lutein and zeaxanthin are present in the lens, their concentrations are approximately 100-fold lower than α-tocopherol (Yeum *et al.,* 1995). Data from a limited number of studies suggest that lutein and zeaxanthin may be the only

carotenoids present in the lens of the human eye (Yeum *et al.*, 1995, 1999). Neither lycopene nor β-carotene has been detected in the lens (Yeum *et al.*, 1995, 1999) and it is unclear if the presence of other carotenoids has been assessed. The concentration of lutein and/or zeaxanthin in the lens is, on average, approximately 10- to 20-fold less than that measured in the macular retina (Bernstein *et al.*, 2001; Zhao *et al.*, 2006; Bhosale *et al.*, 2007). Whereas several studies have examined the correlation between dietary or circulating levels of lutein and/or zeaxanthin and retinal levels of lutein and zeaxanthin, data related to lens lutein and/or zeaxanthin concentrations appear to be scarce. One recent study documented unusually high concentrations of lutein/zeaxanthin in the retinas and lenses of a subset of elderly eye donors; levels in both the retinas and lenses of these "outlier" subjects were approximately 3-fold greater than those in the rest of the group (Bhosale *et al.*, 2007). Retrospective assessment revealed that the majority of these outliers were regularly consuming high-dose lutein supplementation before death. Although preliminary, these data indicate that lens concentrations of lutein/zeaxanthin may be elevated by increased dietary intake.

Since the protective fiber cells of the lens do not renew themselves, the lens is thought to be the ocular structure most susceptible to oxidative damage – crystalline proteins in the lens cross-link and aggregate when the underlying epithelial cells are exposed to reactive oxygen species, resulting in the formation of cataracts (Santosa and Jones, 2005). From a functional point of view, the presence of oxidative metabolites of lutein and zeaxanthin in the lens suggests an antioxidant role for these carotenoids in this tissue (Bernstein *et al.*, 2001). In addition, an inverse correlation between macular pigment optical density (MPOD) and lens density has been reported in older subjects but not in young subjects, suggestive of a possible role for lutein and zeaxanthin in delaying the increase in lens density that is associated with aging (Hammond *et al.*, 1997a; Berendschot *et al.*, 2002).

Lutein and zeaxanthin, though present throughout the tissues of the visual system, are most concentrated in the center of the retina (Hammond, 2007). The retina is a thin neural tissue that lines the back of the eye; it contains photoreceptors that convert light into a neural signal (Hammond, 2007). The center of the retina is called the macula, and because of the accumulation of lutein and zeaxanthin in the macula to the exclusion of the other carotenoids, lutein and zeaxanthin, which give the macula its yellowish color, are referred to as the macular pigments (MP) (Hammond, 2007). The macula contains the cone-rich fovea, which is responsible for relaying visual information to the brain (Hammond, 2007). Thus, lutein and zeaxanthin are present in the area of the retina that is vital for vision (Hammond, 2007). The relative locations of the retina, macula, and fovea are shown in Figure 1.1.2-1.

Figure 1.1.2-1 Illustration of the Eye



The macular pigments are most concentrated in the macula of the eye (NEI, 2006).

Of the total carotenoid content of the retina, lutein, zeaxanthin, and meso-zeaxanthin account for 36, 18, and 18%, respectively, with the remainder accounted for by additional isomers of lutein and zeaxanthin (Khachik *et al.,* 1997; Landrum and Bone, 2001). The concentration of zeaxanthin is twice that of lutein in the inner macula; however, with increasing eccentricity from the fovea, lutein becomes the dominant carotenoid (Bone *et al.,* 1997). The macula concentrates lutein and zeaxanthin; while the concentration of these xanthophylls is approximately 1 mM within the central macula, the concentration of these carotenoids is approximately 3 times lower in plasma (Landrum and Bone, 2001).

1.1.3 Proposed Functions of Macular Pigment

Two functions have been proposed for the macular pigment. First, the absorbance spectrum for lutein and zeaxanthin peaks at 460 nm, and so lutein and zeaxanthin are potent filters of blue light (Pease *et al.,* 1987), which is the part of visible light with the highest energy and considered to be most damaging to the retina; in this respect, lutein and zeaxanthin are proposed to protect underlying structures (*i.e.,* the fovea) from phototoxic damage. In addition, blue light filtration is thought to reduce chromatic aberration and improve visual performance by reducing glare sensitivity, accelerating recovery from light stress, and improving visibility through contrast enhancement (Hammond, 2007). Second, retinal tissue is reportedly the most metabolically active tissue in the body; it is constantly exposed to oxygen and light energy, and due to the presence of polyunsaturated-rich cellular membranes, there is high potential for formation of reactive oxygen species and lipid oxidation (Hammond, 2007). Lutein and zeaxanthin are electron-rich molecules which function as effective lipid antioxidants; thus, they may attenuate the formation of reactive oxygen species and lipid oxidation products, potentially attenuating risks of age-related macular degeneration (ARMD) and cataract formation.

Preliminary evidence that lutein and zeaxanthin may play a role in the maintenance of vision comes from a study conducted in 3- to 10-year-old non-human primates, in which animals were fed xanthophyll-free semi-purified diets for up to 5.5 years (Malinow *et al.,* 1980). It was observed that, in contrast to control animals fed regular chow, animals maintained on the xanthophyll-free diets had undetectable levels of xanthophylls in plasma, lost yellow pigmentation of the macula, and developed drusen in the retina, which is an early sign of ARMD in humans. Drusen-like bodies also were present in some of the chow fed animals but at a lower incidence (the exact numbers of animals with drusen in either the chow or xanthophyll-free diets were not reported). Because monkeys are the only species apart from humans that have a macula, it was suggested that the xanthophylls may be essential nutrients for the maintenance of eye health in humans. The concentration of xanthophylls in the chow diet was reported as 21.72 µg/gm (~0.002%) chow, and was below detection in the xanthophyll-free liquid diet. Since a range of doses was not studied, it is not possible to determine a minimum dose that would be without effect on the pigmentation compared to controls. The authors noted that the functional significance of the macular anomalies remained to be established as no gross visual disturbances were observed in any of the animals.

A more recent study involving 18 rhesus monkey fed xanthophyll-free semipurified diets from birth until 7 to 16 years also demonstrated a lack of macular pigment and non-detectable serum levels of lutein and zeaxanthin (Neuringer *et al.,* 2004); however, in a second phase to this study, in which two groups of six monkeys were then supplemented with either lutein or zeaxanthin (2.2 mg/kg body weight/day) for an additional 24 to 56 weeks, it was found that serum levels of xanthophylls increased rapidly as did the macular pigment. With supplementation, xanthophyll serum levels increased rapidly and reached steady state after 4 weeks (serum levels were several fold higher than with the unsupplemented stock diet). The central peak of macular pigment optical density, which reached a study state by 24 to 32 weeks, was about 50% of the mean value of control animals on the stock diet. The serum xanthophyll levels did not correlate with the macular pigment optical density which may be attributable to a saturation effect. Although accumulation of macula pigment was not fully compensated for, this study demonstrated that the retina retained the mechanism to accumulate macular pigment from either lutein or zeaxanthin after retinal maturation of the retina occurred in the absence of xanthophylls. Furthermore, as the levels of lutein/zeaxanthin were not the only differences between the chow and the low L/Z diets, it is not clear if the differences in eye results are entirely due to L/Z or to some other factor.

In pediatric and adult patients on long-term total parenteral nutrition (TPN), which is free of xanthophylls, visual disturbances, abnormal electroretinograms, and early signs of macular degeneration, including granularity of the retinal pigmented epithelium and soft drusen, have been reported (Vinton *et al.,* 1990; Porter *et al.,* 2005). Lutein and zeaxanthin levels were not assessed in either of these studies, but given that TPN formulations do not contain carotenoids, plasma levels were likely low. That vitamin E supplementation caused symptom resolution in

the vitamin E deficient patient reported by Porter *et al.* (2005) indicates that nutrients other than (or in addition to) lutein and zeaxanthin are important in eye health maintenance. Likewise, the subjects studied by Vinton *et al.* (1990) were found to be deficient in selenium and linolenic acid, the latter which is the precursor to docosahexaenoic acid, a long-chain omega-3 fatty acid that is known to be important for proper retinal and visual function. Thus, although it can be inferred from these studies that lutein and zeaxanthin may be important to eye health, all of the subjects studied suffered from short bowel syndrome and associated co-morbidities and were likely generally nutritionally compromised, making it difficult to attribute a deficiency in any single nutrient as the sole cause.

1.2 Background on Age-Related Eye Diseases

1.2.1 Introduction

Age-related cataract and ARMD are the leading causes of visual impairment and blindness in the elderly population worldwide (Johnson, 2005). Approximately 1/3 of the population over the age of 65 has some kind of vision impairment (Johnson, 2005). It is anticipated that the prevalence of ARMD and age-related cataract in the U.S. will increase by 50% over the next 20 years, with the ageing of the American population (Chiu and Taylor, 2007). It has been estimated that approximately 6.3 million Americans will have ARMD by the year 2030 (Granado *et al.,* 2003).

1.2.2 Age-Related Cataract

Clinically significant age-related cataract affects 5% of Americans at age 65 and about 50% over the age of 75 (Chiu and Taylor, 2007). Fifteen (15) to 25 million cases of blindness worldwide (approximately 50% of the total) are the result of cataract formation (Johnson, 2005). In the U.S., it is estimated that over 1.3 million cataract operations are performed each year, with an associated cost of approximately 3.5 billion dollars (Vinson, 2006). The prognosis for patients with age-related cataract is often better than for those with ARMD, as vision can be restored in cataract sufferers by replacement of the damaged lens (Schalch, 1992). The success rate of reparative cataract surgery in the U.S. is very high, despite the high economic burden (Johnson, 2005; Zhao *et al.,* 2006). In countries that can't afford the surgery, cataracts are the leading cause of blindness (Zhao *et al.,* 2006).

The formation of cataracts is multifactorial, but oxidative stress has been implicated in the process, as the lens sustains extensive photo-oxidative damage (Zhao *et al.,* 2006). Identified risk factors for cataract development include gender, age, family history of cataract, obesity, smoking, alcohol consumption, diabetes, exposure to ultraviolet radiation, and the use of therapeutic drugs such as steroids (Hiller *et al.,* 1998; Taylor, 1999; Weintraub *et al.,* 2002; Robman and Taylor, 2005; Abraham *et al.,* 2006). Cataractogenesis involves the transition of the lens from transparent to opaque, which results in the reduced ability of the lens to transmit

and focus light on the retina (Johnson, 2005; Zhao *et al.,* 2006). The anterior surface of the healthy lens is covered by a single layer of epithelial cells (called fiber cells when fully matured), which have no organelles and are filled with a repeating lattice pattern of protein called crystalline (Johnson, 2005). The crystalline lattice forms a medium of nearly uniform refractive index (Johnson, 2005). Cataracts are formed when the lattice pattern is disrupted (presumably by oxidant damage to proteins and phospholipids), increasing light scattering due to opacity in the lens, and blurring vision (Johnson, 2005).

1.2.3 Age-related Macular Degeneration (ARMD)

ARMD is the most common cause of visual impairment in the developed world, is the main cause of blindness in people over age 65, and affects up to 30% of Americans over the age of 80 (Schalch, 1992; Bird *et al.,* 1995; Alves-Rodrigues and Shao, 2004; Hogg and Chakravarthy, 2004; Johnson, 2005; Chiu and Taylor, 2007). The most common risk factors for ARMD are age and smoking, with gender, iris color, heredity, cardiovascular health, nutrient status, body mass index, and lifetime exposure to sunlight also contributing significantly to risk (Hogg and Chakravarthy, 2004; Alves-Rodrigues and Shao, 2004). Lifetime oxidative stress is believed to play a role in the etiology of ARMD (Hogg and Chakravarthy, 2004).

ARM (age-related maculopathy – the earlier stages of ARMD) is divided into 4 stages, of which the first 3 are sub-clinical (Hogg and Chakravarthy, 2004). Stages 1 through 3 are typified by the presence of drusen (yellowish retinal deposits), patchy atrophy, and/or pigmentary abnormalities (without indication that they are secondary to any other ocular disorder) (Bird *et al.,* 1995; Hogg and Chakravarthy, 2004). Stage 4 of ARM is known as ARMD, and has clinically detrimental effects on vision (Hogg and Chakravarthy, 2004). It is characterized by more extensive degeneration of the retinal pigment epithelium, choriocapillaris (a layer of capillaries adjacent to Bruch's membrane), and photoreceptors (collectively referred to as geographic atrophy), and/or exudative disease (the presence of serous fluid, lipid exudates, hemorrhage, neovascularization, and fibrosis in the posterior pole of the eye) (Hogg and Chakravarthy, 2004).

The stages or clinical characteristics of ARMD may be referred to as 'wet' or 'dry' ARMD (Bird *et al.,* 1995). While both classifications can occur concurrently within an individual, they rarely occur in overlapping areas. Dry, or early, ARMD is characterized by geographic atrophy (observed as the accumulation of drusen and depigmentation of retina), while wet, or late, ARMD is associated with exudative disease, neovascularization, scarring, and/or retinal detachment (Bird *et al.,* 1995; Alves-Rodrigues and Shao, 2004). Later-stage ARMD affects 1 to 9% of Americans over 65 years of age (mostly Caucasian), with geographic atrophy present in 1/3 of cases, and macular neovascularization in the remaining 2/3 (Schalch, 1992; Hogg and Chakravarthy, 2004). Exudative disease is responsible for 90% of ARMD cases with severe vision loss (Hogg and Chakravarthy, 2004).

The formation of drusen is thought to occur as a consequence of an age-related accumulation of improperly digested cellular debris in the macula. This may occur as a result of the death of non-replaceable retinal pigment epithelial cells or their inability to extrude the accumulated debris through Bruch's membrane (which becomes less permeable with age) (Schalch, 1992; Johnson, 2005). Unlike the photoreceptor cells of the retina, the phagocytic retinal pigment epithelium cannot regenerate, and is therefore quite sensitive to the high levels of radiant energy and oxygen in the eye (Schalch, 1992). The functioning of the macula is compromised when the retinal pigment epithelium degenerates and drusen forms, which allows fluid to leak into the area behind the fovea (Alves-Rodrigues and Shao, 2004). The avascular foveal region is the most sensitive part of the retina due to the few cell layers separating incoming light from the cone cells (Schalch, 1992). It is made up exclusively of cone cells, which are more sensitive to blue light than rod cells, and cannot regenerate as easily as the rest of the retinal photoreceptor cells (Schalch, 1992). Clinically significant vision loss occurs when the photo-sensing cone cells in the fovea begin to die (Alves-Rodrigues and Shao, 2004). There is no treatment or cure for advanced ARMD, which often leads to blindness (Schalch, 1992; Alves-Rodrigues and Shao, 2004; Zhao *et al.*, 2006).

1.3 Objective of Scientific Assessment

Olestra is being proposed for use in several food categories that will be consumed as components of mixed meals; thus, there is the potential for reduced absorption of lutein and zeaxanthin. DRIs do not exist for lutein and zeaxanthin, and the essentiality of these carotenoids for the maintenance of eye health has not been established by any authoritative body. Also, the FDA recently rejected a qualified health claim petition for lutein and zeaxanthin and reduced risk of ARMD and cataract formation due to insufficient scientific evidence (U.S. FDA, 2005a). Nevertheless, the science-base on lutein and zeaxanthin and eye health has expanded rapidly over the last few years, and so the objective of the current assessment was to evaluate the totality of scientific evidence from human studies to better understand the roles of lutein and zeaxanthin in the maintenance of eye health and to better understand the implications, if any, of olestra-related reductions in lutein and zeaxanthin absorption.

1.4 Method of Scientific Assessment

The method used to critically evaluate the literature regarding the roles of lutein and zeaxanthin in the maintenance of eye health is presented in Table 1.4-1.

Table 1.4-1 Method of Scientific Assessment

Step	Description
Step 1: Characterization of Biomarkers	The methodological and biological validity of various biomarkers to the claimed effect was assessed.
Step 2: Literature Search	A comprehensive literature search was conducted. Details on databases searched as well as search terms used were provided.
Step 3: Filtration of Identified Literature	Pre-defined inclusion and exclusion criteria were applied to the identified studies.
Step 4: Assessment of Study Methodological Quality	A quality appraisal tool was developed in collaboration with two of the Panel members. The quality of each human intervention and observational study meeting pre-defined inclusion and exclusion criteria was then appraised by two independent raters using a study quality appraisal tool.
Step 5: Tabulation of Data	Relevant data from human intervention and observational studies were summarized, in tabular format, in descending order of study quality score.
Step 6: Evaluation of Totality of Evidence	The strength and consistency of the totality of scientific evidence was assessed, and the causal nature of the relationship was evaluated.[1]
Step 7: Final Conclusion	A final statement regarding the relationship of the nutrient to the claimed effect was made.

1.5 Characterization of Biomarkers (Step 1)

1.5.1 Biomarkers of Exposure

Biomarkers of lutein and zeaxanthin status include dietary intake estimates of lutein and zeaxanthin, circulating levels of lutein and zeaxanthin, and MPOD. The methodological and biological validities of these biomarkers are discussed below.

1.5.1.1 Dietary Intakes of Lutein and Zeaxanthin – Methodological Validity

Observational studies assessing the relationship between intake of lutein and zeaxanthin and risk of age-related eye disease typically utilize validated food frequency questionnaires to estimate dietary intakes. Carotenoid intakes are then estimated using food composition tables. Food composition tables are required to translate food consumption data into estimates of lutein and zeaxanthin; thus, errors in food composition data or food composition data that are incomplete are likely to result in the misclassification of lutein and zeaxanthin intake, thereby limiting interpretation of reported diet-disease relationships (VandenLangenberg *et al.,* 1996).

1.5.1.2 Dietary Intakes of Lutein and Zeaxanthin – Biological Validity

Several factors affect carotenoid bioavailability, including molecular linkage, amount consumed and matrix, effectors of absorption and bioconversion, and nutrient status and genetic factors of the host (Castenmiller and West, 1998). Although dietary intakes and serum levels of lutein and zeaxanthin are generally correlated (Forman *et al.,* 1993), this is not always the case (Hammond *et al.*, 1996a). There is great variability in plasma response to carotenoid intake,

and several factors (both dietary and non-dietary) affect carotenoid absorption (Castenmiller and West, 1998). Thus, intake estimates do not provide a good estimate of bioavailability, a fact supported by several studies in which correlations between intakes and plasma levels of lutein and zeaxanthin were reported to be poor, even after adjustment for several covariates (Brown *et al.,* 1999: r=0.19; Chasan-Taber *et al.,* 1999: r=0.27). The majority of studies assessing dietary intakes of lutein and zeaxanthin report intakes of the 2 xanthophylls together; relationships with age-related eye diseases may not be discernable if one of these carotenoids is more important than the other. Furthermore, dietary intakes of lutein and zeaxanthin may not correlate with tissue uptake, specifically uptake in retinal tissue. Nevertheless, in prospective cohort studies, which are least vulnerable to recall bias, dietary intakes of lutein and zeaxanthin may provide good estimates of long-term/chronic intakes of these carotenoids. Since age-related eye diseases are thought to occur gradually, over a period of several decades, such measures of habitual intake may be informative.

1.5.1.3 Circulating Levels of Lutein and Zeaxanthin – Methodological Validity

Circulating levels of lutein and/or zeaxanthin are determined in plasma or serum samples *via* reverse-phase high-performance liquid chromatography (HPLC). Until recently, lutein and zeaxanthin could not be reliably separated by HPLC and so publications generally reported combined lutein+zeaxanthin concentrations in the plasma/serum. However, as it is now possible to more accurately quantify lutein and zeaxanthin separately, the more recent practice has been to report plasma/serum levels of these carotenoids individually. There is great variability with regard to the amount of detail on sample extraction and HPLC analysis procedures that is provided in the scientific literature. Some publications provide no or minimal information on the extraction procedure, recovery efficiency, HPLC internal standards, inter-assay variability, or other potentially important factors while other publications provide extensive details on these matters.

1.5.1.4 Circulating Levels of Lutein and Zeaxanthin – Biological Validity

There are a number of factors that influence carotenoid bioavailability, including molecular linkage, the amount and matrix in which they are consumed, effectors of absorption and bioconversion, as well as nutrient status and genetic factors of the host (Castenmiller and West, 1998). These and other factors likely underlie the numerous observations of poor correlation between intakes and plasma levels of lutein and/or zeaxanthin (Brown *et al.,* 1999: r=0.19; Chasan-Taber *et al.,* 1999: r=0.27; Ciulla *et al.,* 2001: r=0.20; Nolan *et al.,* 2004: r=0.200 to 0.294; Mares *et al.,* 2006: r=0.39).

Plasma/serum levels of lutein/zeaxanthin have been found to generally correlate well with measures of MPOD. Statistically significant positive correlations between circulating lutein and/or zeaxanthin levels and MPOD have been reported in a number of studies (Hammond *et al.*, 1996a; Ciulla *et al.*, 2001; Nolan *et al.*, 2004; Burke *et al.*, 2005). Despite the generally good

correlation between circulating levels of lutein and zeaxanthin and MPOD, approximately 20% of healthy subjects and subjects with ARMD have been found to be "retinal-non-responders" [*i.e.,* supplementation with lutein and zeaxanthin is typically associated with increases in circulating levels of lutein and zeaxanthin, but not with increases in MPOD (Hammond *et al.*, 1996a; Trieschmann *et al.,* 2007)]. Moreover, in several human intervention studies, MPOD has been shown to remain elevated for up to 6 months following the end of the supplementation period, despite a return to baseline in plasma/serum levels of lutein and zeaxanthin (Hammond *et al.*, 1996a; Johnson *et al.,* 2000; Trieschmann *et al.,* 2007). Thus, there are limitations to the use of circulating levels of lutein and zeaxanthin as biomarkers of status in that these levels do not always correlate with MPOD, particularly in "retinal non-responders" and following chronic supplementation with lutein and zeaxanthin.

1.5.1.5 Macular Pigment Optical Density – Methodological Validity

Due to their accumulation in the macula, lutein and zeaxanthin are collectively referred to as the MP (Rock *et al.*, 2002; Granado *et al.*, 2003; Nolan *et al.*, 2004; Johnson, 2005). Measurement of MPOD, discussed in more detail below, provides an indication of the amount of MP present in the eye, with higher MPOD reflective of a higher concentration of lutein and zeaxanthin. There are 2 recognized methods for determining MPOD, namely heterochromatic flicker photometry (HFP) and Raman spectroscopy (RS).

Although HFP was the first technique established for the measurement of MPOD, and is still widely used, assessment obtained *via* RS is regarded as equally reliable (Landrum and van Kuijk, 2004; Neelam *et al.*, 2005). Both methods have been validated *in vitro*, and both can produce precise and accurate results under the right circumstances. Although it has been recommended that researchers use only one instrument type for the duration of a single experiment (to reduce variance in results due to differing underlying principles and techniques), results from one can be comparable to the other by means of a simple calculation (Neelam *et al.*, 2005).

HFP provides a subjective assessment of MPOD, can be time-consuming, and shows high variability in subjects with low MPOD (Neelam *et al.*, 2005). Furthermore, because HFP measures relative carotenoid concentrations within the individual subject's eye, it may not be as responsive to changes in MPOD upon carotenoid supplementation if carotenoid concentrations in both foveal and parafoveal areas increase with treatment (Bernstein *et al.*, 2004). However, HFP can correct for prereceptorial optical properties because it is derived from a ratio from within each individual's eye (Neelam *et al.*, 2005).

RS measures the absolute concentration of carotenoids in only one area, and doesn't take into consideration the possible variable distribution of carotenoids in the retina (Bernstein *et al.*, 2004). Compared to HFP, RS is faster and provides an objective measurement of macular carotenoids. It has been suggested that RS may be more useful in subjects with low MPOD as

long as they maintain the ability to center the eye on a stimulus (≥20/80 visual acuity) to enable the centering of the eye in the apparatus (Zhao *et al.*, 2003; Neelam *et al.*, 2005). While MPOD measures obtained *via* RS and HFP have been shown to be well-correlated in healthy subjects (Neelam *et al.,* 2005), there is currently no data to suggest that either method of MPOD measurement is superior to the other in subjects with ocular pathologies.

1.5.1.6 Macular Pigment Optical Density – Biological Validity

A considerable amount of evidence suggests that MPOD is a reliable marker of lutein and zeaxanthin status. Several cross-sectional studies have documented a positive correlation between MPOD and dietary intake (Ciulla *et al.*, 2001; Nolan *et al.*, 2004; Burke *et al.*, 2005; Mares *et al.*, 2006) or circulating levels (Hammond *et al.*, 1996a; Ciulla *et al.*, 2001; Nolan *et al.*, 2004; Burke *et al.*, 2005; Mares *et al.*, 2006) of lutein and/or zeaxanthin. Data from intervention studies demonstrate that MPOD generally increases in response to lutein and/or zeaxanthin supplementation (Hammond *et al.*, 1997b; Koh *et al.*, 2004; Richer *et al.*, 2007; Schalch *et al.*, 2007; Trieschmann *et al.*, 2007). These intervention studies provide valuable support for the notion that MPOD can serve as a surrogate (and perhaps more biologically valid) measure of lutein and zeaxanthin status.

Lutein and/or zeaxanthin supplementation generally resulted in increased MPOD compared to baseline and/or to the placebo group, regardless of whether subjects were free of ocular disease or not (Hammond *et al.*, 1997b; Koh *et al.*, 2004; Richer *et al.*, 2007; Schalch *et al.*, 2007; Trieschmann *et al.*, 2007). In 2 of these studies, it was suggested that there may exist a sub-set of individuals (approximately 20% of subjects studied, including both healthy subjects and subjects with ARMD) who are “retinal non-responders” (Hammond *et al.,* 1997b; Trieschmann *et al.*, 2007). Retinal non-responders typically have increased circulating levels of lutein and zeaxanthin in response to supplementation with lutein and zeaxanthin; however, MPOD appears resistant to increases. Another important finding in both of these studies is that increases in MPOD remained elevated for up to 6 months after the intervention stopped (Hammond *et al.,* 1997b; Trieschmann *et al.*, 2007), despite a return to baseline in serum levels of lutein and zeaxanthin (Hammond *et al.*, 1997b), indicating a prolonged retention and low turnover of lutein and zeaxanthin in the retina. Johnson *et al.* (2000) also have reported increases in serum levels of lutein and zeaxanthin and MPOD following the 15-week consumption of spinach (60 g/day) and corn (150 g/day), with a maintenance in MPOD (but not serum levels) following a 2-month follow-up period.

MPOD can be influenced by a number of factors including, but not limited to, sex (Hammond *et al.*, 1996a), smoking status (Hammond *et al.*, 1996b), iris color (Hammond *et al.*, 1996c), and body fat (Nolan *et al.*, 2004). Not all of these factors are always accounted for in studies assessing MPOD; as a result, these may contribute to variability in MPOD data, particularly in studies with limited numbers of subjects.

The results of the studies cited above indicate that a number of factors can influence MPOD determination in healthy and diseased individuals. Importantly, there appears to be a subset of individuals that is able to absorb lutein and zeaxanthin from the gastrointestinal tract but for unknown reasons is unable to incorporate these carotenoids into MP in the retina. Whether this is due to a defect in transport or uptake of these carotenoids into retinal tissue or to some other factor(s) is unknown. Regardless, these data highlight 2 important points. The first is that MPOD is a much more reliable indicator of tissue lutein and zeaxanthin levels than either dietary assessment or the measurement of circulating concentrations of lutein and zeaxanthin, as MPOD is not always correlated with either of these measures. The second is that MPOD remains elevated long after the supplementation of lutein and/or zeaxanthin *via* dietary modification (Hammond *et al.*, 1997b; Johnson *et al.,* 2000) or capsule administration (Trieschmann *et al.*, 2007) has ended, indicating a prolonged retention of lutein and zeaxanthin in the retina that is not necessarily reflective of dietary intake or circulating levels measured at a particular point in time. The third is that MPOD is the most direct measure of tissue levels of lutein and zeaxanthin, and therefore the most relevant in assessing risk of disease in that tissue. These findings suggest that, in understanding the roles of lutein and zeaxanthin in reducing the risk of age-related eye diseases, the most biologically valid measure of lutein and zeaxanthin may be MPOD.

1.5.2 Biomarkers of Outcome

The assessment of the methodological and biological validity of study endpoints is often necessary when a surrogate biomarker of disease, rather than the disease itself, is measured. The primary endpoints of interest are cataract and ARM/ARMD, both of which are disease endpoints (as opposed to surrogate biomarkers of disease). There are several different classification systems for assessing cataract and ARM/ARMD (**Attachment I** to **Appendix E**). While the differing methods for the subjective assessment of cataract and ARMD may slightly affect the consistency of the results, all methods are validated procedures, and typically include specific instructions intended to reduce inter- and intra-assessor variability.

A surrogate measure of ARMD was not identified in the literature. For cataract, outcome measures consisted of lens opacity or optical density, incident/prevalent cataract, and cataract extraction. Incident/prevalent cataract and cataract extraction are both manifestations of disease; in contrast, lens opacity or lens optical density is considered an early stage of cataract development.

Other biomarkers of outcome that were identified include measures of visual performance (Table 1.5.2-1).

Table 1.5.2-1 Biomarkers of Visual Performance

Outcome	Test	Definition	Description	Reference
Visual Acuity	Snellen letters	Clarity of vision	The subject is asked to read lines of text of decreasing size, and the smallest text they can read is compared to that of a subject with normal vision	Richer *et al.,* 2004 Stringham and Hammond, 2008 AMD Alliance International, 2007
Glare recovery	Visual stress	The ability to adapt the eyesight to varying light conditions	Subject's vision is adapted to a brightly colored light box for 1 minute, and then the time required to read a low-contrast line of print is recorded	Richer *et al.,* 2004 Stringham and Hammond, 2008 Kent, 2007
Glare sensitivity	Brightness acuity test	Reduced central vision due to a light source elsewhere in the visual field; often associated with pain/discomfort	Measures visual acuity at 3 different light situations (sunny day, cloudy day, and fluorescent light)	Olmedilla *et al.,* 2001 Holladay *et al.,* 1987 AMD Alliance International, 2007
Contrast acuity/sensitivity	Contrast sensitivity function/Contrast acuity assessment	A measure of the luminance variation necessary for a target to be seen; reduced by glare	Measures the least amount of contrast needed to detect visual stimuli at different spatial frequencies	Richer *et al.,* 2004 Kvansakul *et al.,* 2006 Lasa *et al.,* 1993 Stringham and Hammond, 2008 AMD Alliance International, 2007
Wavefront aberrations	Shack-Hartmann wavefront sensing technique	Determine the quality/sharpness of the image formed on the retina, which changes with the shape, position, and health of the lens[1]	A laser of fixed wavelength is shone into the subject's eye, and the change in wavelength in the reflected light is recorded	Kvansakul *et al.,* 2006 Radhakrishnan and Charman, 2007 Elliott, 1993
Intraocular light scatter	Forward light scatter test/flicker cancellation technique		The luminance of a dark disc in the centre of a flickering blue light source is adjusted to eliminate the perception of flicker at the centre of the dark disc. The luminance of the central disk needed to achieve this is a direct measure of the amount of light scattered in the eye.	

[1] A healthy lens will minimize wavefront aberrations.

1.6 Literature Search (Step 2)

The preliminary search of the published literature on lutein and zeaxanthin was very broad and was intended to identify all relevant published data pertaining to supplementation with lutein and zeaxanthin and eye health. The literature search was conducted in January 2008 using Dialog, an electronic searching tool, to access a number of scientific databases, including Medline, ToxFile, Agricola, Agris, JICST-EPlus, Biosis Previews, Food Science & Technology Abstracts, Foodline (R): Science, NTIS, and Embase. The search was limited to studies conducted in human subjects. The terms "lutein" or "zeaxanthin" were searched in conjunction with "eye", "eyes", "eye health", "age-related macular degeneration", "age related macular degeneration", "AMD", "age-related maculopathy", "age related maculopathy", "macular pigment optical density", "MPOD", "cataract", or "cataracts". This resulted in the identification of 210 unique titles. Abstracts of articles determined to be relevant were reviewed, and pertinent articles were subsequently retrieved and reviewed for inclusion or exclusion in the current analysis. Additional articles also were identified *via* reference lists of identified articles and selected review papers.

1.7 Filtration of Identified Literature (Step 3)

Literature retrieved was filtered using the inclusion and exclusion criteria specified in Table 1.7-1.

Table 1.7-1 Inclusion and Exclusion Criteria Used to Filter Pertinent Identified Literature

Inclusion Criteria
A study was included in the current assessment if:

- It was a human intervention or observational study;
- It was published in English as a full-length article in a peer-reviewed journal;
- For human intervention studies, the amount of lutein and/or zeaxanthin administered, the length of administration, and associated tissue levels or circulating levels of lutein and/or zeaxanthin were quantified;
- For observational studies, tissue levels or circulating levels of lutein and/or zeaxanthin were quantified and/or dietary intakes of lutein and/or zeaxanthin were estimated using a validated tool;
- Effects or associations between tissue levels/circulating levels/dietary intakes of lutein and/or zeaxanthin and ARM/ARMD, cataract formation, lens opacity, or visual performance (visual acuity, glare sensitivity, contrast acuity) were reported.

Exclusion Criteria
A study was excluded from the current analysis if:

- It was not primary research (*e.g.,* opinion letter, position statement, review, meta-analysis);
- It was published in abstract form only;
- It was published in a language other than English;
- It was an animal or *in vitro* study;
- For human intervention studies:
  - The amount of lutein and/or zeaxanthin administered, the length of administration, and associated tissue levels or circulating levels of lutein and/or zeaxanthin were not quantified;
  - The treatment combined lutein and/or zeaxanthin with other nutritional or pharmaceutical interventions as treatment, the effects of which could not be isolated[1];
- For observational studies, tissue levels or circulating levels of lutein and/or zeaxanthin were not quantified and/or dietary intakes of lutein and/or zeaxanthin were not quantified (*i.e.,* the study examined intakes of

Table 1.7-1 Inclusion and Exclusion Criteria Used to Filter Pertinent Identified Literature
foods considered sources of lutein and/or zeaxanthin, but did not quantify intakes of lutein and/or zeaxanthin *per* se); • The study was a kin publication without a unique data set; • Effects or associations between tissue levels/circulating levels/dietary intakes of lutein and/or zeaxanthin and ARM/ARMD, cataract formation, lens opacity, or visual performance (visual acuity, glare sensitivity, contrast acuity) were not reported.

Abbreviations: AREDS, Age-elated Eye Disease Study; ARM, age-related maculopathy; ARMD, age-related macular degeneration.
[1] Because the current evaluation was intended to provide information on the efficacy of lutein+zeaxanthin, *per se*, studies in which lutein+zeaxanthin were combined with other nutritional or pharmacological treatments as intervention had to be excluded from the assessment, unless the placebo group was administered the other nutritional or pharmacological treatments, thereby permitting the determination of the independent effects of lutein+zeaxanthin.

A total of 19 observational studies (in 21 publications) were identified in which relationships between dietary intakes or tissue levels of lutein and/or zeaxanthin and risk of cataract were investigated; these are listed in Table 1.8-1. A total of 26 observational studies (in 25 publications) were identified in which relationships between dietary intakes or tissue levels of lutein and/or zeaxanthin and risk of ARM/ARMD were investigated; these studies are listed in Table 1.8-2. A total of 6 human intervention trials were identified in which the effects of lutein and zeaxanthin on measures of visual performance were assessed; these studies are listed in Table 1.8-3. Studies not meeting the inclusion/exclusion criteria specified in Table 1.7-1, as well as reasons for exclusion, are presented in Tabular format in **Attachment II** to **Appendix E**.

1.8 Assessment of Study Methodological Quality

A quality appraisal tool, developed *a priori* in collaboration with two of the Panel members, was used to assess the methodological quality of the studies identified. Each study was assigned a "quality score" based on the number of items accounted for. Studies were scored by 2 independent raters; if scores deviated by ≥5% for any study, then the raters discussed discrepancies and reached a consensus on the final score. Quality appraisals for each individual study can be provided upon request.

Study quality scores, as well as a brief summary of the methodological deficiencies of each study, are summarized in Table 1.8-1 for studies in which the endpoint under investigation was related to cataract; in Table 1.8-2 for studies in which the endpoint under investigation was related to age-related maculopathy or macular degeneration; and in Table 1.8-3 for studies in which the biomarker under investigation was related to visual performance. While an attempt was made to present the studies in descending order of study quality, it was determined to be more appropriate to group the studies according to the cohort studied, since a single cohort or a cross-section of that cohort was often the subject of numerous investigations. The scientific assessment was based only on studies of higher quality (defined as a quality score greater than or equal to 60%).

Table 1.8-1 Quality Scores for Studies Assessing Cataract Risk as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Valero *et al.,* 2002	Case-control	23/27	85.2	Diet	Prevalent nuclear, subcapsular, or cortical cataract	• Study did not assess intakes prospectively • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not account/adjust for hyperlipidemia/hypercholesterolemia or family history of eye disease
Vu *et al.,* 2006 (Melbourne VIP)	Cross-sectional	21/25	84.0	Diet	Prevalent nuclear, subcapsular, or cortical cataract	• Study did not assess intakes prospectively • Analysis did not adjust for colinearity of individual/total carotenoids with L/Z intakes • Statistical models did not account/adjust for hyperlipidemia/hypercholesterolemia or presence of eye disease at baseline
Moeller *et al.,* 2008 (CAREDS)	Retrospective (Associations with MPOD were cross-sectional)	24/29	82.3	Diet, serum, MPOD	Prevalent nuclear cataract, severe nuclear cataract, extraction	• Power calculations were not performed • Statistical models did not account/adjust for alcohol intake, diabetes, hyperlipidemia/hypercholesterolemia, or presence of eye disease at baseline
Mares-Perlman *et al.,* 1995a (Nutritional Factors in Eye Disease Study – subset of Beaver Dam Eye Study)	Retrospective	12/23	52.2	Diet	Prevalent nuclear lens opacity	• Study did not assess intakes prospectively • Power calculations were not performed • Analysis did not adjust for colinearity of intakes of individual/total carotenoids or other antioxidants with L/Z intakes • Statistical models did not adjust/account for sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, family history of eye disease, or the presence of eye disease at baseline
Mares-Perlman *et al.,* 1995b (Nutritional Factors in Eye Disease Study – subset of Beaver Dam Eye Study)	Cross-sectional	17/23	73.9	Serum	Severity of nuclear and cortical lens opacity	• Study did not assess serum levels prospectively • Analysis did not account for colinearity of serum levels of individual/total carotenoids or other antioxidants with L/Z levels • Statistical models did not account/adjust for medication use, hypertension, family history of eye disease

Table 1.8-1 Quality Scores for Studies Assessing Cataract Risk as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Lyle *et al.,* 1999b (p.802) (Nutritional Factors in Eye Disease Study – subset of Beaver Dam Eye Study)[2]	Cross-sectional	16/25	64.0	Diet	Incident nuclear cataract	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat, individual/total carotenoids, or other antioxidants with L/Z intakes • Statistical models did not adjust/account for sunlight exposure, hyperlipidemia/hypercholesterolemia, family history of eye disease, or the time period of assessment • Similarity of dropout rates and reasons among groups not reported
Lyle *et al.,* 1999a (p. 272) (Nutritional Factors in Eye Disease Study – subset of Beaver Dam Eye Study)[2]		18/21	85.7	Serum		• Analysis did not account for colinearity of serum levels of other antioxidants with L/Z intakes • Statistical models did not adjust/account for sunlight exposure or family history of eye disease
Chasan-Taber *et al.,* 1999 (Nurses' Health Study)	Prospective cohort	15/22	68.2	Diet	Incident nuclear and subcapsular cataract extraction	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Blinding of outcome assessors not reported • Differences in dropout rates and reasons not reported
Jacques *et al.,* 2001 (Nutrition and Vision Project – subset of Nurses' Health Study)[3]	Cross-sectional	21/26	80.7	Diet	Prevalent nuclear cataract	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for medication use, hyperlipidemia/hypercholesterolemia, or family history of eye disease

Table 1.8-1 Quality Scores for Studies Assessing Cataract Risk as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Taylor *et al.,* 2002 (Nutrition and Vision Project – subset of Nurses' Health Study)[3]		21/27	77.8		Prevalent cortical or posterior subcapsular cataract	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for sunlight exposure, hyperlipidemia/ hypercholesterolemia, or family history of eye disease • Dropout rates and reasons among groups not reported
Jacques *et al.,* 2005 (Nutrition and Vision Project, a subset of Nurses' Health Study)	Cross-sectional	20/26	76.9	Diet	Change in nuclear opacification from baseline	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for medication, hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease
Christen *et al.,* 2008 (WHS)	Prospective cohort	19/26	73.1	Diet	Incident cataract	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for sunlight exposure or family history of eye disease • Dietary intakes were not assessed repeatedly • Blinding of outcome assessors and drop out rates and reasons among groups not reported
Brown *et al.,* 1999 (Health Professionals' Follow-up Study)	Prospective cohort	16/25	64.0	Diet	Incident nuclear and subcapsular cataract extraction	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat, individual/total carotenoids, or other antioxidants with L/Z intakes • Statistical models did not adjust/account for hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Blinding of outcome assessors and drop out rates and reasons among groups not reported

Table 1.8-1 Quality Scores for Studies Assessing Cataract Risk as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Delcourt *et al.,* 2006 (The POLA Study)	Cross-sectional	17/23	73.9	Plasma	Prevalent nuclear, subcapsular, or cortical cataract	• Study did not assess plasma levels prospectively • Power calculations were not performed • Analysis did not account for colinearity of serum levels of individual/total carotenoids with L/Z levels • Study did not account for supplement use • Statistical models did not adjust/account for alcohol intake or family history of eye disease
Gale *et al.,* 2001 (subset of MRC study participants)	Cross-sectional	15/22	68.2	Plasma	Prevalent nuclear, subcapsular, or cortical cataract	• Study did not assess plasma levels prospectively • Power calculations were not performed • Analysis did not account for colinearity of serum levels of individual/total carotenoids with L/Z levels • Statistical models did not adjust/account for sunlight exposure, hypertension, or family history of eye disease • Outcome assessors not blinded to exposure status
Dherani *et al.,* 2008	Cross-sectional	14/23	60.9	Serum	Prevalent nuclear, subcapsular, or cortical cataract	• Study did not assess serum levels prospectively • Power calculations were not performed • Subjects' inclusion and exclusion criteria not specified • Analysis did not account for colinearity of serum levels of individual/total carotenoids or other antioxidants with L/Z levels • Statistical models did not adjust/account for diabetes, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Unknown if outcome assessors blinded to exposure status
Rodríguez-Rodríguez *et al.,* 2006	Case-control	15/27	55.5	Diet	Prevalent cataract	• Study did not assess intakes prospectively • Power calculations were not performed • Reliable assessment and validity of case condition not reported • Analysis did not account for colinearity of intake of total fat, individual/total carotenoids, or other antioxidants with L/Z intakes • Statistical models did not adjust/account for sunlight

Table 1.8-1 Quality Scores for Studies Assessing Cataract Risk as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
						exposure, medication use, diabetes, hyperlipidemia/hypercholesterolemia or family history of eye disease at baseline • Blinding of outcome assessors not reported
Hammond *et al.,* 1997a (Harvard Cooperative Program on Aging)	Cross-sectional	12/22	54.5	MPOD	Lens optical density	• Study did not assess MPOD prospectively • Study did not account for supplement use • Statistical models did not account/adjust for body composition, alcohol intake, iris color, sunlight exposure, medication use, or family history of eye disease • Blinding of outcome assessors not reported • Details on statistical methods not provided
Berendschot *et al.,* 2002	Cross-sectional	11/21	52.4	Serum, adipose tissue, MPOD	Prevalent cataract	• Study did not assess tissue levels prospectively • Power calculations were not performed • Statistical models did not adjust/account for alcohol intake, sunlight exposure, medication use, hypertension, diabetes, family history of eye disease, or the presence of eye disease at baseline • Outcome assessors were not blinded to exposure status
Ciulla and Hammond, 2004	Cross-sectional	8/20	40.0	MPOD	Prevalent cataract	• Study did not assess MPOD prospectively • Power calculations were not performed • Study did not account for supplement use • Statistical models did not account/adjust for gender, body composition, smoking status, alcohol intake, iris color, sunlight exposure, medication use, hyperlipidemia/hypercholesterolemia, or family history of eye disease
Olmedilla *et al.,* 2002	Case-control	10/26	38.5	Serum	Prevalent cataract	• Study did not assess serum levels prospectively • Power calculations were not performed • Selection of controls from the source of population of the cases not reported • Analysis did not account for colinearity of serum levels of individual/total carotenoids, other antioxidants, or

Table 1.8-1 Quality Scores for Studies Assessing Cataract Risk as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
						supplement use with serum L/Z levels • Statistical models did not adjust/account for body composition, smoking status, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia or family history of eye disease at baseline • Outcome assessors not blinded to exposure status

Abbreviations: CAREDS, Carotenoids in Age-Related Eye Disease Study; L/Z, lutein/zeaxanthin; MPOD, macular pigment optical density; MRC, Medical Research Council; POLA, Pathologies Oculaires Liées à l'Age; VIP, Visual Impairment Project; WHS, Women's Health Study.
[1] Studies with a quality score ≥60% were defined as having high methodological quality compared to studies with a quality scores <60%.
[2] Although results from the Nutritional Factors in Eye Disease Study (a cohort nested in the Beaver Dam Eye Study) were reported separately, the same cohort and study design were used in both of these studies, and the only variable that differed is that Lyle *et al.* (1999b) presented results on dietary intakes of lutein and zeaxanthin, while Lyle *et al.* (1999a) presented results on serum levels of lutein and zeaxanthin. Thus, these 2 publications were counted as 1 study.
[3] Although results from the Nutrition and Vision Project were published separately, the same cohort and study design were used in both of these studies, and the only variable that differed was that Jacques *et al.* (2001) presented results on nuclear cataract, while Taylor *et al.* (2002) presented results on cortical or posterior subcapsular cataract. Thus, these two publications were considered as 1 study.

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
LaRowe *et al.,* 2008 (CAREDS)	Cross-sectional	22/24	91.6	MPOD	Prevalent intermediate ARMD and pigmentary abnormalities	• Study did not assess MPOD prospectively • Blinding of outcome assessors not reported
Moeller *et al.,* 2006 (CAREDS)	Retrospective	20/24	83.3	Diet Serum	Prevalent intermediate ARMD	• Study did not assess intakes/serum levels prospectively • Power calculations were not performed • Analysis did not account for colinearity of intake of individual/total carotenoids • Statistical models did not adjust/account for hyperlipidemia/hypercholesterolemia
Morris *et al.,* 2007 (Nutrition and Vision Project, a cross-section of the Nurses' Health Study)	Cross-sectional	18/22	81.8	Diet	Prevalent early ARM (pigmentary abnormalities and large drusen)	• Power calculations were not performed • Statistical models did not adjust/account for hyperlipidemia/hypercholesterolemia or family history of eye disease • Blinding of outcome assessors not reported
SanGiovanni *et al.*, 2007 (AREDS)	Case-control	20/25	80.0	Diet	ARMD severity	• Study did not assess intakes prospectively • Power calculations were not performed • Statistical models did not adjust/account for alcohol intake, hyperlipidemia/hypercholesterolemia or family history of eye disease at baseline
Nolan *et al.,* 2007	Cross-sectional	16/21	76.2	Diet, serum, MPOD	Risk of ARM	• Study did not assess intakes/serum levels/MPOD prospectively • Power calculations were not performed • Statistical models did not adjust/account for sunlight exposure or diabetes • Blinding of outcome assessors not reported

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Cho *et al.,* 2004 (Nurses' Health Study and Health Professionals' Follow-up Study)	Prospective cohort	18/24	75.0	Diet	Incident ARM, ARMD	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for sunlight exposure, diabetes, family history of eye disease • Outcome assessors not blinded to exposure status
Delcourt *et al.,* 2006 (The POLA Study)	Cross-sectional	17/23	73.9	Plasma	Prevalent early and late ARM	• Study did not assess plasma levels prospectively • Power calculations were not performed • Analysis did not account for colinearity of serum levels of individual/total carotenoids with L/Z levels • Study did not account for supplement use • Statistical models did not adjust/account for alcohol intake or family history of eye disease
Tan *et al.,* 2008 (BMES)	Prospective cohort	19/27	70.4	Diet	Incident early, late, and any ARM	• Power calculations were not performed • Analysis did not account for colinearity of intake of fat with intakes of L/Z • Statistical models did not adjust/account for body composition, alcohol intake, sunlight exposure, or hypertension • Dietary intakes were not assessed repeatedly • Blinding of outcome assessors not reported
Seddon *et al.,* 1994 (Eye Disease Case-Control Study Group)[2]	Case-control	19/27	70.4	Diet	Prevalent neovascular ARMD	• Study did not assess intakes prospectively • Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for sunlight exposure, medication use, diabetes, hyperlipidemia/hypercholesterolemia or family history of eye disease

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Eye Disease Case-Control Study Group, 1993[2]		15/26	57.7	Serum		• Study did not serum levels prospectively • Analysis did not account for colinearity of serum levels of individual/total carotenoids, other antioxidants, or supplement use with serum L/Z levels • Statistical models did not adjust/account for body composition, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, or family history of eye disease
Mares-Perlman *et al.,* 1996 (Nutritional Factors in Eye Disease Study, a subset of the Beaver Dam Eye Study)	Retrospective	14/21	66.7	Diet	Prevalent early and late ARM	• Study did not assess intakes prospectively • Power calculations were not performed • Colinearity of intake of total fat with L/Z intakes not reported • Statistical models did not adjust/account for body composition, medication use, hypertension, or family history of eye disease
Mares-Perlman *et al.,* 1995 (Nutritional Factors in Eye Disease Study, a subset of the Beaver Dam Eye Study)	Nested case-control	18/25	72.0	Serum	Severity of ARM, ARMD	• Study did not assess serum levels prospectively • Analysis did not account for colinearity of serum levels of individual/total carotenoids with serum L/Z levels • Statistical models did not adjust/account for body composition, medication use, hypertension, diabetes, or family history of eye disease at baseline
VandenLangenberg *et al.,* 1998 (Nutritional Factors in Eye Disease Study, a subset of the Beaver Dam Eye Study)	Cross-sectional	16/24	66.7	Diet	Incident early ARM (large drusen, pigmentary abnormalities)	• Analysis did not account for colinearity of intake of total fat, individual/total carotenoids or other antioxidants with L/Z intakes • Statistical models did not adjust/account for body composition, hyperlipidemia/hypercholesterolemia, or family history of eye disease, the difference in dropout rates and reasons among groups, or the time period of assessment

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Mares-Perlman *et al.,* 2001 (NHANES III)	Cross-sectional	15/21	71.4	Serum	Prevalent early and late ARM	• Study did not assess serum levels prospectively • Power calculations were not performed • Analysis did not account for supplement use • Statistical models did not adjust/account for sunlight exposure or family history of eye disease • Blinding of outcome assessors not reported
		18/24	75.0	Diet		• Study did not assess intakes prospectively • Power calculations were not performed • Analysis did not account for supplement use • Statistical models did not adjust/account for sunlight exposure or family history of eye disease • Blinding of outcome assessors not reported
van Leeuwen *et al.,* 2005 (The Rotterdam Study)	Prospective cohort	19/27	70.4	Diet	Incident early and late ARM	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat with L/Z intakes • Statistical models did not adjust/account for sunlight exposure, medication use, hyperlipidemia/ hypercholesterolemia, family history of eye disease • Dietary intakes were not assessed repeatedly • Time period of assessment not accounted for
Dasch *et al.,* 2005 (MARS)	Case-control	16/25	64.0	Serum	Prevalent early and late ARM	• Study did not assess serum levels prospectively • Analysis did not account for colinearity of serum levels of individual/total carotenoids with serum L/Z levels • Statistical models did not adjust/account for alcohol intake, sunlight exposure, medication use, hypertension, diabetes, or family history of eye disease at baseline • Blinding of outcome assessors not reported

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Simonelli *et al.,* 2002	Case-control	16/26	61.5	Serum	Prevalent early and late ARM	• Study did not assess serum levels prospectively • Power calculations were not performed • Baseline characteristics of subjects were not reported • Analysis did not account for colinearity of serum levels of individual/total carotenoids and other antioxidants with serum L/Z levels • Study did not account for supplement use • Statistical models did not adjust/account for BMI, medication use, or family history of eye disease • Blinding of outcome assessors not reported
Gale *et al.,* 2003 (subset of MRC study participants)	Cross-sectional	14/22	63.6	Plasma	Prevalent early and late ARM	• Study did not assess plasma levels prospectively • Power calculations were not performed • Study did not account for supplement use • Statistical models did not adjust/account for sunlight exposure, medication use, hypertension, or family history of eye disease • Unknown if outcome assessors blinded to exposure status
Bernstein *et al.,* 2002	Case-control	14/24	58.3	MPOD	Prevalent ARMD	• Study did not assess MPOD prospectively • Power calculations were not performed • Statistical models did not adjust/account for body composition, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, or family history of eye disease at baseline
Cardinault *et al.,* 2005	Case-control	15/24	62.5	Serum	Prevalent early and late ARM	• Study did not assess serum levels prospectively • Power calculations were not performed • Analysis did not account for supplement use • Statistical models did not adjust/account for body composition, alcohol intake, iris color, sunlight exposure, diabetes, or family history of eye disease at baseline

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Sanders *et al.,* 1993	Case-control	13/22	59.1	Plasma	Prevalent ARM	• Study did not assess plasma levels prospectively • Statistical models did not adjust/account for body composition, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, or family history of eye disease
Snellen *et al.,* 2002	Case-control	14/25	56.0	Diet	Prevalent neovascular ARMD	• Study did not assess intakes prospectively • Power calculations were not performed • Analysis did not account for colinearity of intake of total fat, individual/total carotenoids, other antioxidants, or supplement use with L/Z intakes • Statistical models did not adjust/account for body composition, alcohol intake, medication use, hypertension, or hyperlipidemia/hypercholesterolemia
Beatty *et al.,* 2001	Case-control	12/24	50.0	MPOD, diet	Prevalent ARMD	• Study did not assess iMPOD/ntakes prospectively • Power calculations were not performed • Subjects' inclusion and exclusion criteria not specified • Selection of controls from the source of population of the cases not specified • Statistical models did not adjust/account for body composition, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia or family history of eye disease at baseline
Robman *et al.,* 2007	Retrospective longitudinal cohort	12/26	46.2	Diet	ARM progression	• Power calculations were not performed • Analysis did not account for colinearity of intake of total fat, individual/total carotenoids, other antioxidants, or supplement use with L/Z intakes • Statistical models did not adjust/account for gender, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, or hyperlipidemia/hypercholesterolemia • Tissue levels/dietary intakes not assessed

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
						repeatedly • Dropout rates and reasons similar among groups not reported
Obana *et al.,* 2008	Case-control	10/25	40.0	MPOD	Prevalent early and late ARM	• Study did not assess MPOD prospectively • Power calculations were not performed • Unknown if controls selected from the source of population of the cases • Study did not account for supplement use • Statistical models did not adjust/account for body composition, smoking status, alcohol intake, iris color, sunlight exposure, medication use, hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Unknown if outcome assessors blinded to exposure status • Details on statistical methods not provided
Ciulla and Hammond, 2004	Cross-sectional	8/20	40.0	MPOD	Prevalent ARMD	• Study did not assess MPOD prospectively • Power calculations were not performed • Study did not account for supplement use • Statistical models did not account/adjust for gender, body composition, smoking status, alcohol intake, iris color, sunlight exposure, medication use, hyperlipidemia/hypercholesterolemia, or family history of eye disease

Table 1.8-2 Quality Scores for Studies Assessing ARM/ARMD as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Bone *et al.,* 2001	Case-control	10/23	43.5	MPOD	Prevalent ARMD	• Study did not assess MPOD prospectively • Power calculations were not performed • Definition of cases not explicit and condition of cases not reliably assessed and validated • Statistical models did not adjust/account for body composition, smoking status, alcohol intake, iris color, sunlight exposure, medication use, hypertension, hyperlipidemia/hypercholesterolemia, family history of eye disease

Abbreviations: AREDS, Age-Related Eye Disease Study; ARM, age-related maculopathy; ARMD, age-related macular degeneration; BMES, Blue Mountain Eye Study; CAREDS, Carotenoids in Age-Related Eye Disease Study; CHARM, Cardiovascular Health and Age-Related Maculopathy Study; L/Z, lutein/zeaxanthin; MARS, Muenster Aging and Retina Study; MPOD, macular pigment optical density; MRC, Medical Research Council; POLA, Pathologies Oculaires Liées à l'Age; NHANES III, Third National Health and Nutrition Examination Survey; VIP, Visual Impairment Project; WHI, Women's Health Initiative.

[1] Studies with a quality score ≥60% were defined as having high methodological quality compared to studies with a quality scores <60%.

[2] Although results from the Eye Disease Case-Control Study Group were reported separately, the same cohort and study design were used in both of these studies, and the only variable that differed is Seddon *et al.* (1994) presented results on dietary intakes of lutein and zeaxanthin, while the 1993 publication presented results on serum levels of lutein and zeaxanthin. Thus, these 2 publications were counted as 1 study.

Table 1.8-3 Quality Scores for Studies Assessing Visual Performance as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Richer *et al.,* 2004	Randomized, double-blind, placebo-controlled	26/33	78.8	MPOD	Visual acuity, glare recovery, contrast sensitivity	• Statistical models did not adjust/account for sunlight exposure, hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Background diet analysis did not account for total fat or other antioxidants • Analysis did not include an intention to treat analysis
Rosenthal *et al.*, 2006	Uncontrolled intervention	19/32	59.4	Serum lutein/ zeaxanthin	Visual acuity	• Placebo group not included • Blinding of subjects not reported • Power calculations not performed • Statistical models did not adjust/account for iris color, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, family history of eye disease, or intake of total fat • Intention to treat analysis not included • Subjects completing the study were not compared with those who did not
Olmedilla *et al.,* 2003	Randomized, double-blind, placebo-controlled	14/29	48.3	None	Visual acuity, glare sensitivity	• Power calculations were not performed • Statistical models did not adjust/account for age, gender, body composition, smoking status, alcohol intake, sunlight exposure, medication use, hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Background diet analysis did not account for total fat, individual carotenoids, or other antioxidants • Analysis did not include an intention to treat analysis • Subjects completing the study are not compared with those who did not

Table 1.8-3 Quality Scores for Studies Assessing Visual Performance as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Stringham and Hammond, 2008	Uncontrolled intervention	8/28	28.6%	MPOD	Glare sensitivity and photostress recovery	• Placebo group not included • Blinding of outcome assessors not reported • Power calculations not performed • Statistical models did not adjust/account for body composition, smoking status, alcohol intake, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, family history of eye disease, or intake of individual/total carotenoids, other antioxidants, total fat, or supplement use • Compliance of subjects with intervention not reported • Insufficient detail provided in description of statistical methods • Intention to treat analysis not included • Adverse events not reported
Kvansakul *et al.,* 2006 (the Visual Performance Study- including a subset of participants from the Lutein Zeaxanthin Eye Accumulation trial)	Intervention	8/31	25.8	MPOD	Contrast, acuity, wavefront aberration, light scatter	• Detail provided in description of placebo not sufficient • Power calculations were not performed • Baseline levels of outcome variable in question not accounted for • Statistical models did not adjust/account for smoking status, alcohol intake, iris color, sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Background diet analysis did not account for total fat, individual/total carotenoids, other antioxidants, or supplement use • Compliance of subjects with the intervention not reported • Detail provided in description of statistical methods not sufficient • Analysis did not include an intention to treat analysis • Adverse events not reported • Subject attrition not numerically accounted for • Reasons for subject attrition not provided • Subjects completing the study were not compared with those that did not

Table 1.8-3 Quality Scores for Studies Assessing Visual Performance as an Outcome[1]

Reference	Study Design	Score		Biomarkers		Methodological Limitations
		Absolute	%	Exposure	Outcome	
Olmedilla *et al.*, 2001	Intervention	7/28	25.0	Serum lutein	Visual acuity, glare sensitivity	• Placebo group not included • Not randomized • Subjects and outcome assessors not blinded • Power calculations were not performed • Statistical models did not adjust/account for age, gender, body composition, alcohol intake, iris color, sunlight exposure, hypertension, hyperlipidemia/hypercholesterolemia, or family history of eye disease • Background diet analysis did not account for total fat, individual/total carotenoids, or other antioxidants • Compliance of subjects with intervention not reported • Analysis did not include an intention to treat analysis • Subject attrition, reason for subject attrition, and comparison of subjects completing the study with those that did not were not reported

[1] Studies with a quality score ≥60% were defined as having high methodological quality compared to studies with a quality scores <60%.

1.9 Evaluation of Totality of Evidence – Overview

For a claimed effect to be valid, the relationship between the food/constituent and the claimed effect must be demonstrated to be causal (*i.e.,* consumption of "X "leads to "Y", where "X" is lutein and zeaxanthin and "Y" is reduced risk of cataract or ARMD or enhanced visual performance). In the demonstration of causality, several causality criteria are required to be satisfied, including those listed in Table 1.9-1 (U.S. FDA, 1999 http://www.cfsan.fda.gov/~dms/SSAguide.html#totality).

The totality of evidence regarding the association between lutein and zeaxanthin and risk of cataract and ARMD is presented in Sections 1.10 and 2.0, respectively. In Section 3.0, the totality of evidence regarding the roles of lutein and zeaxanthin in enhancing visual performance is reviewed. In Section 4.0, the totality of evidence is summarized, and implications regarding the proposed GRAS amendment are discussed.

Table 1.9-1 Causality Criteria

Consistency	Similar results are reported in different studies by different investigators
Magnitude of effect and statistical significance	Alteration in risk should be biologically significant; statistically significant relationships between the variables of interest should be demonstrated
Opposing/neutral evidence	Corroborating evidence must be greater than opposing or neutral evidence
Dose-response	Increases in the consumption of the food/constituent are accompanied by increases in the magnitude of the claimed effect
Temporality	The exposure must precede the claimed effect
Effect of dechallenge	The claimed effect is lost once the food/constituent is no longer consumed
Specificity of effect and alternative explanations	Assurance that the claimed effect is, indeed, due to lutein and zeaxanthin; alternative explanations for the claimed effect (due to uncontrolled confounding or other methodological artifacts) should be ruled out
Biological plausibility[1]	Potential mechanistic explanations for the cause-effect relationship should be presented

[1] The reader is referred to Section 1.1.3 for a review of the biological mechanisms proposed for the roles of lutein and zeaxanthin in reducing the risk of age-related cataract, reducing the risk of ARMD, and improving measures of visual performance.

1.10 Evaluation of Totality of Evidence – Age-Related Cataract

1.10.1 Overview

Nineteen observational studies (reported in 21 publications) evaluated the relationship between dietary intakes/circulating levels of lutein and/or zeaxanthin and risk of cataract (Table 1.10.1-1). Of the 19 studies, 13 (68.4%) were considered to have good methodological quality (*i.e.,* quality score ≥60%), while 6 (31.6%) were considered to have poor methodological quality (*i.e.,* quality score <60%). Results from all 19 studies are summarized in Table 1.10.1-1; however, the

discussion on totality of evidence is based only on the 13 studies considered to have good methodological quality.

Of the 13 studies with good methodological quality, 5 studies (38.5%) were based on populations made up exclusively of women (the Nurses' Health Study, the Nutrition and Vision Project, the Women's Health Study, and the Carotenoids in Age-Related Eye Disease Study); 1 study (7.7%) was based on a cohort made up exclusively of men (the Health Professionals' Follow-up Study); and 7 studies (53.8%) were based on populations that included both men and women, including 2 from the Nutritional Factors in Eye Disease Study; 1 case-control study (Valero *et al.,* 2002); and 4 cross-sectional studies (Gale *et al.,* 2001; Delcourt *et al.,* 2006; Vu *et al.,* 2006; Dherani *et al.,* 2008). Of the 13 studies, 8 (61.5%) were conducted in the U.S.; 3 (23.1%) in Europe; 1 (7.7%) in Australia; and 1 (7.7%) in India. Given that the majority of data collected were from U.S. populations, the results are generalizable to the U.S. population.

Of the 13 observational studies with good methodological quality, 7 (53.8%) assessed risk of cataract as a function of dietary intakes of lutein+zeaxanthin; 4 (30.8%) assessed risk of cataract as a function of circulating levels of lutein and/or zeaxanthin; 1 (7.7%) assessed risk of cataract as a function of either dietary intakes or circulating levels of lutein+zeaxanthin; and 1 (7.7%) assessed risk of cataract as a function of either dietary intakes or circulating levels of lutein+zeaxanthin or MPOD. Thus, study findings were evaluated according to the biomarker of lutein and zeaxanthin status assessed (*i.e.,* dietary intakes, circulating levels, or MPOD).

If a study assessed more than 1 outcome (*e.g.,* nuclear cataract, subcapsular cataract, cortical cataract, and/or any cataract type), or more than one subgroup within the study (*e.g.,* males *vs.* females; young *vs.* old), it was considered to support a significant reduction in risk of cataract with increased status of lutein and/or zeaxanthin if significant inverse associations were reported for at least 1 outcome measure in at least 1 subgroup. The level of significance was set at $P<0.05$. The study was considered to support a significant reduction in risk of cataract with increased status of lutein and/or zeaxanthin if it reported a significant inverse trend, significantly lower levels in cases *versus* controls, or a significant reduction in cataract risk in 1 category of lutein and/or zeaxanthin status *versus* the lowest category of lutein and/or zeaxanthin status.

The totality of evidence in support of each causality criteria was rated as follows:

- "very low", if the proportion of studies in support of the causality criteria was ≤50%;
- "low", if the proportion of studies in support of the causality criteria was 51 to 60%;
- "moderate", if the proportion of studies in support of the causality criteria was 61 to 80%; or,
- "high", if the proportion of studies in support of the causality criteria was >80%.

A causality criterion was considered to be established if the proportion of studies in support of that criterion was either moderate or high.

Table 1.10.1-1 Studies Assessing the Relationship Between Lutein/Zeaxanthin and Risk of Cataract[1]

Country of Study	Type of Study	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
Spain	Case-control	No significant association	343 subjects with cataracts aged ≥55 years and 334 matched controls[2]	NA	Diet	Prevalent nuclear, subcapsular, or cortical cataract	85.2%	Valero *et al.,* 2002
Australia (Melbourne VIP)	Cross-sectional	Significant inverse association	2,322 subjects participating in the 5-year follow-up FFQ (no FFQ at baseline) aged ≥45 years	NA	Diet	Prevalent nuclear, subcapsular, or cortical cataract	84.0%	Vu *et al.,* 2006
U.S. CAREDS	Retrospective (Associations with MPOD were cross-sectional)	Significant inverse association	1,802 women aged 50-79 years residing in Iowa, Wisconsin, and Oregon with lutein and zeaxanthin intakes above the 78th and below the 28th percentile at baseline in the WHI Observational Study were recruited 4-7 years later into the CAREDS	NA	Diet	Prevalent nuclear cataract, severe nuclear sclerosis	82.3%	Moeller *et al.,* 2008
		Significant inverse association			Serum			
		No significant association			MPOD			
U.S. (Nutritional Factors in Eye Disease Study)	Retrospective	Significant inverse association	1,919 (859 females and 1,060 males aged 43-86 years) participating in the Nutritional Factors in Eye Disease Study, a 50% random sample of the non-institutionalized participants of the Beaver Dam Eye Study	NA (study assessed food intake retrospectively, 10 years prior to baseline lens assessment in 1988-1990)	Diet	Prevalent nuclear lens opacity	52.2%	Mares-Perlman *et al.,* 1995a
U.S. (Nutritional Factors in Eye Disease Study)	Cross-sectional	Significant positive association	400 subjects aged 50-86 years randomly selected from the Nutritional Factors in Eye Disease Study, a cohort nested in the Beaver Dam Eye Study	NA	Serum	Severity of nuclear and cortical lens opacity	73.9%	Mares-Perlman *et al.,* 1995b

Table 1.10.1-1 Studies Assessing the Relationship Between Lutein/Zeaxanthin and Risk of Cataract[1]

Country of Study	Type of Study	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S. (Nutritional Factors in Eye Disease Study)	Cross-sectional	Significant inverse association	1,354 subjects aged 43-84 years participating in the Nutritional Factors in Eye Disease Study, a sub-set of the Beaver dam Eye Study	5 years (1988-1990 to 1993-1995)	Diet	Incident nuclear cataract	64.0%	Lyle *et al.,* 1999b (pg. 802)[3]
		No significant association	325 adults ≥50 years of age at baseline randomly sampled from the Nutritional Factors in Eye Disease Study, a sub-set of the Beaver dam Eye Study	5 years (1988-1990 to 1993-1995)	Serum		85.7%	Lyle *et al.,* 1999a (p. 272)[3]
U.S. (Nurses' Health Study)	Prospective cohort	Significant inverse association	Nurses' Health Study (77,466 female nurses aged 45-71 years at baseline)	12 years (1980-1992)	Diet	Incident cataract extraction (cortical, nuclear, posterior subcapsular)	68.2%	Chasan-Taber *et al.,* 1999
U.S. (Nutrition and Vision Project)	Cross-sectional	Significant inverse association	478 non-diabetic women aged 53-73 years from the Boston, Mass., area participating in the Nutrition and Vision Project, a cross-section of the Nurses' Health Study	13-15 years	Diet	Prevalent nuclear lens opacity	80.7%	Jacques *et al.,* 2001[4]
		No significant association	492 non-diabetic female nurses aged 54-73 years from the Boston, Mass., area participating in the Nutrition and Vision Project, a cross-section of the Nurses' Health Study	13-15 years	Diet	Prevalent cortical and subcapsular lens opacity	77.8%	Taylor *et al.,* 2002[4]
U.S. (Nutrition and Vision Project)	Cross-sectional	No significant association	408 female nurses aged 54-73 years from the Boston, Mass., area participating in the Nutrition and Vision Project, a prospective cross-section of the Nurses' Health Study	13-15 years	Diet	Change in nuclear opacification from baseline	76.9%	Jacques *et al.,* 2005
U.S. (WHS)	Prospective cohort	Significant inverse association	35,551 healthy female health professionals aged ≥45 years and free of cataract at baseline	10 years	Diet	Incident cataract	73.1%	Christen *et al.,* 2008

Table 1.10.1-1 Studies Assessing the Relationship Between Lutein/Zeaxanthin and Risk of Cataract[1]

Country of Study	Type of Study	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S. (Health Professionals' Follow-up Study)	Prospective Cohort	Significant inverse association	U.S. Male Health Professional' Study (36,644 male health professionals aged 45-75 years at baseline)	8 years (1986-1994)	Diet	Incident cataract extraction (cortical, nuclear, posterior subcapsular)	64.0%	Brown *et al.,* 1999
India	Cross-sectional	Significant inverse association	1,112 males and females ≥50 years and residing in 1 of 11 villages in a rural peri-urban region of Balbagarh, Faridabad district	NA	Serum[5]	Prevalent nuclear, subcapsular, or cortical cataract	60.9%	Dherani *et al.,* 2008
France (The POLA Study)	Cross-sectional	Significant inverse association	815 males and females ≥60 years and residing in Sète (southern France)	NA	Plasma[6]	Prevalent nuclear, subcapsular, or cortical cataract	73.9%	Delcourt *et al.,* 2006
U.K. (subset of MRC study participants)	Cross-sectional	Significant inverse association	200 males and 172 females aged 66-75 years who had participated in one of the MRC studies in Sheffield, England	NA	Plasma[5]	Prevalent cataract (cortical, nuclear, posterior subcapsular)	68.2%	Gale *et al.,* 2001
Spain	Case-control	Significant inverse association	177 institutionalized elderly (61 males and 116 females aged ≥65 years)	NA	Diet	Prevalent cataract	55.5%	Rodríguez-Rodríguez *et al.,* 2006
U.S. (Harvard Cooperative Program on Aging)	Cross-sectional	Significant inverse association	7 young females (aged 24-36 years) and 5 males (aged 24-31 years) and 23 older females (aged 55 to 78 years) and 16 older males (aged 48-82 years); all healthy	NA	MPOD	Lens optical density	54.5%	Hammond *et al.,* 1997a
The Netherlands	Cross-sectional	Significant inverse association	376 subjects (177 males and 199 females) aged 18-75 years	NA	Serum, MPOD	Lens optical density	52.4%	Berendschot *et al.,* 2002

Table 1.10.1-1 Studies Assessing the Relationship Between Lutein/Zeaxanthin and Risk of Cataract[1]

Country of Study	Type of Study	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S.	Cross-sectional	No significant association	29 elderly subjects with varying levels of lenticular opacities (considered "normal") and 22 elderly subjects with cataracts severe enough to require extraction	NA	MPOD	Severe cataract[7]	40.0%	Ciulla and Hammond, 2004
Spain	Case-control	Significant positive association	248 hospital outpatients (97 males and 150 females aged 70±10.6 years)	N/A	Serum	Prevalent cataract	38.5%	Olmedilla *et al.,* 2002

Abbreviations: CAREDS, Carotenoids in Age-Related Eye Disease Study; L/Z, lutein/zeaxanthin; MPOD, macular pigment optical density; MRC, Medical Research Council; POLA, Pathologies Oculaires Liées à l'Age; VIP, Visual Impairment Project; WHS, Women's Health Study.

[1] Studies with a quality score ≥60% were considered to have good methodological quality, while studies with a quality score <60% were considered to have poor methodological quality. Studies with poor methodological quality (*i.e.,* shaded studies) were not considered in the evaluation of totality of evidence.

[2] Almost 10% of control subjects had ARMD.

[3] Although results from the Nutritional Factors in Eye Disease Study (a cohort nested in the Beaver Dam Eye Study) were reported separately, the same cohort and study design were used in both of these studies, and the only variable that differed is that Lyle *et al.* (1999b) presented results on dietary intakes of lutein and zeaxanthin, while Lyle *et al.* (1999a) presented results on serum levels of lutein and zeaxanthin. Thus, these 2 publications were counted as 1 study.

[4] Although results from the Nutrition and Vision Project were published separately, the same cohort and study design were used in both of these studies, and the only variable that differed was that Jacques *et al.* (2001) presented results on nuclear cataract, while Taylor *et al.* (2002) presented results on cortical or posterior subcapsular cataract. Thus, these two publications were considered as 1 study.

[5] Cataract risk was assessed as a function of lutein or zeaxanthin.

[6] Cataract risk was assessed as a function of lutein, zeaxanthin, and lutein+zeaxanthin.

[7] It should be noted that MPOD was also assessed in 59 elderly subjects with nonexudative AMD, and statistical analyses were conducted by t-tests as opposed to analysis of variance.

1.10.2 Consistency

1.10.2.1 Dietary Intakes of Lutein+Zeaxanthin and Risk of Cataract

Of the 9 studies assessing the relationship between dietary intakes of lutein+zeaxanthin and risk of cataract, 7 (77.8%) reported a significant reduction in risk of cataract with increased intake of lutein+zeaxanthin (Brown *et al.,* 1999; Chasan-Taber *et al.,* 1999; Lyle *et al.,* 1999b; Jacques *et al.,* 2001; Vu *et al.,* 2006; Christen *et al.,* 2008; Moeller *et al.,* 2008) and 2 (22.2%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of cataract (Valero *et al.,* 2002; Jacques *et al.,* 2005).

With 7/9 (77.8%) studies reporting a statistically significant reduction in risk of cataract with increased intakes of lutein+zeaxanthin, there is moderate agreement that the evidence in favor of the claimed effect is consistent.

1.10.2.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of Cataract

Of the 6 studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of cataract, 4 (66.7%) reported a significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin (Gale *et al.,* 2001; Delcourt *et al.,* 2006; Dherani *et al.,* 2008; Moeller *et al.,* 2008) and 2 (33.3%) reported no significant associations between circulating levels of lutein and/or zeaxanthin and risk of cataract (Mares-Perlman *et al.,* 1995b; Lyle *et al.,* 1999a).

With 4/6 (66.7%) studies reporting a statistically significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin, there is moderate agreement that the evidence in favor of the claimed effect is consistent.

1.10.2.3 MPOD and Risk of Cataract

The one study assessing the relationship between risk of cataract and MPOD reported no significant associations (Moeller *et al.,* 2008). Given the limited number of studies assessing cataract risk as a function of MPOD, the consistency of the evidence in favor of the claimed effect could not be evaluated.

1.10.2.4 Overall Conclusions on Consistency

Cataract risk was assessed as a function of dietary intakes of lutein+zeaxanthin in 9 studies; as a function of circulating levels of lutein and/or zeaxanthin in 6 studies; and as a function of MPOD in one study. With 7/9 studies (77.8%) reporting a significant reduction in risk of cataract with increased intake of lutein and zeaxanthin, there is moderate agreement that the evidence in favor of the claimed effect is consistent. Likewise, with 4/6 (66.7%) studies reporting a

significant decrease in risk of cataract with increased circulating levels of lutein and/or zeaxanthin, there is moderate agreement that the evidence in favor of the claimed effect is consistent. Because only 1 study assessed the association between MPOD and risk of cataract, the consistency of the evidence in favor of the claimed effect could not be evaluated.

Thus, the totality of evidence is consistent that increased dietary intakes and circulating levels of lutein and/or zeaxanthin are associated with decreased risk of cataract.

1.10.3 Magnitude of Effect and Statistical Significance

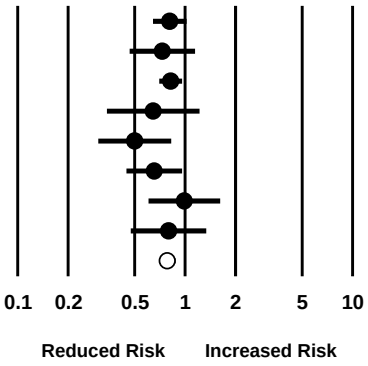
A meta-analysis was conducted on studies considered to have good methodological quality. Because studies used either dietary intakes or circulating levels of lutein and zeaxanthin, separate meta-analyses were conducted for each biomarker of exposure. For prospective cohort studies, the relative risk (RR) or hazards ratio (HR) was used as the measure of the relationship between intake of lutein and zeaxanthin and cataract risk at the highest *versus* the lowest intake/circulating level. For case-control and cross-sectional studies, the odds ratio (OR) was used as a surrogate measure of RR, because the absolute risk of cataract was low in each of the studies, a situation in which the OR should provide an accurate estimate of the RR (Whelton *et al.,* 2004). RRs, HRs, and ORs from each study were transformed by taking the natural logarithm, and the standard error was calculated from the reported confidence intervals. Because the studies identified were conducted in different populations, the random effects model (which assumes that the populations studied differed from each other in ways that could impact risk of cataract) (Borenstein *et al.,* 2007) was chosen.

The pooled estimate for risk of cataract (any type) in subjects with the highest intakes of lutein+zeaxanthin was significantly reduced when the analysis was restricted to prospective cohort studies only and when the analysis was restricted to cross-sectional and case-control studies only; thus, the meta-analysis was conducted with all studies, irrespective of study design. High intakes of lutein+zeaxanthin were associated with a pooled estimate for risk of cataract/cataract extraction of 0.78 [CI, 0.71-0.87; P<0.0001; Figure 1.10.3-1(A)]. High plasma levels of lutein+zeaxanthin, however, were not associated with reduced risk of cataract/cataract surgery [pooled estimate = 0.87; CI, 0.65-1.17; P=0.318; Figure 1.10.3-1(B)]. Moreover, neither plasma levels of lutein, alone, nor zeaxanthin, alone, were associated with reduced risk of cataract (data not shown).

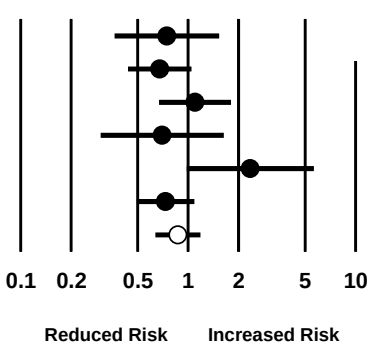
The general observation that dietary intakes of lutein+zeaxanthin, but not circulating levels of lutein and/or zeaxanthin, are associated with reduced risk of cataract indicates that i) Plasma/serum levels of lutein and zeaxanthin may not be indicative of levels available to the retina; ii) Dietary intake estimates of lutein and zeaxanthin reflect chronic/habitual intakes (which may be more relevant to age-related cataract) while serum/plasma levels reflect more recent intakes; or iii) Lutein and zeaxanthin are not causally related to age-related cataract, but are markers of other dietary patterns (Mares-Perlman *et al.,* 2001).

Figure 1.10.3-1 Pooled Estimate of Risk of Cataract/Cataract Extraction for Lutein and Zeaxanthin Intakes (A) or Circulating Levels (B) in the Highest *vs.* Lowest Categories

Study name	Outcome	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Brown et al., 1999	Total cataract extraction	0.810	0.650	1.010	-1.874	0.061
Chasen-Taber et al., 1999	Combined	0.731	0.471	1.136	-1.393	0.164
Christen et al., 2008	Cataract	0.820	0.709	0.949	-2.671	0.008
Jacques et al., 2001	Combined	0.645	0.345	1.206	-1.373	0.170
Lyle et al., 1999b	Nuclear cataract	0.500	0.306	0.816	-2.770	0.006
Moeller et al., 2008	Combined	0.655	0.451	0.949	-2.234	0.026
Valero et al., 2002	Cataract	0.990	0.611	1.603	-0.041	0.967
Vu et al., 2006	Combined	0.797	0.479	1.324	-0.878	0.380
		0.783	0.706	0.867	-4.685	0.000



Study name	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Delcourt et al., 2006	Combined	0.746	0.367	1.516	-0.810	0.418
Dherani et al., 2008	Combined	0.677	0.442	1.036	-1.795	0.073
Gale et al., 2001	Combined	1.099	0.677	1.784	0.382	0.703
Lyle et al., 1999a	Nuclear cataract	0.700	0.303	1.617	-0.835	0.404
Mares-Perlman et al., 1995	Combined	2.353	0.991	5.585	1.940	0.052
Moeller et al., 2008	Combined	0.733	0.499	1.076	-1.585	0.113
		0.869	0.645	1.171	-0.925	0.355



Closed circles represent adjusted risks in each study; open circles represent the pooled estimate of risk. In studies reporting on various subgroups (*e.g.,* male *vs.* female) the study was used as the unit of analysis. In studies reporting risks of several outcomes (*e.g.,* cataract types), the mean of the selected outcomes was used, hence the term "combined". Details on the outcomes evaluated in each study can be found in **Attachment III** to **Appendix E**. Data from Jacques *et al.* (2005) were not published in a form that could be included in the meta-analysis on the relationship between dietary intakes of lutein and zeaxanthin and risk of cataract.

1.10.4 Opposing/Neutral Evidence

1.10.4.1 Dietary Intakes of Lutein+Zeaxanthin and Risk of Cataract

As reviewed in Section 1.10.2.1, 7/9 studies (77.8%) reported a significant reduction in risk of cataract with increased intakes of lutein+zeaxanthin, while 2/9 studies (22.2%) reported no significant associations. A comparison of the observational studies reporting significant inverse associations between dietary intakes of lutein+zeaxanthin and risk of cataract and those not reporting such associations is provided in Table 1.10.4.1-1.

Compared to studies failing to report statistically significant inverse associations between dietary intakes of lutein+zeaxanthin and risk of cataract, those reporting statistically significant inverse associations tended to include larger numbers of subjects, to have study designs that were prospective, and to assess associations with *incidence* of cataract (*i.e.,* the number of newly diagnosed cases of cataract over a specified period of time), as opposed to *prevalence* of cataract (*i.e.,* the proportion of individuals in a population having cataract). Studies assessing associations of lutein+zeaxanthin intakes with prevalent cataract are more subject to recall bias (*i.e.,* inaccurate reporting of dietary intakes), and tend to bias associations away from the null if dietary intakes are collected retrospectively. Although 3/7 (42.9%) studies reporting a significant inverse association between lutein+zeaxanthin intakes and risk of cataract assessed associations with prevalent cataract, dietary intakes were assessed prospectively in 1 of these studies (Jacques *et al.,* 2001), thereby limiting the potential for recall bias.

Table 1.10.4.1-1 Characteristics of Supporting and Non-supporting Studies Assessing Dietary Intake as the Biomarker of Exposure[1]

	Supporting Studies	Non-supporting Studies
Mean number of participants per study[2]	22,232 (range, 478 – 77,466)	543 (range, 408 – 677)
Number/total number of studies	7/9 (77.8%)	2/9 (22.2%)
Proportion of prospective cohort studies	3/7 (42.9%)	0/2 (0%)
Proportion of cross-sectional studies	3/7 (42.9%)	1/2 (50.0%)
Proportion of case-control studies	0/7 (0%)	1/2 (50.0%)
Proportion of retrospective longitudinal studies	1/7 (14.3%)	0/2 (0%)
Proportion of studies assessing prevalence (as opposed to incidence)	3/7 (42.9%)	2/2 (100.0%)

[1] Supporting studies reported significant inverse associations between dietary intakes of lutein+zeaxanthin and risk of cataract, while non-supporting studies did not.
[2] Data from meta-analysis - Calculated by dividing the overall number of subjects by the number of studies.

The 2 non-supporting studies were either case-control (Valero *et al.,* 2002) or cross-sectional (Jacques *et al.,* 2005). Although intakes in the cross-sectional study were assessed prospectively, in the case-control study, dietary intakes were assessed at the time of cataract

assessment. Because cataract develops over several years, it is likely that past intake may be more relevant in the assessment of diet-disease relationships than current intake. Additional limitations of the non-supporting studies are discussed below:

- In the case-control study, Valero *et al.* (2002) reported no significant association between cataract risk and dietary intake of lutein and zeaxanthin. A notable limitation of this study is that nearly 10% of controls had ARMD. Since it is hypothesized that lutein and zeaxanthin intakes are lower in subjects with ARMD, inclusion of these individuals in the control group may have reduced the difference in xanthophyll intakes between cases and controls, lessening the likelihood of a discernible difference.

- In the cross-sectional study by Jacques *et al.* (2005), nuclear opacification was assessed at baseline and after a 5-year follow-up in a cross-section of women (*i.e.,* the Nutrition and Vision Project) who had previously participated in the Nurses' Health Study. No association was observed between dietary intake of lutein and zeaxanthin (as assessed prospectively over 12 years in the Nurses' Health Study) and change in nuclear opacification. Limited statistical power was likely in this study, given that the number of participants at follow-up was reduced by approximately 10% of the original population enrolled in the Nutrition and Vision Project (Jacques *et al.,* 2005). Also, participation bias (*i.e.,* the possibility that subjects experiencing progression in nuclear opacification declined to participate at follow-up) cannot be ruled out. Participation bias would result in associations biased towards the null. Although 42.9% of studies reporting significant inverse associations between lutein+zeaxanthin intakes and risk of cataract were cross-sectional (Table 1.10.4.1-1), all had a greater number of study participants than did the cross-sectional study by Jacques *et al.* (2005).

Overall, studies reporting a significant reduction in risk of cataract with increased intakes of lutein+zeaxanthin were based on larger numbers of subjects, and had better study designs (*i.e.,* included prospective cohorts and assessed incidence as opposed to prevalence of cataract).

1.10.4.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of Cataract

As reviewed in Section 1.10.2.2, 4/6 studies (66.7%) reported a significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin, while 2/6 studies (33.3%) reported no significant inverse associations. A comparison of the observational studies reporting significant inverse associations between circulating levels of lutein and/or zeaxanthin and risk of cataract and those not reporting such associations is provided in Table 1.10.4.2-1.

Compared to studies failing to report statistically significant inverse associations between circulating levels of lutein and/or zeaxanthin and risk of cataract, those reporting statistically significant inverse associations tended to include larger numbers of subjects, to assess

associations with prevalent cataract, and to report associations for lutein and zeaxanthin separately.

Table 1.10.4.2-1 Characteristics of Supporting and Non-supporting Studies Assessing Serum/Plasma as the Biomarker of Exposure[1]

	Supporting Studies	Non-supporting Studies
Mean number of participants per study[2]	1025 (range, 372 – 1,802)	363 (range, 325 – 400)
Number/total number of studies	4/6 (66.7%)	2/6 (33.3%)
Proportion of prospective cohort studies	0/4 (0%)	0/2 (0%)
Proportion of cross-sectional studies	3/4 (75.0%)	2/2 (100.0%)
Proportion of case-control studies	0/4 (0%)	0/2 (0%)
Proportion of retrospective longitudinal studies	1/4 (25.0%)	0/2 (0%)
Proportion of studies assessing prevalence (as opposed to incidence)	4/4 (100.0%)	1/2 (50.0%)
Proportion of studies assessing independent associations with lutein and zeaxanthin	3/4 (75.0%)	0/2 (0%)

[1] Supporting studies reported significant inverse associations between dietary intakes of lutein+zeaxanthin and risk of cataract, while non-supporting studies did not.
[2] Calculated by dividing the overall number of subjects by the number of studies.

Of the 6 studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of cataract, 1 study reported no significant association (Lyle *et al.,* 1999a) while 1 study reported a significant increase in risk of cataract with increased serum levels of lutein (Mares-Perlman *et al.,* 1995b). Both of these studies were based on the Nutritional Factors in Eye Disease Study, with Mares-Perlman *et al.* (1995b) reporting on the associations between circulating levels of lutein at baseline and *prevalent* cataract and Lyle *et al.* (1999a) reporting on associations between circulating levels of lutein and zeaxanthin at baseline and *incident* cataract 5 years later. In the Mares-Perlman *et al.* (1995b) study, which included subjects with pre-existing cataracts, plasma lutein levels may not have been reflective of past intakes, particularly in cataract subjects who may have altered their diets. Nonetheless, 3/4 studies (75.0%) reporting a significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin were similar to the study by Mares-Perlman *et al.* (1995b) in that the studies also were cross-sectional, and the outcome measure also was *prevalent* cataract. The reasons for these discrepancies are not readily apparent. Furthermore, it is unclear why serum levels of lutein and zeaxanthin were not associated with *incident* cataract in the study by Lyle *et al.* (1999a). In this latter study, diet instability would not have been an issue, given that subjects with cataract at baseline were excluded from the analysis at the 5-year follow-up.

An interesting observation in Table 1.10.4.2-1 is that the majority (*i.e.,* 75.0%) of studies reporting a significant reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin assessed relationships with each carotenoid separately. In contrast, the 2

non-supporting studies assessed risk of cataract only as a function of circulating levels of lutein. Of the three studies assessing risk of cataract as a function of either circulating levels of lutein or zeaxanthin, 2 (66.7%) reported significant reductions in cataract risk with increased circulating levels of zeaxanthin but not lutein (Delcourt *et al.,* 2006; Dherani *et al.,* 2008), while 1 (33.3%) reported significant reductions in risk of cataract with increased circulating levels of lutein but not zeaxanthin (Gale *et al.,* 2001). While data are limited, these studies suggest that it may be important to quantify serum levels of lutein and zeaxanthin separately. Nonetheless, there currently is no biological mechanism to support a benefit of zeaxanthin over lutein in the lens (*i.e.,* there is currently no indication that a specific spatial distribution of lutein and zeaxanthin exists in the lens).

1.10.4.3 MPOD and Risk of Cataract

The one study assessing risk of cataract as a function of MPOD did not report a statistically significant reduction in cataract risk in individuals with increased MPOD; nevertheless, in this same study, significant reductions in cataract risk were reported with increased dietary intakes or circulating levels of lutein+zeaxanthin (Moeller *et al.,* 2008). In this study, MPOD was assessed cross-sectionally. MPOD measures may have been affected by confounding due to recent diet change in subjects with known cataracts. Since MPOD is known to increase with increased intakes of lutein and zeaxanthin in approximately 80% of the population (Hammond *et al.,* 1997b; Trieschmann *et al.,* 2007), MPOD assessed cross-sectionally may not reflect MPOD prior to the development of cataract. Alternatively, failure to observe a significant reduction in cataract risk with increased MPOD may indicate that diets rich in lutein and zeaxanthin reflect other measures of diet or lifestyle that protect against cataract.

1.10.5 Dose-response

Ideally, evidence of dose-response should come from human experimental studies; however, human intervention studies assessing the effects of lutein and zeaxanthin supplementation on risk of cataract were not identified. Cataracts develop gradually over one's lifetime, and an intervention trial assessing incident cataract as an outcome variable is likely not feasible (*i.e.,* such a study would have to be long in duration). While lens optical density appears to be a risk factor for age-related cataract (Hammond *et al.,* 1997a; Berendschot *et al.,* 2002), no intervention study was identified in which the effects of lutein/zeaxanthin supplementation on lens optical density were evaluated. In the absence of human intervention studies, there *is no definitive evidence* of a dose-response relationship between intake of lutein and zeaxanthin and risk of cataract. In observational studies, trends that are reported to be significant only *suggest* that reductions in risk of cataract may be dose-dependently influenced by intakes of lutein and zeaxanthin.

1.10.5.1 Intakes of Lutein+Zeaxanthin and Risk of Cataract

Of the 9 studies assessing risk of cataract as a function of lutein+zeaxanthin intakes, dose responses were assessed in all 9 studies. Of these 9 studies 6 (66.7%) reported significant inverse trends (Brown *et al.,* 1999; Chasan-Taber *et al.,* 1999; Lyle *et al.,* 1999b; Vu *et al.,* 2006; Christen *et al.,* 2008; Moeller *et al.,* 2008), while 3 studies (33.3%) did not report significant inverse trends (Jacques *et al.,* 2001; Valero *et al.,* 2002; Jacques *et al.,* 2005). Significant inverse trends are presented in Figure 1.10.5.1-1.

With 6/9 studies (66.7%) reporting a significant and dose-dependent reduction in risk of cataract with increased intakes of lutein+zeaxanthin, there is moderate agreement that the relationship is dose-dependent.

1.10.5.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of Cataract

Of the 6 studies assessing risk of cataract as a function of circulating levels of lutein and/or zeaxanthin, dose-responses were assessed in all 6 studies. Of these 6 studies, 4 (66.7%) reported significant inverse trends (Gale *et al.,* 2001; Delcourt *et al.,* 2006; Dherani *et al.,* 2008; Moeller *et al.,* 2008), while 2 studies (33.3%) reported no significant inverse trends (Mares-Perlman *et al.,* 1995b; Lyle *et al.,* 1999a). Significant inverse trends are presented in Figure 1.10.5.1-2.

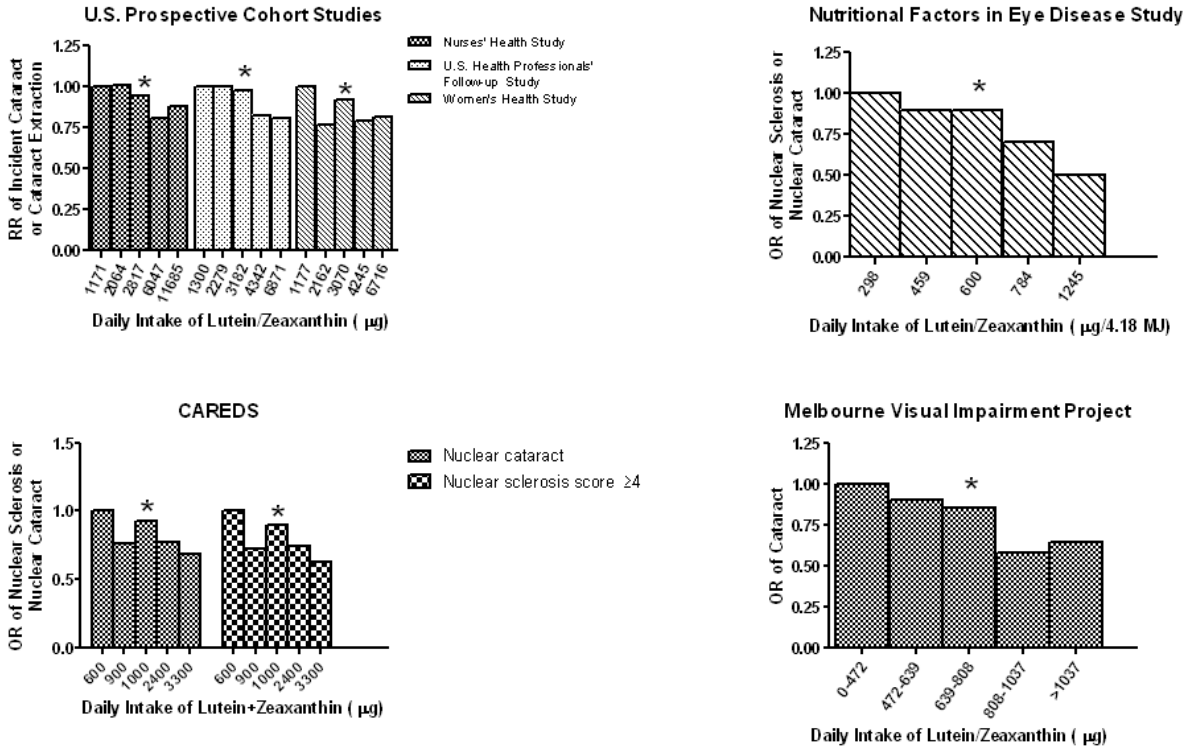
With 4/6 studies (66.7%) reporting a significant and dose-dependent reduction in risk of cataract with increased circulating levels of lutein and/or zeaxanthin, there is moderate agreement that the relationship is dose-dependent.

1.10.5.3 MPOD and Risk of Cataract

In the 1 study assessing cataract risk as a function of MPOD, no significant inverse trend between MPOD and cataract risk was observed (Moeller *et al.,* 2008). Because MPOD was assessed cross-sectionally in this study, additional studies are required to understand whether MPOD early in life is associated with cataract risk later on in life, and whether the relationship is dose-dependent.

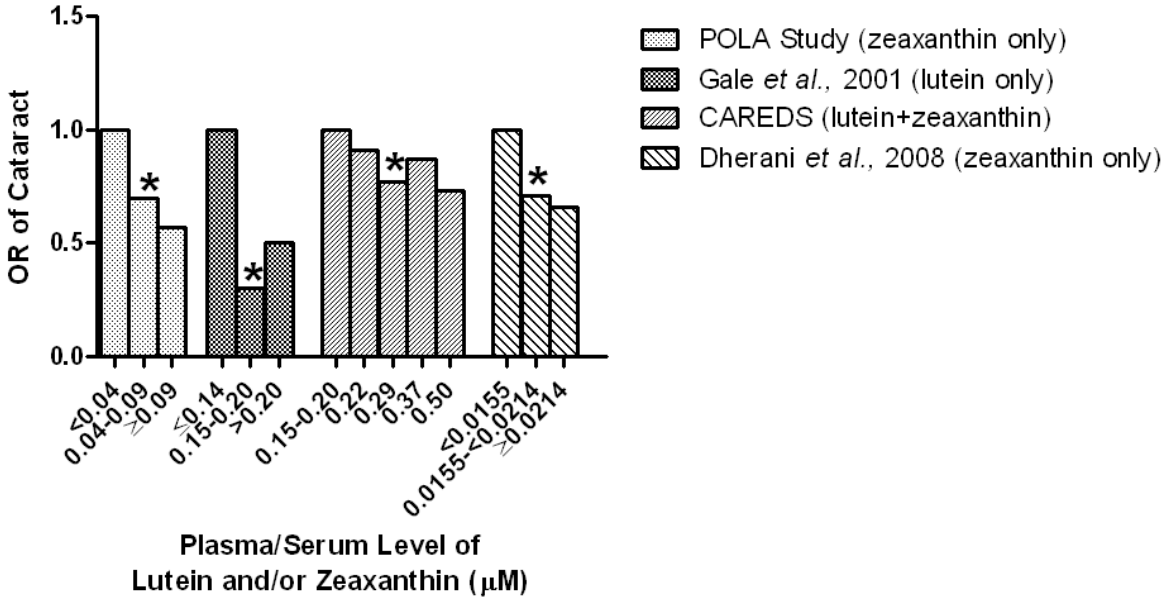
With 0 studies reporting a significant and dose-dependent reduction in risk of cataract with increased MPOD, there is very low agreement that the relationship is dose-dependent.

Figure 1.10.5.1-1 Risk of Cataract as a Function of Lutein and Zeaxanthin Intakes



U.S. prospective cohort studies, including the Nurses' Health Study (Chasan-Taber *et al.,* 1999), the Health Professionals' Follow-up Study (Brown *et al.,* 1999), and the Women's Health Study (Christen *et al.,* 2008) reported decreased risk of cataract or cataract extraction with increasing intake of lutein and zeaxanthin. In the Nutritional Factors in Eye Disease Study, which was nested in the Beaver Dam Eye Study, a significant inverse trend was reported between intake of lutein and zeaxanthin in the distant past and risk of nuclear cataract (Lyle *et al.,* 1996). In the CAREDS, risk of nuclear cataract and nuclear sclerosis was significantly and inversely associated with intakes of lutein+zeaxanthin (Moeller *et al.,* 2008). In a cross-sectional study (the Melbourne Visual Impairment Project; Vu *et al.,* 2006), risk of nuclear cataract was significantly reduced with increasing intake of lutein and zeaxanthin.
* indicates trend was significant (P<0.05).
Abbreviations: CAREDS, Carotenoids in the Age-Related Eye Disease Study; OR, odds ratio; RR, relative risk.

Figure 1.10.5.1-2 Risk of Cataract as a Function of Circulating Levels of Lutein and/or Zeaxanthin



In all studies, the OR of cataract was significantly reduced with increased quintile or tertile of serum/plasma lutein and/or zeaxanthin. Studies were either cross-sectional (Gale *et al.,* 2001; the POLA Study; Dherani *et al.,* 2008) or retrospective (CAREDS). Cataract types that were significantly and inversely associated with plasma/serum levels of lutein and/or zeaxanthin include nuclear or any cataract type (POLA, Delcourt *et al.,* 2006; Dherani *et al.,* 2008); nuclear cataract (CAREDS; Moeller *et al.,* 2008); posterior subcapsular cataract (Gale *et al.,* 2001); and any cataract (Dherani *et al.,* 2008)
* indicates trend was significant (P<0.05).
Abbreviations: CAREDS, Carotenoids in Age-Related Eye Disease Study; OR, odds ratio; POLA, Pathologies Oculaires Liées à l'Age.

1.10.6 Temporality

To satisfy the causality criteria, temporality, it must be demonstrated that exposure to the food/constituent precedes the claimed effect. Again, human intervention trials are required to demonstrate temporality, but such trials were not identified with cataract or lens optical density as an outcome variable.

1.10.6.1 Intakes of Lutein+Zeaxanthin and Risk of Cataract

Of the 9 studies assessing the relationship between dietary intakes of lutein+zeaxanthin and cataract risk, 6 had study designs that permitted assessment of temporality (*i.e.,* intakes of lutein+zeaxanthin were assessed *prior to* the assessment of incident cataract). Of these 6 studies, 5 (83.3%) support temporality [The Health Professionals' Follow-up Study (Brown *et al.,* 1999); The Nutritional Factors in Eye Disease Study (Lyle *et al.,* 1999b); The Nurses' Health

Study (Chasan-Taber *et al.,* 1999); The Nutrition and Vision Project (Jacques *et al.,* 2005); The Women's Health Study (Christen *et al.,* 2008)]; while 1 (16.7%) does not support temporality [The Nutrition and Vision Project (Jacques *et al.,* 2005)].

With 5/6 studies (83.3%) suggesting that intakes of lutein+zeaxanthin earlier in life are associated with reduced risk of cataract later on in life, there is very high agreement that the relationship is temporal. Verification of temporality requires the conduct of well-controlled human intervention trials.

1.10.6.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of Cataract

Of the 6 studies assessing risk of cataract as a function of circulating levels of lutein and/or zeaxanthin, 1 had a study design that permitted assessment of temporality (Lyle *et al.,* 1999a). In this study, circulating levels of lutein at baseline were not associated with incident cataract 5 years later.

With 0 studies supporting a temporal relationship between circulating levels of lutein and zeaxanthin and risk of cataract, there is very low agreement that the relationship is temporal.

1.10.6.3 MPOD and Risk of Cataract

The one study assessing the relationship between MPOD and cataract risk was cross-sectional and was not designed to permit an assessment of temporality. Additional studies are required to determine whether MPOD earlier in life is associated with risk of cataract later on in life.

1.10.7 Effect of Dechallenge

Human intervention studies are required to demonstrate a reversal or cessation of effects upon discontinuation of supplementation. Human intervention studies assessing the effects of lutein and zeaxanthin supplementation on lens optical density or cataract risk were not identified, and so this causality criterion cannot be supported by the available literature.

1.10.8 Specificity of Effect and Alternative Explanations

The demonstration of specificity of effect requires evidence that reduced risk of cataract is related *specifically* to intakes of lutein and zeaxanthin, and not to some other variable that is correlated with intakes of lutein and zeaxanthin. When the subject of a claimed effect is a specific component of foods rather than a category of foods (such as fruits and vegetables), the demonstration of specificity of effect can only be accomplished using controlled human intervention trials. In the absence of controlled human intervention trials, specificity of effect can only be *suggested* by human observational studies, so long as intake estimates are accurate, outcomes are validated, and potential confounding variables (*i.e.,* covariates or alternative explanations) were appropriately controlled for. Although outcome (*i.e.,* cataract) was validated

in all observational studies identified (*i.e.,* by either direct ophthalmologic examination or by review of medical records), intake estimates were determined not to be accurate, and potential confounding variables were found to be insufficiently accounted for. In addition, observational studies are associated with several methodological shortcomings, which limit interpretation of study findings. Thus, for these reasons, which are discussed in detail below, specificity of effect cannot be supported by any of the observational studies identified.

1.10.8.1 Errors in Intake Estimates

In the majority of studies identified, the primary carotenoid composition database used was the US Department of Agriculture (USDA) – National Cancer Institute (NCI) carotenoid food composition database (USDA-NCI) (Table 1.10.8.1-1). A less commonly used carotenoid composition database was that developed for the Block-NCI Health Habits and History Questionnaire (HHHQ, Block, 1989) (Table 1.10.8.1-1). Both of these carotenoid composition databases contain values for the 5 major carotenoids, α-carotene, β-carotene, lycopene, β-cryptoxanthin, and lutein+zeaxanthin. The USDA-NCI carotenoid database contains carotenoid data for fruits and vegetables and multi-component foods containing fruits and vegetables (Chug-Ahuja *et al.,* 1993; Mangels *et al.,* 1993). The HHHQ carotenoid database contains carotenoid data for these foods as well as additional foods including eggs, dairy products, and fats. Eggs contain the highest levels of lutein and zeaxanthin (Sommerburg *et al.,* 1998), and recently, it was demonstrated that egg lutein is approximately 3 times more bioavailable than lutein present either in spinach or in supplemental form (Chung *et al.,* 2004).

In a study comparing carotenoid intakes using the USDA-NCI *vs.* HHHQ carotenoid composition databases, it was determined that although median lutein and zeaxanthin intakes were significantly different, the 2 databases ranked individuals similarly according to lutein and zeaxanthin intake (VandenLangenberg *et al.,* 1996). This study was conducted in older adults (≥50 years) whose egg intakes were likely low, given that a prevailing nutritional recommendation for this age group was to limit egg consumption to avoid elevations in cholesterol and risk of heart disease. Data from the USDA 1994-1996 CSFII and the 1998 Supplemental Children's Survey indicate that, amongst users only, the mean egg consumption for persons <50 years is 670.4 mg/kg body weight/day, and for persons ≥50 years, 456.3 mg/kg body weight/day (analysis conducted internally). Thus, the relevance of the reported findings to the younger populations evaluated in the various observational studies is questionable.

In one U.S. observational study, eggs accounted for 15% of the average lutein intake [which, according to the results of Chung *et al.* (2004), accounts for approximately 50% of the lutein that is bioavailable from food sources)], and younger subjects in the highest quintile of egg consumption were found to have a significantly reduced risk of nuclear cataract compared with those in the lowest quintile (Lyle *et al.,* 1999b). Although the same association was documented for spinach, spinach and egg intakes were poorly correlated (Pearson's r = -0.02), indicating that high egg consumers may have high lutein and zeaxanthin intakes despite not

being high vegetable consumers. Thus, studies accounting only for the carotenoid content of fruits and vegetables may not have accurately estimated intakes of lutein and zeaxanthin.

The carotenoid composition database utilized by each high methodological quality study is summarized in Table 1.10.8.1-1. The lutein and zeaxanthin content of eggs was definitely accounted for in 1/7 supporting studies (14.3%) and in 0/2 non-supporting studies (0%).

Table 1.10.8.1-1 Carotenoid Composition Databases Used in Cataract Observational Studies

Population	Reference	Results	Quality Score	Carotenoid Composition Database Used	Accounted for Carotenoid Content of Eggs
Nutritional Factors in Eye Disease Study, a sub-set of the Beaver Dam Eye Study	Lyle *et al.,* 1999b	Significant inverse association	64.0%	HHHQ	Yes
Nurses' Health Study	Chasan-Taber *et al.,* 1999	Significant inverse association	68.2%	USDA-NCI	No
Nutrition and Vision Project, a sub-set of the Nurses' Health Study	Jacques *et al.,* 2001	Significant inverse association	80.7%	USDA-NCI	No
	Taylor *et al.,* 2002		77.8%	USDA-NCI	No
	Jacques *et al.,* 2005	No significant association	73.1%	USDA-NCI	No
Health Professionals' Follow-up Study	Brown *et al.,* 1999	Significant inverse association	64.0%	USDA-NCI	No
Carotenoids in Age-Related Eye Disease Study	Moeller *et al.,* 2008	Significant inverse association	82.3%	Unknown	Unknown
Women's Health Study	Christen *et al.,* 2008	Significant inverse association	73.1%	USDA-NCI	No
Case-Control Study	Valero *et al.,* 2002	No significant association	85.2%	Spanish study[1]	No
Melbourne Visual Impairment Project	Vu *et al.,* 2006	Significant inverse association	84.0%	USDA-NCI	No

[1] The study was reported to have analyzed the carotenoid content of the most commonly consumed fruits and vegetables.

1.10.8.2 Assessment of Colinearity of Lutein and Zeaxanthin with Other Nutrients

Most of the criteria in the quality appraisal tool were related to control of potential confounding variables, including age, gender, BMI, smoking status, alcohol intake, iris color (for studies assessing MPOD), sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/ hypercholesterolemia, family history of eye disease, and presence of eye disease at baseline.

Studies maintained in the assessment of totality of evidence had good methodological quality, and so these studies controlled for the majority of these potential confounding variables.

In demonstrating that reduced risk of cataract is due *specifically* to increased intakes or circulating levels of lutein and zeaxanthin, consideration must be given to the colinearity between intakes/circulating levels of these xanthophylls with other nutrients known to significantly affect cataract risk. Because the primary source of carotenoids is fruits and vegetables, intakes/circulating levels of each carotenoid are correlated with intakes/circulating levels of the other carotenoids (Mares-Perlman *et al.,* 1995b; Jacques *et al.,* 2001; Delcourt *et al.,* 2006; Christen *et al.,* 2008), and likely with other antioxidants, such as vitamin C. In addition, subjects with the highest intakes/circulating levels of lutein and zeaxanthin (highest intakes of fruits and vegetables) may consume the lowest amounts of fat, the latter of which is independently and positively associated with increased risk of cataract (Tavani *et al.,* 1996; Lu *et al.,* 2005). For an effect to be related specifically to lutein and zeaxanthin, the effect must be statistically independent of other nutrients for which significant associations are reported.

<u>Studies Assessing Cataract Risk as a Function of Dietary Intakes of Lutein+Zeaxanthin</u>

Of the 7 observational studies supporting a significant inverse association between increased intake of lutein+zeaxanthin and decreased risk of cataract, 3 did not account for colinearity of intakes of lutein and zeaxanthin with other nutrients/carotenoids/antioxidants found to be significantly associated with risk of cataract (Lyle *et al.,* 1999b; Brown *et al.,* 1999; Vu *et al.,* 2006). In the 4 other studies reporting significant inverse associations between dietary intakes of lutein+zeaxanthin, the independence of the association was examined. The findings of these studies are reviewed in detail below.

- In the Nurses' Health Study, Chasan-Taber *et al.* (1999) assessed 2 nutrients in a model simultaneously to determine independent effects. When vitamin A and lutein/zeaxanthin were placed in a model simultaneously, high lutein and zeaxanthin intakes remained significantly and inversely associated with cataract extraction risk; however, when β-carotene and lutein/zeaxanthin were placed in a model simultaneously, protective effects of lutein and zeaxanthin were reduced and no longer significant.

- In the Women's Health Study, lutein+zeaxanthin intakes were significantly and inversely associated with reduced risk of cataract, as were β-carotene and vitamin E (Christen *et al.,* 2008). The independent contribution of each nutrient was examined in Cox regression models using backward selection procedures. After stepwise removal of nonsignificant nutrients, only vitamin E remained significantly associated with cataract risk (P for trend=0.03). When the significance level for retention was set at 0.20, vitamin E (P for trend=0.04) and lutein and zeaxanthin (P for trend = 0.06) were retained in the final model.

- In the Carotenoids in Age-Related Eye Disease Study (Moeller *et al.,* 2008), intakes of lutein+zeaxanthin were significantly and inversely associated with risk of cataract and nuclear sclerosis. Intakes of total dietary fat and lutein/zeaxanthin were significantly and inversely correlated (r=-0.35; P<0.001); adjusting for total fat intake resulted in significant attenuations between dietary intakes of lutein and zeaxanthin and risk of cataract. It was also noted that several other nutrients and food components attenuated the association between nuclear cataract and dietary intakes of lutein and zeaxanthin, including vitamin C, lycopene, β-carotene, and fiber. The authors did not include these in their statistical models because of their high correlations with dietary lutein (r ranged from 0.61 to 0.77).

- In the Nutrition and Vision Project, the prevalence of nuclear opacification was significantly lower in the upper 4 quintiles than in the lowest quintile of lutein+zeaxanthin intakes; however, significant reductions in risk of nuclear cataract were associated with intakes of several nutrients including vitamin C, riboflavin, folate, β-carotene, and vitamin E. To evaluate the independent contribution of each nutrient, all nutrients that were significantly associated with nuclear opacities when entered individually into the logistic regression model were entered simultaneously into a logistic regression model using the nutrient quintile median variables. Only vitamin C remained significantly associated with nuclear opalescence after stepwise removal of nonsignificant nutrients. Moreover, none of the other nutrients remained significantly associated with the prevalence of nuclear opacities in models that included these nutrients in pairwise adjustment with vitamin C, whereas vitamin C remained significantly associated with nuclear opalescence in all of the pairwise models.

Studies Assessing Cataract Risk as a Function of Circulating Levels of Lutein and/or Zeaxanthin

Of the 4 studies reporting significant inverse associations between circulating levels of lutein and/or zeaxanthin and risk of cataract, 3 did not account for colinearity of circulating levels of lutein and/or zeaxanthin with circulating levels of other nutrients/carotenoids/antioxidants found to be significantly associated with risk of cataract. In the CAREDS study, serum levels of lutein+zeaxanthin were significantly and inversely associated with cataract risk (Moeller *et al.,* 2008). Although the relationship persisted following adjustment for total intake of dietary fat, the authors did not assess colinearity with serum levels of other antioxidants or carotenoids. Thus, as for studies assessing risk of cataract as a function of dietary intakes of lutein+zeaxanthin, there is very low support for specificity of effect from studies assessing cataract risk as a function of circulating levels of lutein and/or zeaxanthin.

Conclusions on Specificity of Effect

Although the majority of observational studies identified (*i.e.,* 7/9 dietary intake studies and 4/6 plasma/serum studies) reported significant inverse associations between dietary intakes/circulating levels of lutein and zeaxanthin and cataract risk, it is evident that high consumers of lutein and zeaxanthin have other dietary habits which appear to be more strongly

associated with reduced cataract risk, including low-fat intakes and high intakes of other carotenoids and antioxidants. Thus, these studies suggest that several nutritional factors are likely related to reduced risk of cataract, and that the effect may not be *specifically* or causally related to lutein and zeaxanthin. Although lutein and zeaxanthin are present in the lens, they are not particularly concentrated in the lens, and there is no strong biologically plausible mechanism for the roles of lutein and zeaxanthin in reducing the risk of cataract as there is for ARM/ARMD. The lack of biological plausibility further puts into question specificity of effect. Only a randomized controlled trial would provide definitive evidence that lutein and zeaxanthin are specifically associated with a reduced risk of cataract.

1.10.9 Conclusions on Totality of Evidence – Age-Related Cataract

The association between dietary intakes/circulating levels of lutein and zeaxanthin and cataract risk has been critically evaluated by determining whether sufficient data exist to support the various causality criteria (*i.e.,* consistency, magnitude of effect, opposing/neutral evidence, dose-response, temporality, effect of dechallenge, and specificity of effect). A total of 13 observational studies with good methodological quality were identified in which these associations were examined. Risk of cataract was assessed as a function of dietary intakes of lutein+zeaxanthin in 9 studies; as a function of circulating levels of lutein and/or zeaxanthin in 6 studies; and as a function of MPOD in 1 study. Conclusions from the assessment of causality are summarized in Table 1.10.9-1.

Table 1.10.9-1 Summary of Evidence Regarding Causality[1]

Causality Criteria	Biomarker of Lutein and Zeaxanthin Status (proportion of relevant studies supporting the causality criteria)		
	Dietary Intakes	**Circulating Levels**	**MPOD**
Consistency	Moderate (7/9; 77.8%)	Moderate (4/6; 66.7%)	[2]
Magnitude of effect	0.78 (CI, 0.71 – 0.87; P<0.0001)[3]	0.87 (CI, 0.65 – 1.17; P=0.36)[3]	[2]
Dose-response	Moderate (6/9; 66.7%)	Moderate (4/6; 66.7%)	Very low (0/1; 0%)
Temporality	High (5/6; 83.3%)	Very low (0/1; 0%)	[2]
Effect of dechallenge	[4]	[4]	[4]
Specificity of effect	[4]	[4]	[4]

Abbreviations: CI, confidence intervals; MPOD, macular pigment optical density.
[1] The totality of evidence in support of each causality criteria was rated as "very low", if the proportion of studies in support of the causality criteria was ≤50%; "low", if the proportion of studies in support of the causality criteria was 51 – 60%; "moderate", if the proportion of studies in support of the causality criteria was 61 – 80%; or, "high", if the proportion of studies in support of the causality criteria was >80%.
[2] Insufficient data precluded assessment of causality criteria.
[3] Values represent the pooled estimate for risk of cataract.
[4] While data from observational studies may be used to support the various causality criteria, to establish the effect of dechallenge and specificity of effect, data from well-controlled human intervention trials are required. Since such trials were not identified in the literature, neither the effect of dechallenge nor specificity of effect could be established.

There was moderate consistency that increased dietary intakes and circulating levels of lutein and zeaxanthin were significantly associated with decreased risk of cataract, with 7/9 (77.8%) of dietary intake studies and 4/6 (66.7%) of plasma/serum studies supporting the relationship; however, limited data precluded an assessment of the consistency regarding the relationship between MPOD and cataract risk.

To assess the magnitude of effect, meta-analyses were conducted for studies reporting cataract risk as a function of dietary intakes of lutein and zeaxanthin and for studies reporting cataract risk as a function of circulating levels of lutein and/or zeaxanthin. The pooled estimate for risk of cataract was significantly lower with high intakes of lutein and zeaxanthin (RR=0.78; CI, 0.71-0.87; P<0.0001) but not with high circulating levels of lutein and zeaxanthin (OR=0.87; CI, 0.65-1.17; P=0.36). The general observation that dietary intakes of lutein and zeaxanthin, but not plasma/serum levels, are associated with reduced risk of cataract and ARMD indicates that i) Plasma/serum levels of lutein and/or zeaxanthin may not be indicative of levels available to the lens; ii) Dietary intake estimates of lutein and zeaxanthin reflect chronic/habitual intakes (which may be more relevant to age-related cataract) while serum/plasma levels reflect more recent intakes; or iii) Lutein and zeaxanthin are not causally related to age-related cataract, but are markers of other dietary patterns (Mares-Perlman *et al.,* 2001).

There is moderate support that intakes of lutein+zeaxanthin and circulating levels of lutein and/or zeaxanthin (but not MPOD) may be significantly and dose-dependently associated with reduced risk of cataract. Also, there is high support that intakes of lutein+zeaxanthin (but not circulating levels or MPOD) earlier in life reduce the risk of cataract later on in life (*i.e.,* temporality). Nevertheless, given that all of the studies identified were observational, the effect of dechallenge could not be evaluated, and specificity of effect could not be established due to inaccuracy in the estimations of intakes and inadequate control of nutritional confounding variables. It is impossible to conclude definitively from observational studies that lutein and zeaxanthin, *per se*, reduce the risk of cataract (*i.e.,* correlations do not always translate into causation). Such a conclusion could only be formulated from well-controlled human intervention trials.

Although the data would be considered inadequate to support a definitive relationship between lutein and zeaxanthin and risk of cataract, from a safety perspective, evidence that lutein and zeaxanthin may reduce the risk of cataract is sufficient to warrant consideration.

1.11 Evaluation of Totality of Evidence – ARMD

1.11.1 Overview

Twenty-six observational studies evaluated the association between lutein and zeaxanthin intakes/circulating levels/MPOD and risk of ARMD (Table 1.11.1-1). Of these 26 studies, 8 (30.8%) were considered to have poor methodological quality (*i.e.,* quality score <60%) while 18

(69.2%) were considered to have good methodological quality (*i.e.,* quality score ≥60%). All 26 studies have been summarized in Table 1.11.1-1; however, the discussion on totality of evidence is based only on the 18 studies considered to have good methodological quality.

Of the 18 studies with good methodological quality, 3 studies (16.7%) were based on populations made up exclusively of women (2 on the Carotenoids in Age-Related Eye Disease Study and 1 on the Nutrition and Vision Project) and 15 studies (83.3%) were based on populations that included both men and women, including 3 from the Nutritional Factors in Eye Disease Study; 1 from the Age-Related Eye Disease Study, 1 from the POLA Study, 1 from the Eye Disease Case-Control Study Group, 1 from the Blue Mountain Eye Study, 1 from the Third National Health and Nutrition Examination Survey, 1 from the Meunster Aging and Retina Study, 1 from the Nurses' Health and Health Professional's Follow-up Studies, 1 from the Rotterdam Study; 2 case-control studies (Simonelli *et al.,* 2002; Cardinault *et al.,* 2005) and 2 cross-sectional studies (Gale *et al.,* 2003; Nolan *et al.,* 2007). Of the 18 studies, 10 (55.6%) were conducted in the U.S.; 7 (38.9%) in Europe; and 1 (5.6%) in Australia. Given that the majority of data collected were from U.S. populations, the results may be generalizable to the U.S. population.

Of the 18 observational studies with good methodological quality, 8 (44.4%) assessed risk of ARM/ARMD as a function of dietary intakes of lutein+zeaxanthin; 6 (33.3%) assessed risk of ARM/ARMD as a function of circulating levels of lutein and/or zeaxanthin; 2 (11.1%) assessed risk of ARM/ARMD as a function of either dietary intakes or circulating levels of lutein and zeaxanthin; and 2 (11.1%) assessed risk of ARM/ARMD as a function of MPOD. Thus, study findings are evaluated according to the biomarker of lutein and zeaxanthin status assessed (*i.e.,* dietary intakes, circulating levels, or MPOD).

If a study assessed more than 1 outcome (*e.g.,* early or late ARM), or more than one subgroup within the study (*e.g.,* males *vs.* females; young *vs.* old), it was considered to support a significant reduction in risk of ARM/ARMD with increased status of lutein and/or zeaxanthin if significant inverse associations were reported for at least 1 outcome measure in at least 1 subgroup. The level of significance was set at $P<0.05$. The study was considered to support a significant reduction in risk of ARM/ARMD with increased status of lutein and/or zeaxanthin if it reported a significant inverse trend, significantly lower levels in cases *versus* controls, or a significant reduction in ARM/ARMD risk in 1 category of lutein and/or zeaxanthin status *versus* the lowest category of lutein and/or zeaxanthin status.

The totality of evidence in support of each causality criteria was rated as follows:

- "very low", if the proportion of studies in support of the causality criteria was ≤50%;
- "low", if the proportion of studies in support of the causality criteria was 51 to 60%;
- "moderate", if the proportion of studies in support of the causality criteria was 61 to 80%; or,
- "high", if the proportion of studies in support of the causality criteria was >80%.

For causality to be established, the proportion of studies in support of each causality criteria must be either moderate or high.

Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD[1]

Country of Study	Study Type	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S. (CAREDS)	Cross-sectional	No significant association	1,670 women with a mean age of 69.3 years residing in Iowa, Wisconsin, and Oregon with lutein and zeaxanthin intakes above the 78th and below the 28th percentile at baseline in the WHI Observational Study were recruited 4-7 years later into the CAREDS	NA	MPOD	Prevalent intermediate ARMD	91.6%	LaRowe *et al.,* 2008
U.S. (CAREDS)	Retrospective[2]	Significant inverse association	1,787 women aged 50-79 years residing in Iowa, Wisconsin, and Oregon with lutein and zeaxanthin intakes above the 78th and below the 28th percentile at baseline in the WHI Observational Study were recruited 4-7 years later into the CAREDS	NA	Diet at WHI baseline and 15 years before CAREDS baseline	Prevalent intermediate ARMD	83.3%	Moeller *et al.,* 2006
		No significant association			Serum At WHI Baseline			
U.S. (Nutrition and Vision Project)	Cross-sectional[2]	No significant association	398 women aged 53-75 years residing in the Boston, Mass. area and participating in the Nutrition and Vision Project, a cross-section of the Nurses' Health Study	13-15 years (retrospective)	Diet	Prevalent early ARM (pigmentary abnormalities and large drusen)	81.8%	Morris *et al.,* 2007
U.S. (AREDS)	Case-control	Significant inverse association	3,403 males and females with varying severity of ARM/ARMD and 1,115 matched controls, aged >60 years	NA	Diet	Severity of ARMD	80.0%	SanGiovanni *et al.,* 2007

Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD[1]

Country of Study	Study Type	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
Ireland	Cross-sectional	Significant inverse association	820 males and females aged 20-60 years, 625 of whom had a family history of ARM	NA	MPOD	Risk of ARM in subjects with and without a family history of ARM	76.2%	Nolan *et al.,* 2007
U.S. (Nurses' Health Study and the Health Professionals' Follow-up Study)	Prospective cohorts	No significant association	77,562 females and 40,866 males aged ≥50 years without ARM or cancer at baseline	Up to 12 years (males) and 18 years (females)	Diet	Incident ARM, ARMD	75.0%	Cho *et al.,* 2004
France (The POLA Study)	Cross-sectional	Significant inverse association	640 males and females aged ≥60 years and residing in Sète (southern France)	NA	Plasma[3]	Prevalent early and late ARM	73.9%	Delcourt *et al.,* 2006
The Netherlands (The Rotterdam Study)	Prospective cohort	No significant association	4,170 males and females aged ≥55 years at baseline	8 years	Diet	Incident early and late ARM	70.4%	van Leeuwen *et al.,* 2005
Australia BMES	Prospective cohort	Significant inverse association	2,454 subjects who were ≥49 years at BMES baseline	5-10 years	Diet	Incident early, late, and any ARMD	70.4%	Tan *et al.,* 2008

Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD[1]

Country of Study	Study Type	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S. (Eye Disease Case-Control Study Group)	Case-control	Significant inverse association	356 cases aged 55-80 years diagnosed with neovascular ARMD within 1 year prior to enrolment and 520 matched controls	NA	Diet	Prevalent neovascular ARMD	70.4%	Seddon *et al.,* 1994[4]
		Significant inverse association	421 cases aged 55-80 years diagnosed with neovascular ARMD within 1 year prior to enrolment and 615 matched controls		Serum		57.8%	Eye Disease Case-Control Study Group, 1993[4]
U.S. (Nutritional Factors in Eye Disease Study)	Retrospective longitudinal	No significant association	1,968 subjects (885 males and 1,083 females aged 43 -86 years) randomly selected from the Beaver Dam Eye Study	NA	Diet (assessed 10 years retrospectively)	Prevalent early and late ARM	66.7%	Mares-Perlman *et al.,* 1996
U.S. (Nutritional Factors in Eye Disease Study)	Nested case-control	No significant association	127 cases with retinal pigment abnormalities or soft drusen; 9 cases with late ARMD (geographic atrophy); 31 cases with neovascular and exudative macular degeneration; 167 matched controls	NA	Serum	Severity of ARM, ARMD	72.0%	Mares-Perlman *et al.,* 1995c
U.S. (Nutritional Factors in Eye Disease Study)	Cross-sectional	No significant association	1,586 males and females aged 43 – 84 years randomly selected from the Beaver Dam Eye Study	5 years	Diet (assessed at baseline and 10 years prior to baseline)	Incident early ARM (large drusen, pigmentary abnormalities)	66.7%	VandenLangenberg *et al.,* 1998

Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD[1]

Country of Study	Study Type	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S. (NHANES III)	Cross-sectional	Significant inverse association	8,229 males and females aged ≥40 years participating in the NHANES III	NA	Diet	Prevalent early and late ARM	73.2%	Mares-Perlman *et al.,* 2001
		No significant association		NA	Serum			
Germany (MARS)	Case-control	No significant association	190 males and females with normal maculae; 441 with early ARM, and 279 with late ARM	NA	Serum	Prevalent early and late ARM	64.0%	Dasch *et al.,* 2005
U.K. (subset of MRC study participants)	Cross-sectional	Significant inverse association	207 males and 173 females aged 66-75 years who participated in previous MRC studies and continued to reside in Sheffield, UK	NA	Plasma[3]	Prevalent early and late ARM	63.6%	Gale *et al.,* 2003
France	Case-control	No significant association	37 males and females aged 74.7 ± 1.2 years with early or late ARM and 24 controls	NA	Serum	Prevalent early and late ARM	62.5%	Cardinault *et al.,* 2005
Italy	Case-control	No significant association	48 ARM patients (19 early and 29 late) and 46 matched controls	NA	Serum	Prevalent early and late ARM	61.5%	Simonelli *et al.,* 2002
UK	Case-control	No significant association	65 elderly patients (>65 years) with ARM and 65 age- and sex-matched controls	NA	Plasma	Prevalent ARM	59.1%	Sanders *et al.,* 1993
U.S.	Case-control	Significant inverse association	93 AMD eyes from 63 patients and 220 normal eyes from 138 subjects	NA	MPOD	Prevalent ARMD	58.3%	Bernstein *et al.,* 2002

Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD[1]

Country of Study	Study Type	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
The Netherlands	Case-control	Significant inverse association	72 males and females aged ≥60 years with neovascular AMD and 66 age-matched controls	NA	Diet	Prevalent neovascular AMD	56.0%	Snellen *et al.*, 2002
UK	Case-control	Significant inverse association	46 subjects aged 21-81 years with healthy maculae and 9 subjects with AMD in 1 eye	NA	MPOD	Prevalent ARMD	50.0%	Beatty *et al.*, 2001
		No significant association			Diet			
Australia	Retrospective[2]	Significant positive association	252 subjects aged 51-89 years recruited from the CHARM Study and the Melbourne VIP	NA	Diet (at recruitment into the original cohorts 7 years earlier)	Progression of ARMD	46.2%	Robman *et al.*, 2007
U.S.	Case-control	Significant inverse association	Retinas from 56 donors with unspecified severity of ARM and from 56 controls	NA	MPOD	Prevalent ARMD	43.5%	Bone *et al.*, 2001
Japan	Case-control	Significant inverse association	100 normal eyes of 100 normal subjects and 187 eyes of 97 patients with early or late ARM	NA	MPOD	Prevalent early or late ARM	40.0%	Obana *et al.*, 2008

Table 1.11.1-1 Studies Assessing the Relationship Between Lutein and Zeaxanthin and Risk or ARM, ARMD[1]

Country of Study	Study Type	Results	Population	Duration	Biomarkers		Quality Score	Reference
					Exposure	Outcome		
U.S.	Cross-sectional	No significant association	29 elderly subjects with varying levels of lenticular opacities (considered "normal") and 59 subjects with nonexudative ARMD	NA	MPOD	Prevalent ARMD[5]	40.0%	Ciulla and Hammond, 2004

Abbreviations: AREDS, Age-Related Eye Disease Study; ARM, age-related maculopathy; ARMD, age-related macular degeneration; BMES, Blue Mountain Eye Study; CAREDS, Carotenoids in Age-Related Eye Disease Study; CHARM, Cardiovascular Health and Age-Related Maculopathy Study; MARS, Muenster Aging and Retina Study; MPOD, macular pigment optical density; MRC, Medical Research Council; NHANES III, Third National Health and Nutrition Examination Survey; POLA, Pathologies Oculaires Liées à l'Age; VIP, Visual Impairment Project; WHI, Women's Health Initiative.

[1] Studies with a quality score ≥60% were considered to have good methodological quality, while studies with a quality score <60% were considered to have poor methodological quality. Studies with poor methodological quality (*i.e.,* shaded studies) were not considered in the evaluation of totality of evidence.

[2] Although study designs were retrospective, intake data were collected prospectively.

[3] These are the only studies to report on plasma levels of lutein, zeaxanthin, and lutein+zeaxanthin.

[4] Although results from the Eye Disease Case-Control Study Group were reported separately, the same cohort and study design were used in both of these studies, and the only difference is that Seddon *et al.* (1994) presented results on dietary intakes of lutein and zeaxanthin, while in he 1993 publication, results were presented on serum levels of lutein and zeaxanthin. Thus, these 2 publications were counted as 1 study.

[5] It should be noted that MPOD was also assessed in 22 elderly subjects with cataract, and statistical analyses were conducted by t-tests as opposed to analysis of variance.

1.11.2 Consistency

1.11.2.1 Dietary Intakes of Lutein+Zeaxanthin and Risk of ARM/ARMD

Of the 10 observational studies assessing risk of ARM/ARMD as a function of dietary intakes of lutein+zeaxanthin, 5 (50.0%) reported a significant reduction in risk of ARM/ARMD with increased intake of lutein+zeaxanthin (Seddon *et al.,* 1994; Mares-Perlman *et al.,* 2001; Moeller *et al.,* 2006; SanGiovanni *et al.,* 2007; Tan *et al.,* 2008), while 5 (50.0%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD (Mares-Perlman *et al.,* 1996; VandenLangenberg *et al.,* 1998; Cho *et al.,* 2004; van Leeuwen *et al.,* 2005; Morris *et al.,* 2007).

With 5/10 (50.0%) studies reporting a statistically significant reduction in risk of ARM/ARMD with increased intakes of lutein+zeaxanthin, the consistency of the evidence in favor of the claimed effect is very low.

1.11.2.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of ARM/ARMD

Of the 8 observational studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD, 2 (25.0%) reported a significant reduction in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin (Gale *et al.,* 2003; Delcourt *et al.,* 2006) and 6 (75.0%) reported no significant associations between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD (Mares-Perlman *et al.,* 1995; Mares-Perlman *et al.,* 2001; Simonelli *et al.,* 2002; Cardinault *et al.,* 2005; Dasch *et al.,* 2005; Moeller *et al.,* 2006).

With 2/8 (25.0%) studies reporting a statistically significant reduction in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin, the consistency of the evidence in favor of the claimed effect is very low.

1.11.2.3 MPOD and Risk of ARM/ARMD

Of the 2 studies assessing risk of ARM/ARMD as a function of MPOD, 1 (50.0%) reported significantly lower MPODs in subjects with a family history of ARM/ARMD as compared with subjects without a family history of ARM/ARMD (Nolan *et al.,* 2007); however, in the other study (LaRowe *et al.,* 2008) MPOD was not significantly associated with risk of intermediate ARMD.

With 1/2 (50.0%) studies reporting a significant inverse association between MPOD and risk of ARM/ARMD, the consistency of the evidence in favor of the claimed effect is very low.

1.11.2.4 Overall Conclusions on Consistency

Amongst the 18 observational studies with good methodological quality, risk of ARM/ARMD was assessed as a function of dietary intakes of lutein+zeaxanthin in 10 studies; as a function of circulating levels of lutein and/or zeaxanthin in 8 studies; and as a function of MPOD in 2 studies. With 5/10 studies (50.0%) reporting a significant reduction in risk of ARM/ARMD with increased intakes of lutein+zeaxanthin, the consistency of the evidence in favor of the claimed effect is very low. Likewise, with 2/8 studies (25.0%) reporting a significant reduction in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin, and with 1/2 studies (50.0%) reporting a significant reduction in risk of ARM/ARMD with increased MPOD, the consistency of the evidence in favor of the claimed effect is very low. Thus, overall, the consistency of the totality of evidence in favor of the claimed effect is considered very low.

1.11.3 Magnitude of Effect and Statistical Significance

Only studies reporting dietary intakes of lutein and zeaxanthin and risk of ARMD were included in the meta-analysis. (The limited number of studies using MPOD as a biomarker of exposure and the limited number of plasma/serum studies reporting OR, RR, or HR and 95% CI precluded meta-analyses with these biomarkers). For prospective cohort studies, the RR or HR was used as the measure of the relationship between intake of lutein and zeaxanthin and ARMD risk at the highest *versus* the control group. For case-control and cross-sectional studies, the OR was used as a surrogate measure of RR, because the absolute risk of ARMD was low in each of the studies, a situation in which the OR should provide an accurate estimate of the RR (Whelton *et al.,* 2004). RRs, HRs, and ORs from each study were transformed by taking the natural logarithm, and the standard error was calculated from the reported confidence intervals. Because the studies identified were conducted in different populations, the random effects model (which assumes that the populations studied differed from each other in ways that could impact risk of ARMD) (Borenstein *et al.,* 2007) was chosen.

Dietary intakes of lutein and/or zeaxanthin were not associated with a reduction in risk of ARMD, with a pooled estimate of risk of ARMD of 1.01 (95% CI, 0.87-1.17; P=0.903).

1.11.4 Opposing/Neutral Evidence

1.11.4.1 Dietary Intakes of Lutein+Zeaxanthin and Risk of ARM/ARMD

As discussed in Section 1.11.2.1, 5/10 observational studies (50.0%) reported significant inverse associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD, while 5/10 observational studies (50.0%) reported no significant associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD. A comparison of the observational studies reporting significant inverse associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD and those not reporting such associations is provided in Table 1.11.4.1-1.

Studies reporting no significant association between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD tended to include larger numbers of subjects and to have study designs that were prospective cohort or cross-sectional as opposed to case-control. Moreover, 80% of studies reporting significant inverse associations between intakes of lutein+zeaxanthin and risk of ARM/ARMD assessed *prevalence* of ARM/ARMD. In assessing prevalence of ARM/ARMD (*i.e.,* the proportion of individuals in a population having ARM/ARMD), recall bias (*i.e.,* inaccurate reporting of dietary intakes) is problematic, and tends to bias associations away from the null, as dietary intakes are assessed retrospectively. In contrast, in the non-supporting studies, *prevalence* of ARM/ARMD was assessed in 40.0% of the studies, with the majority (*i.e.,* 60.0%) assessing *incidence* of ARM/ARMD (*i.e.,* the number of newly diagnosed cases of ARM/ARMD over a specified period of time).

Thus, studies reporting no significant associations between dietary intakes of lutein+zeaxanthin and risk of ARM/ARMD generally included larger numbers of subjects and better study designs, and were less prone to recall bias than studies reporting significant inverse associations.

Table 1.11.4.1-1 Characteristics of Supporting and Non-supporting Studies Assessing Dietary Intakes as the Biomarker of Exposure[1]

	Supporting Studies	Non-supporting Studies
Mean number of participants per study[2]	3,573 (range, 876 – 8,229)	25,310 (range, 398 – 118,428)
Number/total number of studies	5/10 (50.0%)	5/10 (50.0%)
Proportion of prospective cohort studies	1/5 (20.0%)	2/5 (40.0%)
Proportion of cross-sectional studies	1/5 (20.0%)	2/5 (40.0%)
Proportion of case-control studies	2/5 (40.0%)	0/5 (0%)
Proportion of retrospective longitudinal studies	1/5 (20.0%)	1/5 (20.0%)
Proportion of studies assessing prevalence (as opposed to incidence)	4/5 (80.0%)	2/5 (40.0%)

[1] Supporting studies reported significant inverse associations between lutein and zeaxanthin status and risk of ARMD, while non-supporting studies did not.
[2] Calculated by dividing the overall number of subjects by the number of studies.

1.11.4.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of ARM/ARMD

As reviewed in Section 1.11.2.2, of the 8 observational studies identified in which associations between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD were assessed, 2/8 studies (25.0%) reported significant inverse associations, while 6/8 studies (75.0%) reported no significant associations. A comparison of the observational studies reporting significant inverse associations between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD and those not reporting such associations is provided in Table 1.11.4.2-1.

None of the studies identified were prospective cohort studies, and in all studies, prevalence of ARM/ARMD (as opposed to incidence) was assessed. Studies reporting no significant inverse associations between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD tended to be predominantly case-control studies (as opposed to cross-sectional studies) and to involve a larger number of study participants. Associations were evaluated separately for lutein and zeaxanthin in 100% of supporting studies and in 66.7% of non-supporting studies.

Table 1.11.4.2-1 Characteristics of Supporting and Non-supporting Studies Assessing Serum/Plasma as the Biomarker of Exposure[1]

	Supporting Studies	Non-supporting Studies
Mean number of participants per study[2]	415 (range, 380 – 640)	1,903 (range, 61 – 8,229)
Number/total number of studies	2/8 (25.0%)	6/8 (75.0%)
Proportion of prospective cohort studies	0/2 (0%)	0/6 (0%)
Proportion of cross-sectional studies	2/2 (100.0%)	1/6 (16.7%)
Proportion of case-control studies	0/2 (0%)	4/6 (66.7%)
Proportion of retrospective longitudinal studies	0/2 (0%)	1/6 (16.7%)
Proportion of studies assessing prevalence (as opposed to incidence)	0/2 (0%)	0/6 (0%)
Proportion of studies assessing independent associations with lutein and zeaxanthin	2/2 (100.0%)	4/6 (66.7%)

[1] Supporting studies reported significant inverse associations between lutein and zeaxanthin status and risk of ARMD, while non-supporting studies did not.
[2] Calculated by dividing the overall number of subjects by the number of studies.

Recently, it was suggested that it may be important to separate zeaxanthin from lutein in assessing associations between these xanthophylls and risk of ARMD (Gale *et al.,* 2003; Delcourt *et al.,* 2006). That zeaxanthin may be more protective than lutein in reducing risk of ARMD is supported by several observations, including the following:

- While the ratio of zeaxanthin:lutein in the plasma is approximately 1:5, in the retina, this ratio is much higher (1:1 in the macula; 2:1 in the fovea) (Delcourt *et al.,* 2006); thus, there appears to be preferential accumulation of zeaxanthin over lutein in the eye. This observation is consistent with the finding that GSTP1, a xanthophyll-binding protein that has recently been isolated from human macula, has high affinity for zeaxanthin but not lutein (Bhosale *et al.,* 2004).

- Recently, conversion of lutein to meso-zeaxanthin was demonstrated in non-human primates (Johnson *et al.,* 2005); this conversion may be of biological significance, given the predominance of zeaxanthin over lutein in the fovea.

- Although both lutein and zeaxanthin protect the lipid matrix from oxidation, zeaxanthin has been shown to be a better photoreceptor during prolonged ultraviolet light exposure (reviewed in Gale *et al.,* 2003).

Of the 8 observational studies assessing risk of ARM/ARMD as a function of circulating levels of lutein and and/or zeaxanthin, in 6 studies (75.0%) risk was expressed as a function of either serum levels of lutein or zeaxanthin (Table 1.11.4.2-2). Only in 1 study (Gale *et al.,* 2003) were circulating levels of zeaxanthin (but not lutein) associated with a significant reduction in risk of ARM/ARMD (Table 1.11.4.2-2). Thus, despite the strong biological plausibility of an importance of zeaxanthin over lutein in reducing the risk of ARM/ARMD, data from a limited number of observational studies do not support an importance of zeaxanthin over lutein.

Because studies reporting and not reporting significant inverse associations between risk of ARM/ARMD and circulating levels of lutein and/or zeaxanthin were retrospective, they are expected to be vulnerable to the same biases, an important one being diet instability. If subjects with ARM/ARMD increased their intakes of lutein and zeaxanthin subsequent to disease diagnosis, circulating levels would increase. ARM/ARMD develops over decades of life, and so a snapshot of circulating levels of lutein and/or zeaxanthin may not accurately reflect levels earlier in life, prior to incidence of ARM/ARMD. Alternatively, circulating levels of lutein and/or zeaxanthin may not be reflective of retinal uptake; otherwise, circulating levels of lutein and/or zeaxanthin may not be at all related with risk of ARM/ARMD.

Table 1.11.4.2-2 Risk of ARM/ARMD as a Function of Circulating Levels of Lutein, Zeaxanthin, or Lutein+Zeaxanthin

Overall Results	Study Design	Reference	Specific Results		
			Lutein	Zeaxanthin	Lutein+ Zeaxanthin
No significant association	Retrospective longitudinal (Carotenoids in Age-Related Eye Disease Study)	Moeller *et al.,* 2006	NS	NS	NS
	Nested case-control (Nutritional Factors in Eye Disease Study)	Mares-Perlman *et al.,* 1995	NS	NS	NS
	Cross-sectional (Third National Health and Nutrition Examination Survey)	Mares-Perlman *et al.,* 2001	NR	NR	NS
	Case-control (Muenster Aging and Retina Study)	Dasch *et al.,* 2005	NS	NS	NR
	Case-control	Cardinault *et al.,* 2005	NS	NS	NR
	Case-control	Simonelli *et al.,* 2002	NR	NR	NS
Significant inverse association	Cross-sectional (The Pathologies Oculaires Liées à l'Age Study)	Delcourt *et al.,* 2006	S	S	S
	Cross-sectional	Gale *et al.,* 2003	NS	S	NS
Proportion of Studies Reporting a Significant Inverse Association			**1/6 (16.7%)**	**2/6 (33.3%)**	**1/6 (16.7%)**

Abbreviations: NR, not reported; NS, not significant; S, significant.

1.11.4.3 MPOD and Risk of ARM/ARMD

In the Carotenoids in Age-Related Eye Disease Study, MPOD was not cross-sectionally associated with decreased risk of intermediate ARMD, even after excluding, from the analyses, women with diet instability or women who were users of lutein+zeaxanthin supplements (LaRowe *et al.,* 2008). In contrast, MPOD was found to be significantly lower in subjects with a family history of ARMD compared to subjects without a family history of ARMD, indicating that MPOD may be useful in characterizing risk of ARMD (Nolan *et al.,* 2007); nevertheless, not all subjects with a family history of ARMD go on to develop the disease, and so additional research is required to better understand the relationship between MPOD and risk of ARM/ARMD.

1.11.5 Dose-response

1.11.5.1 Dietary Intakes of Lutein+Zeaxanthin and Risk of ARM/ARMD

Of the 10 observational studies assessing risk of ARM/ARMD as a function of lutein+zeaxanthin intakes, dose-responses were assessed in 8 studies (80.0%). Of these 8 studies, 6 (75.0%) did

not report significant inverse trends (Mares-Perlman *et al.,* 1996; VandenLangenberg *et al.,* 1998; Cho *et al.,* 2004; van Leeuwen *et al.,* 2005; Morris *et al.,* 2007; Tan *et al.,* 2008), while 2 (25.0%) reported significant inverse trends (Seddon *et al.,* 1994; SanGiovanni *et al.,* 2007) (Figure 1.11.5.1-1).

With 2/8 studies (25.0%) reporting significant dose-dependent reductions in risk of ARM/ARMD with increased intakes of lutein+zeaxanthin, there is very low agreement that the relationship is dose-dependent.

1.11.5.2 Circulating Levels of Lutein and/or Zeaxanthin and Risk of ARM/ARMD

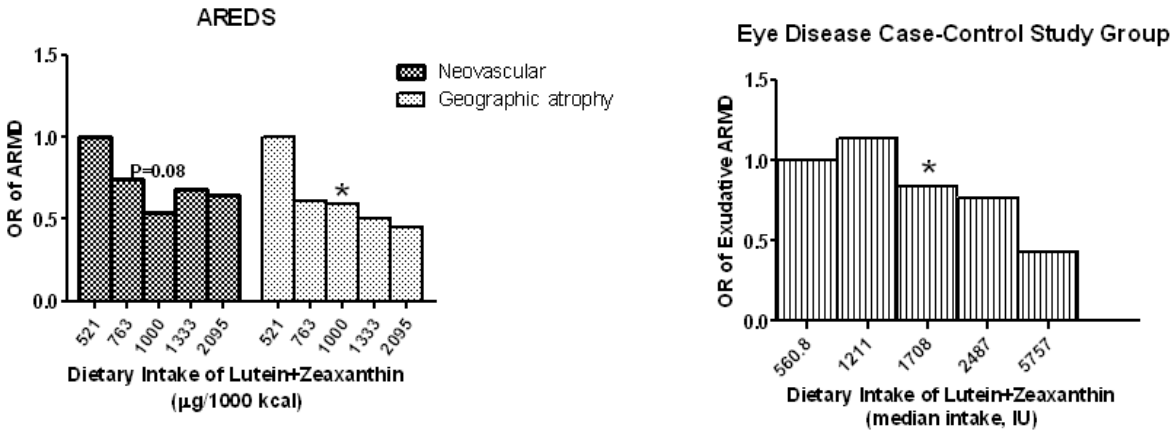
Of the 8 observational studies assessing the relationship between circulating levels of lutein and/or zeaxanthin and risk of ARM/ARMD, dose-responses were assessed in 3 studies (37.5%). Of these 3 studies, 1 (33.3%) did not report significant inverse trends (Moeller *et al.,* 2006), while 2 (66.7%) reported significant inverse trends (Gale *et al.,* 2003; Delcourt *et al.,* 2006) (Figure 1.11.5.2-1).

With 2/3 (66.7%) studies reporting significant dose-dependent reductions in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin, there is moderate agreement that the relationship is dose-dependent. Well-controlled human intervention trials are required to confirm dose-dependent reductions in risk of ARM/ARMD with increasing circulating levels of lutein and/or zeaxanthin.

1.11.5.3 MPOD and Risk of ARM/ARMD

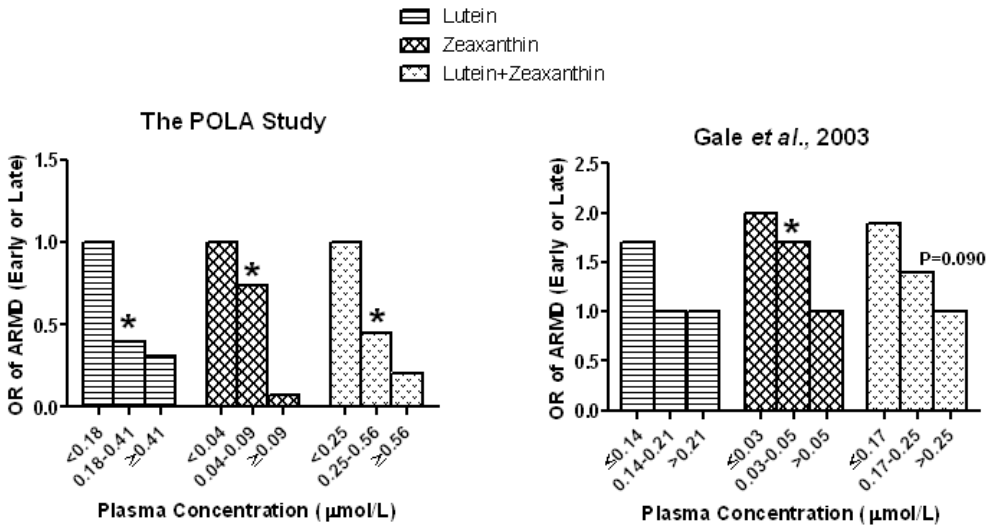
Neither of the 2 studies identified assessed dose-response between risk of ARM/ARMD and MPOD. Thus, limited data precluded assessment of this causality criterion.

Figure 1.11.5.2-1 Risk of ARMD as a Function of Lutein and Zeaxanthin Intakes



The AREDS Study was a case-control study (SanGiovanni *et al.,* 2007).
* indicates trend was significant.
Abbreviations: AREDS, Age-Related Eye Disease Study; ARMD, age-related macular degeneration; OR, odds ratio.

Figure 1.11.5.2-2 Risk of ARMD as a Function of Circulating Levels of Lutein and Zeaxanthin



The POLA study was cross-sectional (Delcourt *et al.,* 2006), as was the study by Gale *et al.* (2003).
* indicates trend was significant.
Abbreviations: ARMD, age-related macular degeneration; OR, odds ratio; POLA, Pathologies Oculaires Liées à l'Age.

1.11.6 Temporality

To satisfy the causality criteria, temporality, it must be demonstrated that exposure to the food/constituent precedes the claimed effect. Again, human intervention trials are required to demonstrate temporality, but such trials were not identified with ARMD or ARMD progression as an outcome variable. Because ARMD is believed to develop over several decades, human intervention trials with incident ARMD as an outcome are likely not feasible. Moreover, at the present time, there are no validated surrogate measures of ARMD risk.

In the absence of human intervention studies, temporality can be *suggested* in studies with a prospective design (*i.e.,* status of lutein and zeaxanthin is assessed *prior* to the occurrence of ARMD). All 8 studies assessing risk of ARM/ARMD as a function of circulating levels of lutein and/or zeaxanthin were retrospective and therefore not supportive of temporality. In 1 study (Nolan *et al.,* 2007) MPOD was found to be significantly lower in subjects with a family history of ARM/ARMD compared to subjects without a family history of ARM/ARMD. Nonetheless, although family history of ARM/ARMD increases risk of ARM/ARMD, not all subjects with a family history of ARM/ARMD go on to develop the disease. Thus, this study cannot be used to demonstrate temporality.

Of the 10 studies assessing risk of ARM/ARMD as a function of dietary intake of lutein+zeaxanthin, 4 (40.0%) assessed risk of incident ARM/ARMD. Of these 4 studies, 3 (75.0%) did not support a significant inverse association between dietary intake of lutein+zeaxanthin and risk of ARM/ARMD, while 1 (25.0%) reported a significant reduction in risk of ARM/ARMD with increased intake of lutein+zeaxanthin.

With 1/4 studies (25.0%) supporting temporality, there is very low agreement that the relationship is temporal.

1.11.7 Effect of Dechallenge

Human intervention studies are required to demonstrate a reversal or cessation of effects upon discontinuation of supplementation. Human intervention studies assessing the effects of lutein and zeaxanthin supplementation on ARMD progression were not identified, and so this causality criterion cannot be supported by the available literature.

1.11.8 Specificity of Effect and Alternative Explanations

As reviewed in Section 1.10.8, specificity of effect refers to the demonstration that reductions in risk of ARMD are due *specifically* to lutein and zeaxanthin and not to other correlates of increased lutein and zeaxanthin status. Human intervention studies are *necessary* in the demonstration of specificity of effect, particularly when the subject of a claimed effect is a

nutrient/food constituent rather than a broad category of foods. Human intervention studies assessing the effects of lutein+zeaxanthin supplementation on risk of ARMD were not identified.

In the absence of human intervention studies on the effects of lutein and zeaxanthin on risk of ARMD, specificity of effect can only be *suggested* by human observational studies, so long as intake estimates are accurate, disease outcomes are validated, and potential confounding variables are statistically accounted for. While ARMD was assessed using validated methods in all studies identified, intake estimates were determined to be inaccurate in several of these studies, and although potential confounding variables were adequately controlled for in some studies, causation still cannot be inferred from correlations. Based on these limitations, which are discussed in greater detail in Section 1.10.8.1 and 1.10.8.2, specificity of effect cannot be demonstrated.

1.11.8.1 Errors in Intake Estimates

As discussed in extensive detail in Section 1.10.8.1, several studies used carotenoid composition databases that did not account for the carotenoid content of eggs, which are the richest and most bioavailable sources of lutein and zeaxanthin (Sommerburg *et al.,* 1998; Chung *et al.,* 2004). Food composition tables are required to translate food consumption data into estimates of lutein and zeaxanthin; thus, errors in food composition data or food composition data that are incomplete are likely to result in the misclassification of lutein and zeaxanthin intakes (*i.e.,* “measurement error”), thereby limiting interpretation of reported diet-disease relationships (VandenLangenberg *et al.,* 1996).

The carotenoid composition databases used in the various ARMD observational studies are summarized in Table 1.11.8.1-1. As reviewed in Section 1.11.2.1, of the 10 observational studies assessing risk of ARM/ARMD as a function of intake of lutein+zeaxanthin, 5 (50.0%) supported a significant reduction in risk of ARM/ARMD with increased intake of lutein+zeaxanthin, while 5 (50.0%) reported no significant associations. As can be seen in Table 1.11.8.1-1, the lutein and zeaxanthin content of eggs was definitely accounted for in 1/5 supporting studies (20.0%), and in 2/5 (40.0%) of non-supporting studies.

Table 1.11.8.1-1 Carotenoid Composition Databases Used in ARMD Observational Studies

Population	Reference	Results	Quality Score	Carotenoid Composition Database Used	Accounted for Carotenoid Content of Eggs
Nutritional Factors in Eye Disease Study, a sub-set of the Beaver Dam Eye Study	Mares-Perlman *et al.,* 1996	No significant association	66.7%	HHHQ	Yes
	VandenLangenberg *et al.,* 1998	No significant association	66.7%	HHHQ	Yes
Nurses' Health Study and Health Professionals' Follow-up Study	Cho *et al.,* 2004	No significant association	75.0%	USDA-NCI	No
Nutrition and Vision Project, a sub-set of the Nurses' Health Study	Morris *et al.,* 2007	No significant association	81.8%	USDA-NCI	No
Carotenoids in Age-Related Eye Disease Study	Moeller *et al.,* 2006	Significant inverse association	87.5%	Unknown	Unknown
Age-Related Eye Disease Study	SanGiovanni *et al.,* 2007	Significant inverse association	80.0%	HHHQ	Yes
The Rotterdam Study	van Leeuwen *et al.,* 2005	No significant association	70.4%	Dutch Food Composition Table	Unknown
Eye Disease Case-Control Study Group	Seddon *et al.,* 1994	Significant inverse association	70.4%	Mangels *et al.,* 1993[1]	No
Third National Health and Nutrition Examination Survey	Mares-Perlman *et al.,* 2001	Significant inverse association	73.2%	USDA-NCI and a "composite database"	Unknown
Blue Mountain Eye Study	Tan *et al.,* 2008	Significant inverse association	70.4%	Chug-Ahuja *et al.,* 1993[2]	No

[1] Mangels *et al.* (1993) reported only the carotenoid content of fruits and vegetables
[2] Chug-Ahuja *et al.* (1993) reported only the carotenoid content of fruits, vegetables, and selected multi-component foods.

1.11.8.2 Assessment of Colinearity of Lutein and Zeaxanthin with Other Nutrients

Most of the criteria in the quality appraisal tool were related to control of potential confounding variables, including age, gender, BMI, smoking status, alcohol intake, iris color (for studies assessing MPOD), sunlight exposure, medication use, hypertension, diabetes, hyperlipidemia/ hypercholesterolemia, family history of eye disease, and presence of eye disease at baseline. Studies maintained in the assessment of totality of evidence had good methodological quality, and so these studies controlled for most of these potential confounding variables.

In demonstrating that reduced risk of ARMD is due *specifically* to increased intakes/circulating levels of lutein and zeaxanthin, consideration must be given to the colinearity between intakes/circulating levels of these xanthophylls with other nutrients known to significantly affect ARMD risk. Because the primary source of carotenoids is fruits and vegetables, intakes of each carotenoid are correlated with intakes of the other carotenoids (Mares-Perlman *et al.,* 1995b; Jacques *et al.,* 2001; Delcourt *et al.,* 2006; Christen *et al.,* 2008), and likely with other antioxidants, such as vitamin C. In addition, subjects with the highest intakes of lutein and zeaxanthin (highest intakes of fruits and vegetables) may consume the lowest amounts of fat, the latter of which is independently associated with increased risk of ARMD (Seddon *et al.,* 2003; Delcourt *et al.,* 2007). For an effect to be related specifically to lutein and zeaxanthin, the effect must be independent of other nutrients for which significant associations are reported.

Studies Assessing ARM/ARMD Risk as a Function of Intakes of Lutein+Zeaxanthin

Of the 5 observational studies supporting a significant inverse association between increased intake of lutein+zeaxanthin and decreased risk of ARMD, all 5 studies provide limited evidence of specificity of effect by controlling for several nutritional covariates. These studies are discussed in detail in the following section.

- In the Age-Related Eye Disease case-control study (SanGiovanni *et al.,* 2007), significant reductions in risks of neovascular ARMD and geographic atrophy ARMD with increased intakes of lutein+zeaxanthin persisted after adjustment for quintiles of long-chain omega-3 fatty acids and arachidonic acid; however, β-carotene, which also was found to be significantly and inversely associated with ARMD risk, was not included in the final multivariate model.

- In the Blue Mountain Eye Study (Tan *et al.,* 2008), several variables were found to be significantly associated with reduced risk of ARMD, including zinc, β-carotene, α-carotene, and vitamin E. Thus, the authors created multinutrient models that simultaneously evaluated the independent associations of each nutrient. The significant inverse association between risk of ARMD and lutein+zeaxanthin intakes persisted.

- In the Third National Health and Nutrition Examination Survey (Mares-Perlman *et al.,* 2001), significant inverse associations between dietary intakes of lutein and zeaxanthin and risk of pigmentary abnormalities and late ARMD persisted after singly adjusting for each potential nutritional confounding variable (dietary intake of β-carotene, zinc, or saturated fat or serum vitamin E); however, all other confounding variables were dropped from these models (including gender, alcohol use, hypertension, smoking, and body mass index), except for age and the specific nutrient under investigation.

- In the Eye Disease Case-Control Study (Seddon *et al.,* 1994), both β-carotene and lutein+zeaxanthin intakes were significantly and inversely associated with risk of exudative

ARMD; when β-carotene and lutein+zeaxanthin intakes were entered in the multivariate model simultaneously, the inverse association with β-carotene was attenuated, but the inverse association with lutein and zeaxanthin intakes persisted.

- In the Carotenoids in Age-elated Eye Disease Study (Moeller *et al.,* 2006), diets rich in lutein+zeaxanthin were found to reduce the risk of intermediate ARMD in healthy women younger than 75 years. To further explore the possible effect of other nutrients on the relationship between lutein+zeaxanthin intake and ARMD, the authors created a crude nutrient index to classify persons with generally healthy *versus* generally unhealthy intakes of other nutrients that have been associated with ARMD. Although results were not statistically significant, the ORs were all in a protective direction.

<u>Studies Assessing ARM/ARMD Risk as a Function of Circulating Levels of Lutein and/or Zeaxanthin</u>

Of the 2 studies supporting a significant reduction in risk of ARM/ARMD with increased circulating levels of lutein and/or zeaxanthin, 1 study assessed the effect of potential confounding nutritional variables (Gale *et al.,* 2003), while the other study did not (Delcourt *et al.,* 2006). Both of these studies are described in greater detail below.

- In a cross-sectional study, Gale *et al.* (2003) reported significant reductions in risk of early or late ARMD in subjects with higher plasma concentrations of zeaxanthin. Individuals with higher plasma levels of zeaxanthin were reported to have higher levels of several other antioxidants, including vitamin E, lycopene, β-carotene, and β-cryptoxanthin. Analyses were therefore adjusted for each of these potential confounding variables, and zeaxanthin maintained an independent inverse association with risk of ARMD.

- Delcourt *et al.* (2006) reported a significant reduction in risk of early and late ARM with increased circulating levels of lutein and/or zeaxanthin. Although plasma lutein and zeaxanthin were found to be highly correlated with several other carotenoids, including β-carotene, α-carotene, β-cryptoxanthin, and lycopene, plasma levels of these other carotenoids were not found to be significantly associated with reduced risk of ARM, thus precluding an assessment of potential nutritional confounding.

<u>Studies Assessing ARM/ARMD Risk as a Function of MPOD</u>

In the study by LaRowe *et al.* (2008), which received the highest quality score (*i.e.,* 91.6%), several variables known to affect MPOD were controlled for. Nonetheless, in this study, MPOD, assessed cross-sectionally, was not significantly associated with decreased risk of ARMD. In a study reporting significantly lower MPODs in subjects with *versus* without a family history of ARMD, several potential confounding variables also were adjusted for (Nolan *et al.,* 2007). The reasons for these discrepant findings are unclear. While diet instability may have been a

problem in the study by LaRowe *et al.* (2008), the authors conducted several analyses following exclusion of participants with diet instability, and still significant inverse associations could not be discerned.

1.11.8.3 Conclusions on Specificity of Effect

Although studies assessing the relationship between dietary intakes or circulating levels of lutein and/or zeaxanthin controlled for several potential nutritional and non-nutritional confounding variables, specificity of effect cannot be concluded from observational studies (*i.e.,* it cannot be definitively concluded from these studies that lutein and zeaxanthin, *per se*, will reduce the risk of ARM/ARMD). High intakes of lutein and zeaxanthin may be correlates of other dietary or non-dietary factors that reduce the risk of ARM/ARMD. Indeed, in the Age-related Eye Disease Study (AREDS), an xanthophyll-free antioxidant supplement containing zinc, vitamin C, vitamin E, and β-carotene effectively reduced risk of ARMD and vision loss, thus supporting that antioxidants other than lutein and zeaxanthin may attenuate the progression of ARM.

1.11.9 Conclusions on Totality of Evidence – ARM, ARMD

The association between lutein and zeaxanthin status (*i.e.,* dietary intakes, circulating levels or MPOD) and risk of ARM/ARMD has been critically evaluated by determining whether sufficient data exist to support the various causality criteria (*i.e.,* consistency, magnitude of effect, opposing/neutral evidence, dose-response, temporality, effect of dechallenge, and specificity of effect). A total of 18 observational studies with good methodological quality were identified in which associations between lutein and zeaxanthin status and risk of ARM/ARMD were evaluated. Risk of ARM/ARMD was assessed as a function of dietary intakes of lutein+zeaxanthin in 10 studies; as a function of circulating levels of lutein and/or zeaxanthin in 8 studies; and as a function of MPOD in 2 studies. Conclusions from the assessment of causality are summarized in Table 1.11.9-1.

Table 1.11.9-1 Summary of Evidence Regarding Causality[1]

	Biomarker of Lutein and Zeaxanthin Status (proportion of relevant studies supporting the causality criteria)		
	Dietary Intakes	**Circulating Levels**	**MPOD**
Consistency	Very low (5/10; 50.0%)	Very low (2/8; 25.0%)	Very low (1/2; 50.0%)
Magnitude of Effect	1.01 (CI=0.87-1.17; P=0.903)	[3]	[3]
Dose-response	Very low (2/8; 25.0%)	Moderate (2/3; 66.7%)	[3]
Temporality	Very low (1/4; 25.0%)	[3]	[3]
Effect of dechallenge	[4]	[4]	[4]
Specificity of effect	[4]	[4]	[4]

Abbreviations: CI, confidence intervals; MPOD, macular pigment optical density.
[1] The totality of evidence in support of each causality criteria was rated as "very low", if the proportion of studies in support of the causality criteria was ≤50%; "low", if the proportion of studies in support of the causality criteria was 51 – 60%; "moderate", if the proportion of studies in support of the causality criteria was 61 – 80%; or, "high", if the proportion of studies in support of the causality criteria was >80%.
[2] Values represent the pooled estimate for risk of ARMD.
[3] Insufficient data precluded assessment of causality criteria.
[4] While data from observational studies may be used to *support* the various causality criteria, to establish the effect of dechallenge and specificity of effect, data from well-controlled human intervention trials are required. Since such trials were not identified in the literature, neither the effect of dechallenge nor specificity of effect could be established.

The consistency of the evidence in favor of an inverse association between lutein and zeaxanthin status and risk of ARM/ARMD was determined to be very low. In 2/8 dietary intake studies (25.0%) and 2/3 plasma/serum studies (66.7%), significant and inverse dose-responses were reported; thus, there is some *suggestion* that increased plasma levels of lutein and/or zeaxanthin (but not dietary intakes) may be associated with significant and dose-dependent reductions in risk of ARM/ARMD. Well-controlled human intervention trials are required to determine whether increased plasma levels of lutein and zeaxanthin dose-dependently reduce risk of ARM/ARMD.

Four observational studies had prospective designs that permitted an assessment of temporality. Of these 4 studies, 1 (25.0%) provided evidence of temporality; thus, there is very low support that intakes of lutein and zeaxanthin earlier in life reduce the risk of ARM/ARMD later on in life. Other causality criteria, including the effect of dechallenge and specificity of effect, can only be substantiated by data from well-controlled human intervention studies.

Lutein and zeaxanthin are concentrated in the macula of the eye to the exclusion of other carotenoids; as well, lutein and zeaxanthin have antioxidant activity and are able to fitter phototoxic blue light. Despite these proposed biological mechanisms, data from methodologically sound human observational studies do not support a reduction in risk of ARM/ARMD with increased dietary intakes or circulating levels of lutein and/or zeaxanthin.

Only 2 studies with good methodological quality were identified in which MPOD was used as the measure of lutein and zeaxanthin status, and results from both of these studies were inconsistent, with 1 study reporting no significant association between MPOD and risk of intermediate ARMD (LaRowe *et al.,* 2008), and the other study reporting significantly lower MPODs in subjects with *versus* without a family history of ARM/ARMD (Nolan *et al.,* 2007). The reasons for these apparent discrepancies are unclear.

The totality of evidence does not support a role for lutein and/or zeaxanthin in reducing the risk of ARM/ARMD.

1.12 Evaluation of Totality of Evidence – Visual Performance

Six human intervention studies were identified in which the effect of lutein and/or zeaxanthin administration on visual performance was assessed. One of the 6 studies, the Veterans Lutein Antioxidant Supplementation Trial (the Veterans LAST; Richer *et al.,* 2004) received a good methodological quality score (*i.e.,* quality score ≥60%) while the other 5 studies all received methodological quality scores <60%. Quality scores are presented in Table 1.8-3. As such, the following discussion is focused primarily on data from the Richer *et al.* (2004) study.

1.12.1 Consistency

Intervention studies assessing the relationship between lutein and/or zeaxanthin administration and visual performance are presented in Table 1.12.1-1. Only 1 study was found to have good methodological quality, and so this causality criterion could not be established.

1.12.2 Magnitude of Effect and Statistical Significance

The small number of intervention studies, their general lack of methodological quality, and the lack of similar endpoints across them precluded a meta-analysis type of assessment of the effects of lutein and/or zeaxanthin on visual performance outcomes. Given that the only study that was found to be of adequate quality was the Veterans LAST (Richer *et al.,* 2004), the discussion on magnitude of effect and statistical significance is restricted to this study.

The objective of the Veterans LAST was to determine whether nutritional supplementation with lutein or lutein together with antioxidants, vitamins, and minerals improves visual function and symptoms in patients with atrophic ARMD. The Veterans LAST was a prospective, 12-month, randomized, double-blind, placebo-controlled trial involving 90 patients (86 women and 4 men) with atrophic ARMD. Subjects were supplemented with 10 mg/day lutein (n=29), 10 mg/day lutein plus an antioxidant formulation (n=30), or a placebo (maltodextrin) (n=31). As the focus of the present discussion is to ascertain the effects of lutein, alone, on visual performance, only results pertinent to the lutein and placebo groups are discussed.

Mean (average of right and left eyes) MPOD increased by 36% in the lutein group, but decreased in the placebo (P<0.05 between groups). Near visual acuity in the left eye, but not in the right eye, and averaged over both eyes increased a mean of 5.4 Snellen equivalent letters (about 1 line of visual acuity) in the lutein group (95% CI, 2.5-8.2) but decreased by 0.2 Snellen equivalent letters in the placebo group (95% CI, -3.0-2.7). Near visual acuity over time was significantly different between the lutein and placebo groups for the left eye (P=0.01) but not for the right eye. There were no statistically significant between-group differences noted for any other measure of visual performance, including distance visual acuity, contrast sensitivity, glare recovery, retinopathy (AREDS staging), lens opacification, or visual quality of life.

While the results of this study suggest that lutein supplementation may improve near visual acuity, the study was small and had several limitations. Many of the subjects were already taking multivitamin and mineral formulations upon enrolment in the study and were permitted to remain on these formulations during the 1-year study. Furthermore, the AREDS retinopathy staging at baseline for the left eyes was not comparable in the lutein and placebo groups. The greater the AREDS staging (from Grade I to Grade IV) the more advanced the disease. For the left eyes, the percentage of subjects with Grade IV was significantly greater in the placebo group (41.7%) *vs.* the lutein group (9.1%) (P=0.0002) at baseline. It is noteworthy that the only significant difference between the lutein and placebo groups was in near visual acuity *in the left eye*; although near visual acuity for the right and left eyes averaged was significantly improved in the lutein *vs.* the placebo group, there were no differences in near visual acuity for the right eye. Since, at baseline, a greater proportion of subjects had more advanced disease in the left eye in the placebo group than in the lutein group, the subjects may not have been comparable with respect to measures of visual performance in the left eye. In contrast, the proportion of subjects with an AREDS retinopathy staging of Stage IV was similar for the right eye in the lutein and placebo groups (31.8% *vs.* 32.0%, respectively; P=0.83) at baseline, and significant differences between groups in near visual acuity in the right eye were not observed, indicating a probable effect of the severity of the disease on the final outcome.

Table 1.12.1-1 Intervention Studies Assessing the Relationship Between Lutein and Zeaxanthin and Visual Performance[1]

Country of Study	Population	Dose and Duration	Endpoint	Results	Quality Score	Reference
U.S. (randomized, double-blind, placebo controlled trial)	60 subjects (57 males and 3 females, aged >70 years) with ARMD	Lutein at 10 mg/day for 12 months	MPOD	Increase[2]	78.8%	Richer *et al.*, 2004
			Near visual acuity (left eye)	Increase[2, 3]		
			Near visual acuity (right eye)	No effect		
			Distance visual acuity	No effect		
			Glare recovery	No effect		
			Contrast sensitivity	Increase[2]		
			Visual change (Amsler grid)	Increase[2]		
U.S. (randomized trial)	45 subjects (females, aged 60 and above) with various severities of ARMD	Lutein at 2.5, 5, or 10 mg/day for 6 months	Visual acuity	No effect	59.4%	Rosenthal *et al.*, 2006
Spain (randomized, double-blind, placebo controlled trial)	10 subjects (3 males and 7 females, aged 55-73 years) with cataract	Lutein at 7 mg/day for 24 months	Visual acuity	Increase[3]	48.3%	Olmedilla *et al.*, 2003[5]
			Glare sensitivity	Decrease[4]		
U.S. (open-label)	40 subjects (17 males and 23 females, aged 17 to 41 years) with no history of visual pathology	Lutein and zeaxanthin (10 mg/day and 2 mg/day, respectively) for 6 months	MPOD	Increase[2]	28.6%	Stringham and Hammond, 2008
			Glare sensitivity	Decrease[2]		
Not described (randomized, double-blind, placebo controlled trial)	17 subjects (males, aged 18 to 40) with no ocular abnormalities	Lutein and/or zeaxanthin at 10 mg/day for 6 months followed by 20 mg/day for 6 months	MPOD	Increase[3,6,7]	55.8%	Kvansakul *et al.*, 2006
			Contrast acuity	Increase[3,6,7]		
			Wavefront aberration	No effect		
			Light scatter	No effect		

Table 1.12.1-1 Intervention Studies Assessing the Relationship Between Lutein and Zeaxanthin and Visual Performance[1]

Country of Study	Population	Dose and Duration	Endpoint	Results	Quality Score	Reference
Spain (open-label trial)	5 subjects (females, aged 55 to 73 years) with cataract	Lutein at 7 mg/day for an average of 13 months (range 4-20 months)	Visual acuity	Increase[4]	25.0%	Olmedilla *et al.*, 2001[5]
			Glare sensitivity	Decrease[4]		
	5 subjects (3 males and 2 females, aged 69 to 75 years) with ARMD	Lutein at 7 mg/day for an average of 26 months (range 16-36 months)	Visual acuity	No effect		

Abbreviations: ARMD, age-related macular degeneration.
[1] Studies with a quality score ≥60% were considered to have good methodological quality, while studies with a quality score <60% were considered to have poor methodological quality. Studies with poor methodological quality (*i.e.,* shaded studies) were not considered in the evaluation of totality of evidence.
[2] Statistically significant with respect to baseline.
[3] Statistically significant with respect to control group.
[4] Statistical significance not reported.
[5] Some of the data presented in the Olmedilla *et al.* (2001) study appear to be the same as some of the data presented in the Olmedilla *et al.* (2003) study, and so the possibility of these 2 studies being kin publications exists. In particular, the data for the subjects with cataract are strikingly similar in both studies and appear to have been derived from subjects with the same anthropomorphic characteristics. However, in the absence of a reliable means to confirm whether this is the case, these 2 studies have been considered to be independent for the purpose of this assessment.
[6] Supporting results were only reported for lutein supplementation and not for supplementation with zeaxanthin or with lutein and zeaxanthin together.
[7] No statistical correlation was observed between MPOD and improvements in contrast acuity.

1.12.3 Opposing/Neutral Evidence

No data suggesting an opposing effect of lutein and/or zeaxanthin on visual performance were presented in the study by Richer *et al.* (2004).

1.12.4 Dose-response

Only 1 dose was studied in the trial by Richer *et al.* (2004), thus precluding assessment of a dose-response relationship.

1.12.5 Temporality

Because the study by Richer *et al.* (2004) was a randomized controlled trial, it supports temporality in that exposure to lutein preceded the outcomes.

1.12.6 Effect of Dechallenge

The effect of dechallenge was not assessed in the study by Richer *et al.* (2004), and so this causality criterion cannot be supported by the available literature.

1.12.7 Specificity of Effect and Alternative Explanations

Assuming that all other confounding factors are accounted for, supplementation with lutein and/or zeaxanthin provides a direct means of assessing potential effects of these compounds on visual performance. Richer *et al.* (2004) accounted for a number of potentially important confounding variables and correspondingly was the only study to receive a good methodological quality score (78.8%). Results of this study indicate that MPOD is increased by lutein supplementation and support a beneficial effect of lutein on visual performance, specifically on near visual acuity in the left eye. However, a major limitation of the study is that a significantly higher proportion of subjects in the placebo group had more severe disease in the left eye in the placebo group (*i.e.,* AREDS Stage IV), and so it is unclear whether visual performance in the left eyes were comparable. It is noteworthy that only in the left eye was near visual acuity significantly improved in the lutein group relative to the placebo group.

1.12.8 Conclusion on Totality of Evidence – Visual Performance

Data from 1 good methodological study indicate that supplementation with lutein and zeaxanthin significantly improves left eye near visual acuity relative to supplementation with maltodextrin. However, the small size of the study, in addition the differences in disease severity at baseline across the groups, limits interpretation of the study findings. Moreover, several other causality criteria, including consistency, dose-response, and effect of dechallenge could not be

demonstrated due to insufficient scientific evidence (Table 1.12.8-1). Thus, additional studies are required to demonstrate causality.

Table 1.12.8-1 Summary of Evidence Regarding Causality[1]

	Consistency	Magnitude of Effect	Dose-response	Temporality	Effect of Dechallenge	Specificity of Effect
Richer *et al.* (2004)	X	✓	X	✓	X	X

[1] Only 1 human intervention study was found to have good methodological quality; "X" means that the causality criteria is not supported by the results of the study, while "✓", means that the causality criteria is supported by the results of the study.

OLESTRA AMENDMENT GRAS NOTICE

ATTACHMENT I TO APPENDIX E:

BIOMARKERS OF AGE-RELATED CATARACT, AGE-RELATED MACULOPATHY, AGE-RELATED MACULAR DEGENERATION

January 18, 2010

ATTACHMENT I TO APPENDIX E:

BIOMARKERS OF AGE-RELATED CATARACT, AGE-RELATED MACULOPATHY, AGE-RELATED MACULAR DEGENERATION

Table of Contents

Page

1.0 BIOMARKERS OF OUTCOME I-2
1.1 Introduction I-2
1.2 Cataracts and ARMD I-2
1.2.1 Methodological Validity I-2
1.2.2 Biological Validity I-6

2.0 REFERENCES I-7

List of Tables

Table E-1 Methods Used to Diagnose Various Types of Cataracts Assessed in Identified Studies I-3
Table E-2 Methods Used to Diagnose Various Classifications of ARMD Assessed in Identified Studies I-5

1.0 BIOMARKERS OF OUTCOME

1.1 Introduction

The assessment of the methodological and biological validity of study endpoints is often necessary when a surrogate biomarker of disease, rather than disease itself, is measured. This is not the case with the majority of the studies listed in Tables E-1 and E-2, as they measured either cataract or some stage of ARMD; both of which are disease endpoints, and not surrogate biomarkers thereof. Although the criteria and methods used to assess the eye diseases in question vary, all are considered as valid methods of disease assessment and classification.

1.2 Cataracts and ARMD

1.2.1 Methodological Validity

The methods used for the assessment of cataracts by study authors varied, but were all based on either the grading of photographs of the lens (Mares-Perlman *et al.*, 1995a,b; Lyle *et al.*, 1999a,b; Gale *et al.*, 2001; Jacques *et al.*, 2001; Taylor *et al.*, 2002; Valero *et al.*, 2002; Jacques *et al.*, 2005; Delcourt *et al.*, 2006; Vu *et al.*, 2006; Dherani *et al*., 2008; Moeller *et al.*, 2008) or subject and ophthalmologist-reported cataract diagnosis (Brown *et al.*, 1999; Chasan-Taber *et al.*, 1999; Christen *et al.*, 2008). The methods used for the assessment of ARMD were also based either on the grading of retinal photographs (Mares-Perlman *et al.*, 1995c; Mares-Perlman *et al.*, 1996; Vandenlangenberg *et al.*, 1998; Mares-Perlman *et al.*, 2001; Gale *et al.*, 2003; Dasch *et al.*, 2005; Delcourt *et al.*, 2006; Moeller *et al.*, 2006; Morris *et al.*, 2007; SanGiovanni *et al.*, 2007; LaRowe *et al.*, 2008; Obana *et al*., 2008; Tan *et al.*, 2008) or subject and ophthalmologist-reported ARMD diagnosis (Seddon *et al.*, 1994; Bernstein *et al.*, 2002; Cho *et al.*, 2004; Cardinault *et al.*, 2005). While the differing methods for the subjective assessment of cataract and ARMD may have slightly affected the consistency of the results, all methods are validated procedures, and included specific instructions intended to reduce inter- and intra-assessor variability.

Table E-1 Methods Used to Diagnose Various Types of Cataracts Assessed in Identified Studies

Population	Reference	Quality Score	Type of Cataract	Method of diagnosis
1,919 (859 females and 1,060 males aged 43-86 years) participating in the Nutritional Factors in Eye Disease Study, a 50% random sample of the non-institutionalized participants of the Beaver Dam Eye Study	Mares-Perlman *et al.,* 1995a	52.2%	Nuclear	Wisconsin System for Classification of Cataracts from Photographs
400 subjects aged 50-86 years randomly selected from the Nutritional Factors in Eye Disease Study, a cohort nested in the Beaver Dam Eye Study	Mares-Perlman *et al.*, 1995b	73.9%	Nuclear	
1,354 subjects aged 43-84 years participating in the Nutritional Factors in Eye Disease Study, a sub-set of the Beaver dam Eye Study	Lyle *et al.*, 1999b	64.0%	Nuclear	
325 adults ≥50 years of age at baseline randomly sampled from the Nutritional Factors in Eye Disease Study, a sub-set of the Beaver dam Eye Study	Lyle *et al.*, 1999a (p. 272)	85.7%	Nuclear	
478 non-diabetic women aged 53-73 years from the Boston, Mass., area participating in the Nutrition and Vision Project, a cross-section of the Nurses' Health Study	Jacques *et al.*, 2001	80.7%	Nuclear	Lens Opacities Classification System III
492 non-diabetic female nurses aged 54-73 years from the Boston, Mass., area participating in the Nutrition and Vision Project, a cross-section of the Nurses' Health Study	Taylor *et al.*, 2002	77.8%	Cortical or PSC	
200 males and 172 females aged 66-75 years who had participated in one of the MRC studies in Sheffield, England	Gale *et al.*, 2001	68.2%	Nuclear, cortical, or PSC	
815 males and females ≥60 years of age and residing in Sète (southern France)	Delcourt *et al.*, 2006[1]	73.9%	Nuclear, cortical, and/or PSC	
343 subjects with cataracts aged ≥55 years and 334 matched controls[2]	Valero *et al.*, 2002	85.2%	Nuclear, cortical, and/or PSC	Lens Opacity Classification System II
1112 males and females ≥50 years of age and residing in Northern India	Dherani *et al.*, 2008	60.9%	Nuclear, cortical, and/or PSC	

Table E-1 Methods Used to Diagnose Various Types of Cataracts Assessed in Identified Studies

Population	Reference	Quality Score	Type of Cataract	Method of diagnosis
U.S. Male Health Professional' Study (36,644 male health professionals aged 45-75 years at baseline)	Brown *et al.*, 1999	64.0%	Nuclear and PSC	Self-reported cataract diagnosis/extraction surgery (if insufficient, then cataract presence confirmed by ophthalmologist)
35,551 healthy female health professionals aged ≥45 years and free of cataract at baseline	Christen *et al.*, 2008	73.1%	Unspecified	
Nurses' Health Study (77,466 female nurses aged 45-71 years at baseline)	Chasan-Taber *et al.*, 1999	68.2%	Nuclear and PSC	
2,322 subjects participating in the 5-year follow-up FFQ (no FFQ at baseline) aged ≥45 years	Vu *et al.*, 2006	84.0%	Nuclear, cortical, or PSC	Lenses were classified according to the Wilmer Standard
408 female nurses aged 54-73 years from the Boston, Mass., area participating in the Nutrition and Vision Project, a prospective cross-section of the Nurses' Health Study	Jacques *et al.*, 2005	76.9%	Nuclear	Lens opacity was assessed using computer-assisted image analysis of digital lens images, and measured as a function of a standard gray scale ranging from 0 (clear) to 255 (black), and reported as pixel density units
1,802 women aged 50-79 years residing in Iowa, Wisconsin, and Oregon with lutein and zeaxanthin intakes above the 78th and below the 28th percentile at baseline in the WHI Observational Study were recruited 4-7 years later into the CAREDS	Moeller *et al.*, 2008	82.3%	Nuclear	Optical density was graded against a series of 7 standard photographs producing scores that ranged from 0.0 to 7.1 (cataract = a score of ≥4 or a history of cataract extraction)

Abbreviations: MPOD, macular pigment optical density; MRC, Medical Research Council; NA, not applicable; POLA, Pathologies Oculaires Liées à l'Age; VIP, Visual Impairment Project.; WHS, Women's Health Study.
[1] This was the only study to assess plasma levels of lutein, zeaxanthin, and lutein+zeaxanthin.
[2] Almost 10% of control subjects had ARMD.

Table E-2 Methods Used to Diagnose Various Classifications of ARMD Assessed in Identified Studies

Population	Reference	Quality Score	ARM classification	Method of diagnosis
398 women aged 53-75 years residing in the Boston, Mass., area and participating in the Nutrition and Vision Project, a cross-section of the Nurses' Health Study	Morris *et al.*, 2007	81.8%	Early-intermediate ARM	Wisconsin Age-related Maculopathy Grading System
1,968 subjects (885 males and 1,083 females aged 43 -86 years) randomly selected from the Beaver Dam Eye Study	Mares-Perlman et al., 1996	66.7%	Early and late ARMD	
1,586 males and females aged 43 – 84 years randomly selected from the Beaver Dam Eye Study	Vandenlangenberg *et al.*, 1998	66.7%	Early ARM (few late cases, but too few for analysis)	
8,229 males and females aged ≥40 years participating in the NHANES III	Mares-Perlman *et al.*, 2001 (diet)	62.5%	Early and late	
8,229 males and females aged ≥40 years participating in the NHANES III	Mares-Perlman *et al.*, 2001 (serum)	65.2%	Early and late	
207 males and 173 females aged 66-75 years who participated in previous MRC studies and continued to reside in Sheffield, UK	Gale *et al.*, 2003	63.6%	ARMD	
2083 Caucasian residents of Australia, aged ≥ 49 years, free of the indicated endpoint at baseline	Tan *et al.*, 2008	66.7%	Late ARMD	
1698 women aged 50-79 years (in 1994-1998) participating in the WHI study, with dietary LZ intakes either > the 78th or < the 28th percentile	LaRowe *et al.*, 2008	91.6%	Overall intermediate ARMD, large drusen, or pigmentary abnormalities	
1,787 women aged 50-79 years residing in Iowa, Wisconsin, and Oregon with lutein and zeaxanthin intakes above the 78th and below the 28th percentile at baseline in the WHI Observational Study were recruited 4-7 years later into the CAREDS	Moeller *et al.*, 2006	87.5%	Intermediate and advanced ARMD	
3,403 males and females with varying severity of ARM/ARMD and 1,115 matched controls, aged >60 years	SanGiovanni *et al.*, 2007	80.0%	Stages 0-4 (up to ARMD)	

Table E-2 Methods Used to Diagnose Various Classifications of ARMD Assessed in Identified Studies

Population	Reference	Quality Score	ARM classification	Method of diagnosis
127 cases with retinal pigment abnormalities or soft drusen; 9 cases with late ARMD (geographic atrophy); 31 cases with neovascular and exudative macular degeneration; 167 matched controls	Mares-Perlman *et al.*, 1995c	72.0%	Some early cases, some late	
640 males and females aged ≥60 years and residing in Sète (southern France)	Delcourt *et al.*, 2006	73.9%	Early and late ARMD	The assessment scheme presented by Bird *et al.* (1995) was used to assess and grade ARMD.
20 male and female controls aged 60 to 80 years and 97 cases aged 50 to 85 years with early and/or late ARM (all Japanese)	Obana *et al*., 2008	40.0%	Early and late ARMD	
77,562 females and 40,866 males aged ≥50 years without ARM or cancer at baseline	Cho *et al.*, 2004	75.0%	Early and neovascular ARM	ARM diagnosis was performed by physician, and was self-reported and confirmed by the subjects' ophthalmologists
356 cases aged 55-80 years diagnosed with neovascular ARMD within 1 year prior to enrolment and 520 matched controls	Seddon *et al.*, 1994	70.4%	Advanced ARMD	
93 ARMD eyes from 63 patients and 220 normal eyes from 138 subjects	Bernstein *et al.*, 2002	60.9%	Late ARMD (according to criteria for presence of ARMD)	
37 males and females aged 74.7 ± 1.2 years with early or late ARM and 24 controls	Cardinault *et al.*, 2005	60.0%	Some early, some late	
190 males and females with normal maculae; 441 with early ARM, and 279 with late ARM	Dasch *et al.*, 2005	64.0%	Stages 0-4 (up to ARMD)	Rotterdam Classification System
625 males and females with no known family history of ARM and 175 males and females with family history of early ARM, GA, and CNV	Nolan *et al.*, 2007	71.4%	NA	Family history of early ARM, GA, and CNV

Abbreviations: ARMD/ARMD, age-related macular degeneration; ARM, age-related Maculopathy; CAREDS, Carotenoids in Age-Related Eye Disease Study; CNV, choroidal neovascularization; GA, geographic atrophy; LZ, lutein and zeaxanthin; MRC, medical research council; NHANES, National Health and Nutrition Examination Survey.

1.2.2 Biological Validity

The most valid indication that a subject has a certain disease is the disease itself; this is the case with most of the studies listed in Tables 1-1 and 1-2. In some cases, lens opacities (Jacques *et al.*, 2001; Taylor *et al.*, 2002) or lens optical density (Hammond *et al.*, 1997;

Berendschot *et al.*, 2002; Jacques *et al.*, 2005) were measured and reported instead of cataract incidence or severity. These are both valid, however, because cataract is defined as "the opacification of the crystalline lens of the eye" (Jacques *et al.*, 2001). Furthermore, the opacity of the lens is assessed by measuring its optical density (or its degree of light scattering, as defined by the LOCS III; Jacques *et al.*, 2001). Therefore, these two measures are not biomarkers of disease, but very specific methods used to objectively quantify the stage of cataract development.

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Morris, M.S.; Jacques, P.F.; Chylack, L.T.; Hankinson, S.E.; Willett, W.C.; Hubbard, L.D.; Taylor, A. 2007. Intake of zinc and antioxidant micronutrients and early age-related maculopathy lesions. Ophthalmic Epidemiol 14(5):288-298.

Nolan, J.M.; O', Donovan, O.; Loane, E.; Beatty, S.; Stack, J.; Beatty, S. 2007. Risk factors for age-related maculopathy are associated with a relative lack of macular pigment. Exp Eye Res 84(1):61-74.

Obana A.; Hiramitsu T.; Gohto Y.; Ohira A.; Mizuno S.; Hirano T.; Bernstein PS.; Fujii H.; Iseki K.; Tanito M.; Hotta Y. 2008. Macular carotenoid levels of normal subjects and age-related maculopathy patients in a Japanese population. Ophthalmology 115(1):147-157.

SanGiovanni, J.P.; Chew, E.Y.; Clemons, T.E.; Ferris, F.L.; Gensler, G.; Lindblad, A.S.; Milton, R.C.; Seddon, J.M.; Sperduto, R.D.; Age-related Eye Disease Study Research Group. 2007. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report no. 22. Arch Ophthalmol 125(9):1225-1232.

Seddon, J.M.; Ajani, U.A.; Sperduto, R.D.; Hiller, R.; Blair, N.; Burton, T.C.; Farber, M.D.; Gragoudas, E.S.; Haller, J.; Miller, D.T.; Yannuzzi, L.A.; Willett, W. 1994. Dietary carotenoids, vitamins A, C and E and advanced age-related macular degeneration. JAMA 272(18):1413-1420.

Tan, J.S.; Wang, J.J.; Flood, V.; Rochtchina, E.; Smith, W.; Mitchell, P. 2008. Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 115(2):334-341.

Taylor, A.; Jacques, P.F.; Chylack, L.T. (Jr.); Hankinson, S.E.; Khu, P.M.; Rogers, G.; Friend, J.; Tung, W.; Wolfe, J.K.; Padhye, N.; Willett, W.C. 2002. Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities. Am J Clin Nutr 75(3):540-549.

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VandenLangenberg, G.M.; Mares-Perlman, J.A.; Klein, R.; Klein, B.E.; Brady, W.E.; Palta, M. 1998. Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 148(2):204-214.

Vu, H.T.V.; Robman, L.; Hodge, A.; McCarty, C.A.; Taylor, H.R. 2006. Lutein and zeaxanthin and the risk of cataract: the Melbourne Visual Impairment Project. Invest Ophthalmol Vis Sci 47(9):3783-3786.

OLESTRA AMENDMENT GRAS NOTICE

ATTACHMENT II TO APPENDIX E:

EXCLUDED STUDIES

January 18, 2010

ATTACHMENT II TO APPENDIX E:

EXCLUDED STUDIES

Table of Contents

Page

Table E-1 Lutein/Zeaxanthin Studies Excluded from Analysis.....II-2

Table E-2 Results from Studies Excluded on the Basis of Combining Lutein and/or Zeaxanthin with Other Nutritional or Pharmacological Agents as Treatment II-6

Table E-1 Lutein/Zeaxanthin Studies Excluded from Analysis

Reference	Reason for Exclusion
Bartlett, H.E.; Eperjesi, F. 2007. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. Eur J Clin Nutr 61(9):1121-1127.	Lutein was combined with other nutritional interventions
Beatty, S.; Donovan, O.O.; Neelam, K.; Rathaille, M.O.; Godinho, M.; Nolan, J. 2005. Perennial measurements of macular pigment optical density and serum levels of its constituent carotenoids. Invest Ophthalmol Vis Sci 46(Suppl. S):1762 [Abstract No. 1762—B531].	Study was published in abstract form only
Bermudez, O.I.; Ribaya-Mercado, J.D.; Talegawkar, S.A.; Tucker, K.L. 2005. Hispanic and non-hispanic white elders from Massachusetts have different patterns of carotenoid intake and plasma concentrations. J Nutr 135(6):1496-1502.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Cangemi, F.E. 2007. TOZAL study: an open case control study of an oral antioxidant and omega-3 supplement for dry AMD. BMC Ophthalmol 7:3 [1-10].	Lutein and zeaxanthin were combined with other nutritional interventions
Castenmiller, J.J.; West, C.E. 1998. Bioavailability and bioconversion of carotenoids. Annu Rev Nutr 18:19-38.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Chitchumroonchokchai, C.; Bomser, J.A.; Glamm, J.E.; Failla, M.L. 2004. Xanthophylls and {({alpha})}-tocopherol decrease uvb-induced lipid peroxidation and stress signaling in human lens epithelial cells. J Nutr 134(12):3225-3232.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Cumming, RGI Mitchell, P; Smith, W. 2000. Diet and Cataract. The Blue Mountains Eye Study. Ophthalmology, 107: 450-456.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Flood, V.; Rochtchina, E.; Wang, J.J.; Mitchell, P.; Smith, W. 2006. Lutein and zeaxanthin dietary intake and age related macular degeneration. Br J Ophthalmol 90(7):927-928.	Not primary or secondary research
Flood, V.; Smith, W.; Wang, J.J.; Manzi, F.; Webb, K.; Mitchell, P. 2002. Dietary antioxidant intake and incidence of early age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology 109(12):2272-2278.	Kin Publication
Glaser, T.; Lienau, A.; Zeeb, D.; Krucker, M.; Dachtler, M.; Albert, K. 2003. Qualitative and quantitative determination of carotenoid stereoisomers in a variety of spinach samples by use of MSOPD before HPLC-UV, HPLC-APCI-MS, and HPLC-NMR on-line coupling. Chromatographia 57(Suppl.):S19-S25.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Hammond, B.R. (Jr.); Wooten, B.R.; Snodderly, D.M. 1996. Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration. Vision Res 36(18):3003-3009.	MPOD measurements were not related to intake or eye health.
Hankinson, SE; Stampfer, MJ; Seddon, JM; Colditz, GA; Rosner, B; Speizer, FE; Willett, WC. 1992. Nutrient intake and cataract extraction in women: a prospective study. BMJ 305: 335-339.	Intakes of Lutein/zeaxanthin were not quantified or examined.
Holcomb, C.A. 2004. Consumption of carotenoid-rich foods and central vision loss: a matched case-control study in Kansas. J Nutr Elder 24(1):1-18.	Intakes of Lutein/zeaxanthin were not quantified or examined.
Iannaccone, A.; Mura, M.; Gallaher, K.T.; Johnson, E.J.; Todd, W.A.; Kenyon, E.; Harris, T.L.; Harris, T.; Satterfield, S.; Johnson, K.C.; Kritchevsky, S.B. for the Health ABC Study. 2007. Macular pigment optical density in the elderly: findings in a large biracial midsouth population sample. Invest Ophthalmol Vis Sci 48(4):1458-1465.	Lutein was combined with other nutritional interventions

Table E-1 Lutein/Zeaxanthin Studies Excluded from Analysis

Reference	Reason for Exclusion
Iannaccone, A.; Gallaher, K.; Mura, M.; Kenyon, E.; Harris, T.L.; Todd, W.A.; Harris, T.; Johnson, K.C.; Satterfield, S.; Kritchevsky, S.B. 2005. Macular pigment optical densitometry in the elderly: findings in a large biracial mid-south sample and effect of optical blur in pseudophakic subjects. Invest Ophthalmol Vis Sci 46(Suppl. S):1567 [Abstract No. 1567—B336].	Study was published in abstract form only
Junghans, A.; Sies, H.; Stahl, W. 2001. Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. Arch Biochem Biophys 391(2):160-164.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated (also, was not a human study)
Khachik, F.; De Moura, F.F.; Chew, E.Y.; Douglass, L.W.; Ferris, F.L. (III); Kim, J.; Thompson, D.J.S. 2006. The effect of lutein and zeaxanthin supplementation on metabolites of these carotenoids in the serum of persons aged 60 or older. Invest Ophthalmol Vis Sci 47(12):5234-5242.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Khachik, F.; Carvalho, L.; Bernstein, P.S.; Muir, G.J.; Zhao, D.-Y.; Katz, N.B. 2002. Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. Exp Biol Med (Maywood) 227(10):845-851.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Kopsell, D.A.; Lefsrud, M.G.; Kopsell, D.E.; Wenzel, A.J.; Gerweck, C.; Curran-Celentano, J. 2006. Spinach cultigen variation for tissue carotenoid concentrations influences human serum carotenoid levels and macular pigment optical density following a 12-week dietary intervention. J Agric Food Chem 54(21):7998-8005.	Intervention study in which subjects were given spinach (not pure lutein)
Manzi, F.; Flood, V.; Webb, K.; Mitchell, P. 2002. The intake of carotenoids in an older Australian population: the Blue Mountains Eye Study. Public Health Nutr 5(2):347-352.	Effects of lutein/zeaxanthin (specifically) and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Mitchell, P.; Smith, W.; Cumming, R.G.; Flood, V.; Rochtchina, E.; Wang, J.J. 2003. Nutritional factors in the development of age-related eye disease. Asia Pac J Clin Nutr 12(Suppl.):S5 [Abstract].	Study was published in abstract form only
Moeller, S.M.; Mares, J.A. 2003. Ethnic differences in diet and age-related maculopathies. Int Ophthalmol Clin 43(4):47-59.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Mohan, M; Sperduto, RD; Angra, SK; Milton, RC; Mathur, RL; Underwood, BA; Jaffery, N; Pandya, CB; Chhabra, VK; Vajpayee, RB; Kalra, VK; Sharma, YR; The India-US Case-Control Study Group. 1989. India-US case-control study of age-related cataracts. Arch Ophthalmol, 107: 670-676.	Intakes of Lutein/zeaxanthin were not quantified or examined.
Morganti, P.; Fabrizi, G.; Bruno, C. 2004. Protective effects of oral antioxidants on skin and eye function. Skinmed 3(6):310-316.	Intervention study in which lutein was combined with other nutritional interventions
Morganti, P.; Morganti, P.; Bruno, C.; Fabrizi, G.; Valenzano, F.; Del, Ciotto, P.; Morganti, G.; Morganti, P. 2004. The antioxidant network of skin and eye. Efficacy of carotenoids. J Appl Cosmetol 22(3):133-142.	Intervention study in which lutein was combined with other nutritional interventions
Olmedilla, B.; Granado, F.; Blanco, I.; Herrero, C. 2003. Luteina y zeaxantina en suero de sujetos control y pacientes con catarata senil: relación con la función visual y efecto de la suplementación con luteína = Lutein and zeaxanthin in serum from control subjects and senile cataract patients: relationship with visual function and effect of lutein supplementation. Quim Clin 22(2):48-54.	Study was not published in English
Peng, Y.M.; Peng, Y.S.; Lin, Y.; Moon, T.; Roe, D.J.; Ritenbaugh, C. 1995. Concentrations and plasma-tissue-diet relationships of carotenoids, retinoids, and tocopherols in humans. Nutr Cancer 23(3):233-246.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated

Table E-1 Lutein/Zeaxanthin Studies Excluded from Analysis

Reference	Reason for Exclusion
Ribarova, F.; Marinova, D. 2006. Dietary antioxidants and cataract prevention. Acta Med Bulg 33(1):92-97.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Richer, S.P. 2003. The age-related eye disease study found an antioxidant/mineral supplement decreases the progression of age-related macular degeneration, while emerging science suggests benefits of spinach and lutein supplementation. Clin Surg Opthalmol 21(7):296-300.	Preliminary report of a study
Rock, C.L.; Thornquist, M.D.; Neuhouser, M.L.; Kristal, A.R.; Neumark-Sztainer, D.; Cooper, D.A.; Patterson, R.E.; Cheskin, L.J. 2002. Diet and lifestyle correlates of lutein in the blood and diet. J Nutr 132(3):525S-530S.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Schalch, W.; Barker, F.M.; LUXEA Study Group. 2005. Ocular and general safety of supplementation with zeaxanthin and lutein; plasma exposure levels of carotenoids and 3-dehydro-lutein-results of the LUXEA study. Invest Ophthalmol Vis Sci 46(Suppl. S):1765 [Abstract No. 1765—B534].	Study was published in abstract form only
Schalch, W. 1992. Carotenoids in the retina--a review of their possible role in preventing or limiting damage caused by light and oxygen. EXS 62:280-298.	No specific information on lutein/zeaxanthin was included
Seddon, J.M.; Gensler, G.; Klein, M.L.; Milton, R.C. 2006. C-reactive protein and homocysteine are associated with dietary and behavioral risk factors for age-related macular degeneration. Nutrition 22(4):441-443.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Smith, W; Mitchell, P; Webb, K; Leeder, SR. 1999. Dietary antioxidants and age-related Maculopathy. The Blue Mountains Eye Study. Ophthalmology, 106: 761-767.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
The Italian-American Cataract Study Group. 1991. Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. American Journal of Epidemiology, 133: 541-553.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Townend, BS; Townend, ME; Flood, V; Burlutsky, G; Rochtchina, E; Wang, JJ; Mitchell, P. 2007. Dietary macronutrient intake and five-year incident cataract: The Blue Mountains Eye Study. American Journal of Ophthalmology, 143: 932-939.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Tyssandier, V.; Cardinault, N.; Caris-Veyrat, C.; Amiot, M.J.; Grolier, P.; Bouteloup, C.; Azais-Braesco, V.; Borel, P. 2002. Vegetable-borne lutein, lycopene, and beta-carotene compete for incorporation into chylomicrons, with no adverse effect on the medium-term (3-wk) plasma status of carotenoids in humans. Am J Clin Nutr 75(3):526-534.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Vinson, J.A. 2006. Oxidative stress in cataracts: oxidative stress and metabolic disease. Pathophysiology 13(3):151-162.	Review was not specific to lutein or zeaxanthin
Vu, HTV; Robman, L; McCarty, CA; Taylor, HR; Hodge, A. 2006. Does dietary lutein and zeaxanthin increase the risk of age related macular degeneration? The Melbourne Visual Impairment Project. British Journal of Ophthalmology, 90:389-393.	Intakes of lutein and zeaxanthin were assessed along with intakes of linoleic acid.
Wang, W.; Connor, S.L.; Johnson, E.J.; Klein, M.L.; Hughes, S.; Connor, W.E. 2007. Effect of dietary lutein and zeaxanthin on plasma carotenoids and their transport in lipoproteins in age-related macular degeneration. Am J Clin Nutr 85(3):762-769.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Wenzel, A.J.; Stringham, J.M.; Sheehan, J.P.; Fuld, K.; Curran-Celentano, J. 2005. The spatial distribution of macular pigment optical density following lutein supplementation. Invest Ophthalmol Vis Sci 46(Suppl. S):1771 [Abstract 1771—B540].	Study was published in abstract form only

Table E-1 Lutein/Zeaxanthin Studies Excluded from Analysis

Reference	Reason for Exclusion
Wintch, S.W.; Zhao, D.; Ermakov, I.V.; McClane, R.W.; Gellermann, W.; Bernstein, P.S. 2003. A double blind, placebo controlled, lutein supplementation study evaluating two macular carotenoid measurement methods: resonance raman spectroscopy and heterochromatic flicker photometry. Invest Ophthalmol Vis Sci 2003:1744 [Abstract No. 1744—B640].	Study was published in abstract form only
Wise, J.A.; Morin, R.J.; Sanderson, R.; Blum, K. 1996. Changes in plasma carotenoid, alpha-tocopherol, and lipid peroxide levels in response to supplementation with concentrated fruit and vegetable extracts: a pilot study. Curr Ther Res 57(6):445-461.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated
Zhao, D.-Y.; Wintch, S.W.; Ermakov, I.V.; Gellermann, W.; Bernstein, P.S. 2003. Resonance raman measurement of macular carotenoids in retinal, choroidal, and macular dystrophies. Arch Ophthalmol 121(7):967-972.	Effects of lutein/zeaxanthin and/or MPOD and/or ARM/AMD/cataract formation were not evaluated

Table E-2 Results from Studies Excluded on the Basis of Combining Lutein and/or Zeaxanthin with Other Nutritional or Pharmacological Agents as Treatment

Study Type	Population	Intervention		Endpoints Measured	Results	Reference
		Daily Dose	Duration			
Randomized controlled trial – double blind between 2 treatment groups; open label for control	Treatment Group A – 20 healthy smoking subjects (gender distribution NR) aged 25 to 36 years Group B – 20 healthy smoking subjects (gender distribution NR) aged 25 to 36 years Control 10 healthy smoking subjects (gender distribution NR) aged 25 to 36 years	Treatment Group A – 6 mg lutein, 90 mg l-ascorbic acid, 10 mg dl-α-tocopherol, and 5 mg a-lipoic acid and sunscreen with SPF 20 Group B – 26 mg carotenoid, 4 mg lycopene, 30 mg dl-α-tocopherol, 120 mg l-ascorbic acid, and 20 mg polyphenol and sunscreen with SPF 20 Control Sunscreen with SPF 20 only	8 weeks	Density of the yellow macular pigment by heterochromatic flicker photometry Global visual acuity (visual resolution capability and visual activity combined with macular pigment density)	Macular density increased from 22% at Week 2 to 48% at Week 8 in Group A. Macular density in Group A was significantly greater than in Group B or Control Global visual acuity significantly greater at Week 2 and Week 8 in Group A compared to control group ($p<0.005$)	Morganti *et al.*, 2004a
Randomized controlled trial – double blind between 2 treatment groups; open label for control	Treatment Group A - 15 healthy subjects (gender distribution NR) aged 62 to 68 Group B – 15 healthy subjects (gender distribution NR) aged 62 to 68 Control 10 healthy subjects (gender distribution NR) aged 62 to 68	Treatment Group A – 30 mg lutein, 120 mg ascorbic acid, 60 mg tocopherol Group B – 26 mg carotenoids, 4 mg lycopene, 60 mg tocopherol, 120 ascorbic acid Control No treatment	8 weeks	Perimetry Photostress test Dark adaptometry CS VER Macular pigment density by heterochromatic flicker photometry	Percent increase in visual function (not further defined) in Group A was significantly increased at Week 8 compared to Week 2 and was significantly greater than Group B or the Control group at Weeks 2, 4, 6, and 8 Percent increase in macular pigment density in Group A was significantly increased at Week 8 compared to Week 2 and was significantly greater than Group B or the Control group at Weeks 2, 4, 6, and 8	Morganti *et al.*, 2004b

Table E-2 Results from Studies Excluded on the Basis of Combining Lutein and/or Zeaxanthin with Other Nutritional or Pharmacological Agents as Treatment

Study Type	Population	Intervention		Endpoints Measured	Results	Reference
		Daily Dose	Duration			
Randomized controlled trial – double blind	Treatment 37 (17 M, 20 F) subjects aged 54 to 90 years diagnosed with dry AMD in at least 1 eye Placebo 15 (5 M, 10 F) subjects aged 66 to 85 years diagnosed with dry AMD in at least 1 eye from the MIRA-1 trial (MIRA-1 study group and Pulido, 2002)	Treatment - 48 mg lutein, 2.4 mg zeaxanthin, 171,840 IU vitamin A, 2,712 mg vitamin C, 1,200 IU vitamin E, 417.6 mg zinc oxide, 9.6 mg copper, 2,400 mg taurine, 1,080 mg EPA, 720 mg DHA Placebo - 400 mg vitamin C, 200 IU vitamin E, 40 mg zinc, 3,000 IU beta-carotene	6 months	- BCVA measured by ETDRS (logMAR) - CS - Fluorescein angiogram, retinal photographs, full-threshold visual fields, macular testing, and the Visual Function Questionnaire-25	ETDRS BCVA (logMAR) - negative mean line change of 1.49 lines at 6 months in placebo group - positive mean line change of 0.54 lines at 6 months in treatment group In treatment group, BCVA score at 6 months (0.409) was significantly improved compared to baseline (0.355), P = 0.045 Fluorescein angiogram, retinal photographs, full-threshold visual fields, macular testing, and the Visual Function Questionnaire-25 did not change significantly at 6 months.	Cangemi, 2007
Randomized controlled trial – double blind	Treatment 15 Caucasian British adults (gender distribution NR) aged 55 to 82 years with at least one eye free from ocular pathology or with no ocular pathology other then ARM Placebo 10 Caucasian British adults (gender	Treatment - 6 mg lutein esters, 750 µg retinol, 250 mg vitamin C, 34 mg vitamin E, 10 mg zinc, 0.5 mg copper Placebo - cellulose	9 months	CS	NSD in change in mean CS score between treatment and placebo groups (z = -0.903, P = 0.366) Mean CS score decreased by 0.02 ± 0.18 log units in the treatment group and increased by 0.07 ± 0.07 log units in the placebo group	Bartlett and Eperjesi, 2007

Table E-2 Results from Studies Excluded on the Basis of Combining Lutein and/or Zeaxanthin with Other Nutritional or Pharmacological Agents as Treatment

Study Type	Population	Intervention		Endpoints Measured	Results	Reference
		Daily Dose	Duration			
	distribution NR) aged 55 to 82 years with at least one eye free from ocular pathology or with no ocular pathology other then ARM					

Abbreviations: AMD, age-related macular degeneration; ARM, age-related maculopathy; BCVA, Best-Corrected visual Acuity; CS, contrast sensitivity; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ETDRS, Early Treatment Diabetic Retinopathy Study; NR, not reported; NSD, no significant difference; SPF, sun protection factor; VER, visually evoked response

OLESTRA AMENDMENT GRAS NOTICE

ATTACHMENT III TO APPENDIX E:

TUBULAR SUMMARIES

(AGE-RELATED CATARACT, AGE-RELATED MACULAR DEGENERATION, VISUAL PERFORMANCE)

January 18, 2010

ATTACHMENT II TO APPENDIX E:

TUBULAR SUMMARIES

(AGE-RELATED CATARACT, AGE-RELATED MACULAR DEGENERATION, VISUAL PERFORMANCE)

Table of Contents

Page

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated.....III-2

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated III-33

Table E-3 Tabulation of Data from Human Intervention Studies.....III-87

REFERENCES.....III-94

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Berendschot *et al.,* 2002	52.4%	Cross-sectional	376 men (n=177) and women (n=199), aged 18 to 75 years, with normal serum cholesterol and triglycerides, and consuming an average western diet	Serum lutein (µmol/L)	0.18 ± 0.08	Lens optical density						NS
				Serum zeaxanthin (µmol/L)	0.049 ± 0.020							NS
				Adipose tissue lutein (µmol/kg wet weight)	0.40 ± 0.26							NS
				MPOD	0.33 ± 0.15							r=-0.12, P=0.05
Brown *et al.,* 1999 (Health Professionals' Follow-up Study)	64.0%	Prospective Cohort (3 to 8 years of follow-up; FFQ administered biannually from 1986 to 1994)	36,644 US male physicians aged 45-75, and free of cancer and cataracts at baseline	1st quintile of LZ intake (µg/day; median)	1300	Cataract extractions	173		1.00		NA	**0.03**
				2nd quintile of LZ intake (µg/day; median)	2279		180		1.00		0.81-1.23	
				3rd quintile of LZ intake (µg/day; median)	3182		181		0.98		0.79-1.20	
				4th quintile of LZ intake (µg/day; median)	4342		153		0.83		0.67-1.04	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				5th quintile of LZ intake (µg/day; median)	6871		153		0.81		0.65-1.01	
Chasan-Taber *et al.,* 1999 (Nurses' Health Study)	68.2%	Prospective Cohort (12 year follow-up; FFQ administered in 1980, 1984, 1986, and 1990)	77,466 Registered female nurses aged 45-71, who were free of diagnosed cataracts and diagnosed cancer in 1980	1st quintile of LZ intake (µg/day)	1172	Cataract extraction	295		1.0		NA	**0.04**
				2nd quintile of LZ intake (µg/day)	2064		306		1.01		0.86-1.19	
				3rd quintile of LZ intake (µg/day)	2817		296		0.95		0.80-1.11	
				4th quintile of LZ intake (µg/day)	6047		265		0.81		**0.69-0.96**	
				5th quintile of LZ intake (µg/day)	11685		309		0.88		0.75-1.03	
Christen *et al.*, 2008 (Women's Health Study)	73.1%	Prospective cohort (up to 11 years of follow-up)	35551 female health professionals aged 45 years or older, without cataracts at baseline	1st quintile of daily LZ intake (µg; median)	1177	Cases of cataract	429/7111		1.0		NA	0.045
				2nd quintile of daily LZ intake (µg; median)	2162		358/7110		0.77		0.67-0.89	
				3rd quintile of daily LZ intake (µg; median)	3070		438/7110		0.92		0.80-1.05	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				4th quintile of daily LZ intake (µg; median)	4245		393/7110		0.79		0.69-0.91	
				5th quintile of daily LZ intake (µg; median)	6716		413/7110		0.82		0.71-0.95	
Ciulla and Hammond, 2004	40.0%	Cross-sectional	22 men and women, aged 64-80 with severe cataracts (n=16), all with visual acuity of 20/30 or better	Average MPOD	0.24 ± 0.16	Severe cataracts	0/22					NS
			29 'normal' (relatively healthy and without retinal disease, but with varying levels of lenticular opacities) men and women, aged 64-80, all with visual acuity of 20/30 or better	Average MPOD	0.2 8 ± 0.21		29/29					

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Delcourt *et al.*, 2006 (POLA study)	73.9%	Cross-sectional	815 residents of Sete (France), over the age of 60	1st tertile of plasma lutein (µM)	<0.17	Nuclear cataract	59			1.0	NA	0.26
				2nd tertile of plasma lutein (µM)	0.17 – 0.41					0.79	0.41-1.53	
				3rd tertile of plasma lutein (µM)	≥0.41					0.60	0.26-1.47	
				1st tertile of plasma zeaxanthin (µM)	<0.04					1.0	NA	0.004
				2nd tertile of plasma zeaxanthin (µM)	0.04 – 0.09					0.47	0.25-0.88	
				3rd tertile of plasma zeaxanthin (µM)	≥0.09					0.25	0.08-0.71	
				1st tertile of plasma lutein (µM)	<0.17	Cortical cataract	30			1.0	NA	0.63
				2nd tertile of plasma lutein (µM)	0.17 – 0.41					0.80	0.33-1.94	
				3rd tertile of plasma lutein (µM)	≥0.41					0.75	0.23-2.47	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st tertile of plasma zeaxanthin (μM)	<0.04					1.0	NA	0.83
				2nd tertile of plasma zeaxanthin (μM)	0.04 – 0.09					0.60	0.24-1.48	
				3rd tertile of plasma zeaxanthin (μM)	≥0.09					1.09	0.37-3.26	
				1st tertile of plasma lutein (μM)	<0.17	Posterior subcapsular cataract	53			1.0	NA	0.60
				2nd tertile of plasma lutein (μM)	0.17 – 0.41					1.17	0.55-2.48	
				3rd tertile of plasma lutein (μM)	≥0.41					1.26	0.52-3.07	
				1st tertile of plasma zeaxanthin (μM)	<0.04					1.0	NA	0.68
				2nd tertile of plasma zeaxanthin (μM)	0.04 – 0.09					1.22	0.60-2.48	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd tertile of plasma zeaxanthin (µM)	≥0.09					0.84	0.34-2.07	
				1st tertile of plasma lutein (µM)	<0.17	Mixed type cataract	66			1.0	NA	0.59
				2nd tertile of plasma lutein (µM)	0.17 – 0.41					0.87	0.40-1.87	
				3rd tertile of plasma lutein (µM)	≥0.41					0.75	0.27-2.10	
				1st tertile of plasma zeaxanthin (µM)	<0.04					1.0	NA	0.49
				2nd tertile of plasma zeaxanthin (µM)	0.04 – 0.09					1.00	0.44-2.26	
				3rd tertile of plasma zeaxanthin (µM)	≥0.09					0.66	0.23-1.91	
				1st tertile of plasma lutein (µM)	<0.17	Cataract surgery	33			1.0	NA	0.93

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				2nd tertile of plasma lutein (μM)	0.17 – 0.41					0.83	0.39-1.76	
				3rd tertile of plasma lutein (μM)	≥0.41					1.07	0.41-2.77	
				1st tertile of plasma zeaxanthin (μM)	<0.04					1.0	NA	0.52
				2nd tertile of plasma zeaxanthin (μM)	0.04 – 0.09					0.69	0.33-1.43	
				3rd tertile of plasma zeaxanthin (μM)	≥0.09					0.75	0.30-1.89	
				1st tertile of plasma lutein (μM)	<0.17	Any cataract	241			1.0	NA	0.48
				2nd tertile of plasma lutein (μM)	0.17 – 0.41					0.85	0.56-1.30	
				3rd tertile of plasma lutein (μM)	≥0.41					0.82	0.48-1.41	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st tertile of plasma zeaxanthin (µM)	<0.04					1.0	NA	0.03
				2nd tertile of plasma zeaxanthin (µM)	0.04 – 0.09					0.70	0.46-1.05	
				3rd tertile of plasma zeaxanthin (µM)	≥0.09					0.57	0.34-0.95	
Dherani *et al.*, 2008	60.9%	Cross-sectional	1112 subjects (52% female) aged ≥50 years; recruited from 11 peri-urban villages in northern India	1st tertile of serum lutein (µmol/L)	<0.0762	All cataracts	778/1054			1	n/a	0.06
				2nd tertile of serum lutein (µmol/L)	≥0.0762 - <0.1137					0.70	0.43-1.15	
				3rd tertile of serum lutein (µmol/L)	≥0.1137					0.66	0.43-1.02	
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.75	0.64-0.87	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st tertile of serum zeaxanthin (µmol/L)	<0.0155					1	n/a	**0.03**
				2nd tertile of serum zeaxanthin (µmol/L)	≥0.0155-<0.0214					0.71	0.44-1.15	
				3rd tertile of serum zeaxanthin (µmol/L)	≥0.0214					0.66	0.45-0.96	
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.75	0.64-0.87	
				1st tertile of serum lutein (µmol/L)	<0.0762	Nuclear Cataract	554/826			1	n/a	0.3
				2nd tertile of serum lutein (µmol/L)	≥0.0762 - <0.1137					0.84	0.42-1.71	
				3rd tertile of serum lutein (µmol/L)	≥0.1137					0.75	0.44-1.31	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.76	0.59-0.99	
				1st tertile of serum zeaxanthin (µmol/L)	<0.0155					1	n/a	0.2
				2nd tertile of serum zeaxanthin (µmol/L)	≥0.0155-<0.0214					0.80	0.44-1.45	
				3rd tertile of serum zeaxanthin (µmol/L)	≥0.0214					0.71	0.43-1.17	
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.76	0.63-0.93	
				1st tertile of serum lutein (µmol/L)	<0.0762	Cortical cataract	208/480			1	n/a	0.1
				2nd tertile of serum lutein (µmol/L)	≥0.0762 - <0.1137					0.75	0.46-1.23	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd tertile of serum lutein (µmol/L)	≥0.1137					0.53	0.28-1.02	
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.67	0.50-0.90	
				1st tertile of serum zeaxanthin (µmol/L)	<0.0155					1	n/a	0.1
				2nd tertile of serum zeaxanthin (µmol/L)	≥0.0155-<0.0214					0.72	0.33-1.57	
				3rd tertile of serum zeaxanthin (µmol/L)	≥0.0214					0.58	0.30-1.12	
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.76	0.57-1.02	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st tertile of serum lutein (µmol/L)	<0.0762	Posterior subcapsular cataract	194/466			1	n/a	0.4
				2nd tertile of serum lutein (µmol/L)	≥0.0762 - <0.1137					0.78	0.24-2.56	
				3rd tertile of serum lutein (µmol/L)	≥0.1137					0.72	0.30-1.71	
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.85	0.56-1.31	
				1st tertile of serum zeaxanthin (µmol/L)	<0.0155					1	n/a	0.6
				2nd tertile of serum zeaxanthin (µmol/L)	≥0.0155-<0.0214					0.68	0.20-2.29	
				3rd tertile of serum zeaxanthin (µmol/L)	≥0.0214					0.84	0.43-1.67	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Log_e (the OR for a doubling of the natural log of the antioxidant level)	n/a					0.90	0.63-1.27	
Gale *et al.*, 2001	68.2%	Cross-sectional	Men (n=200) and women (n=172) aged 66 to 75 years, born and currently residing in Sheffield.	1st tertile of plasma lutein (µmol/L)	≤0.14	Nuclear cataract	NR			1.0	NA	0.911
				2nd tertile of plasma lutein (µmol/L)	0.15-0.20		NR			0.5	0.3-1.0	
				3rd tertile of plasma lutein (µmol/L)	>0.20		NR			0.8	0.4-1.5	
				1st tertile of plasma zeaxanthin (µmol/L)	≤0.03		NR			1.0	NA	0.417
				2nd tertile of plasma zeaxanthin (µmol/L)	0.04-0.05		NR			0.7	0.4-1.4	
				3rd tertile of plasma zeaxanthin (µmol/L)	>0.05		NR			0.7	0.4-1.4	
				1st tertile of plasma lutein (µmol/L)	≤0.14	Cortical cataract	NR			1.0	NA	0.727

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				2nd tertile of plasma lutein (µmol/L)	0.15-0.20		NR			0.7	0.4-1.3	
				3rd tertile of plasma lutein (µmol/L)	>0.20		NR			1.3	0.7-2.4	
				1st tertile of plasma zeaxanthin (µmol/L)	≤0.03		NR			1.0	NA	0.734
				2nd tertile of plasma zeaxanthin (µmol/L)	0.04-0.05		NR			1.2	0.7-2.4	
				3rd tertile of plasma zeaxanthin (µmol/L)	>0.05		NR			1.0	0.5-2.0	
				1st tertile of plasma lutein (µmol/L)	≤0.14	Posterior subcapsular cataract	NR			1.0	NA	0.012
				2nd tertile of plasma lutein (µmol/L)	0.15-0.20		NR			0.3	0.1-0.7	
				3rd tertile of plasma lutein (µmol/L)	>0.20		NR			0.5	0.2-1.0	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st tertile of plasma zeaxanthin (µmol/L)	≤0.03		NR			1.0	NA	0.360
				2nd tertile of plasma zeaxanthin (µmol/L)	0.04-0.05		NR			0.9	0.4-2.0	
				3rd tertile of plasma zeaxanthin (µmol/L)	>0.05		NR			0.7	0.3-1.7	
Hammond *et al.*, 1997	54.5%	Cross-sectional	12 young currently non-smoking men and women, aged 24-36, with no systemic or ocular disease	Relationship between MPOD and lens density	r= 0.07	Lens density	NA					NS
			18 middle-aged currently non-smoking men and women, aged 48-66, with no systemic or ocular disease		r= -0.29		NA					NS

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			21 elderly currently non-smoking men and women, aged 67-82, with no systemic or ocular disease		r= -0.48		NA					P< 0.015
Jacques *et al.,* 2001 (Nutrition and Vision Project, nested in the Nurses' Health Study)[2]	80.7%	Prospective cross-sectional (nested; FFQ data averaged from FFQ administered in 1980, 1984, 1986, and 1990)	478 registered female nurses residing in the Boston area, aged ~61, with no history of diabetes, cancer, or cataracts at baseline	1st quintile of LZ intake (mg/day) (n=94)	NA	Nuclear lens opacity	NR			1.0	NA	0.08
				2nd quintile of LZ intake (mg/day) (n=104)	2,400		NR			0.45	**0.24-0.84**	
				3rd quintile of LZ intake (mg/day) (n=88)	3,300		NR			0.49	**0.25-0.94**	
				4th quintile of LZ intake (mg/day) (n=98)	4,300		NR			0.39	**0.21-0.72**	
				5th quintile of LZ intake (mg/day) (n=94)	5,600		NR			0.52	**0.29-0.91**	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Jacques *et al.*, 2005 (Nurses' Health Study)	73.1%	Prospective cross-sectional (FFQ administered in 1980, 1984, 1986, 1990, and 1993-1995; 5-year follow-up)	408 NHS cohort members aged 52-74 in 1993	1st quintile of daily LZ intake (mg; median; n=73)	NA	5-year mean increases in nuclear density	18.5 (14.3-23.3)					0.23
				2nd quintile of daily LZ intake (mg; median; n=90)	2.4		18.7 (14.3-23.6)					
				3rd quintile of daily LZ intake (mg; median; n=84)	3.3		17.9 (13.8-22.4)					
				4th quintile of daily LZ intake (mg; median; n=82)	4.3		18.0 (13.8-22.6)					
				5th quintile of daily LZ intake (mg; median; n=79)	5.6		16.8 (12.7-21.4)					

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Lyle *et al.*, 1999b (Nutritional Factors in Eye Disease Study, nested in Beaver Dam Study)[1]	69.6%	Prospective cross-sectional (5 years of follow-up; FFQ administered at baseline only)	1,354 subjects aged 43-84, living in south-central Wisconsin (53% female; predominately Caucasian)	1st quintile of Lutein intake (µg/4.18 MJ; median at baseline)	298	Incident nuclear cataract	NR			1.0	NA	0.09
				2nd quintile of Lutein intake (µg/4.18MJ; median at baseline)	459		NR			0.9	0.5-1.5	
				3rd quintile of Lutein intake (µg/4.18MJ; median at baseline)	600		NR			0.9	0.6-1.5	
				4th quintile of Lutein intake (µg/4.18MJ; median at baseline)	784		NR			0.9	0.6-1.5	
				5th quintile of Lutein intake (µg/4.18MJ; median at baseline)	1,245		NR			0.6	0.4-1.1	
				1st quintile of Lutein intake (µg/4.18MJ; median at 10 years before baseline)	298	Incident nuclear cataract	NR			1.0	NA	**0.002**

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				2nd quintile of Lutein intake (µg/4.18MJ; median at 10 years before baseline)	459		NR			0.9	0.6-1.6	
				3rd quintile of Lutein intake (µg/4.18MJ; median at 10 years before baseline)	600		NR			0.9	0.6-1.7	
				4th quintile of Lutein intake (µg/4.18MJ; median at 10 years before baseline)	784		NR			0.7	0.4-1.2	
				5th quintile of Lutein intake (µg/4.18MJ; median at 10 years before baseline)	1,245		NR			0.5	**0.3-0.8**	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Lyle *et al.,* 1999a (p. 272) (Nutritional Factors in Eye Disease Study, nested in Beaver Dam Study)[1]	85.7%	Prospective cross-sectional (3-7 year follow-up; blood samples taken at baseline)	A random subsample of 325 participants in the Nutritional Factors in Eye Disease Study, ≥50 years of age, and free of cataracts at baseline	1st tertile of serum lutein (µmol/L; median)	0.18	Incident nuclear cataract				1.0	NA	0.35
				2nd tertile of serum lutein (µmol/L; median)	0.27					1.1	0.5-2.3	
				3rd tertile of serum lutein (µmol/L; median)	0.38					0.7	0.3-1.6	
Mares-Perlman *et al.,* 1995a (Nutritional Factors in Eye Disease Study, nested in Beaver Dam Study)	52.2%	Retrospective	859 females and 1,060 males ages 43-86 participating in the Nutritional factors in Eye Disease Study, a subset of the Beaver Dam Eye Study	1st quintile of LZ intake (µg/4.18 MJ)	179	Nuclear sclerosis				1.0	NA	**0.02**
				2nd quintile of LZ intake (µg/4.18 MJ)	282					1.06	0.73-1.56	
				3rd quintile of LZ intake (µg/4.18 MJ)	385					1.20	0.82-1.75	
				4th quintile of LZ intake (µg/4.18 MJ)	551					0.81	0.56-1.19	
				5th quintile of LZ intake (µg/4.18 MJ)	949					0.73	0.50-1.06	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Mares-Perlman *et al*., 1995b (Nutritional Factors in Eye Disease Study, nested in Beaver Dam Study)	73.9%	Cross-sectional	400 men and women aged 50 to 84 years and living in south-central Wisconsin (predominately Caucasian; 55% female)	Highest *vs*. lowest median serum lutein levels in women	0.45 *vs*. 0.16 µmol/L	Severe nuclear sclerosis				4.09	1.67-10.03	0.006
				Highest *vs*. lowest median serum lutein levels in men	0.43 *vs*. 0.14 µmol/L					0.71	0.27-1.89	0.93
				Highest *vs*. lowest median serum lutein levels in women	0.45 *vs*. 0.16 µmol/L	Cortical cataract				1.75	0.49-6.21	0.99
				Highest *vs*. lowest median serum lutein levels in men	0.43 *vs*. 0.14 µmol/L					4.84	0.83-28.1	**0.03**
				Highest *vs*. lowest median serum lutein levels in women	0.45 *vs*. 0.16 µmol/L	Any cataract				3.30	1.07-10.14	0.09
				Highest *vs*. lowest median serum lutein levels in men	0.43 *vs*. 0.14 µmol/L					1.50	0.41-5.50	0.38

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Moeller *et al.*, 2008 (CAREDS)	82.3%	Retrospective (Associations with MPOD were cross-sectional)	1802 American women aged 50-79 (in 1994-1998), with LZ intakes above the 78th or below the 28th percentiles (as assessed at baseline in the Women's Health Initiative study)	1st quintile of daily LZ intake (mg; median)	0.6	Nuclear cataract	NR			1.0	NA	0.04
				2nd quintile of daily LZ intake (mg; median)	0.9					0.76	0.54-1.07	
				3rd quintile of daily LZ intake (mg; median)	1.0					0.93	0.66-1.32	
				4th quintile of daily LZ intake (mg; median)	2.4					0.77	0.54-1.08	
				5th quintile of daily LZ intake (mg; median)	3.3					0.68	0.48-0.97	
				1st quintile of serum LZ (µmol/L; median (range))	0.15 (0.04-0.19)		NR			1.0	NA	0.01
				2nd quintile of serum LZ (µmol/L; median (range))	0.22 (0.19-0.25)					0.90	0.64-1.27	
				3rd quintile of serum LZ (µmol/L; median (range))	0.29 (0.25-0.33)					0.75	0.53-1.07	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				4th quintile of serum LZ (µmol/L; median (range))	0.37 (0.33-0.42)					0.83	0.58-1.18	
				5th quintile of serum LZ (µmol/L; median (range))	0.50 (0.42-1.69)					0.68	0.47-0.98	
Olmedilla *et al.,* 2002	38.5%	Case-control	138 cases (48 men and 89 women), aged 60-80, with uni- or bi-lateral senile cataracts. 110 controls (49 men and 61 women, aged 45-61), free of eye diseases, and matched for sex	Serum lutein (units not given), all ages	NR	Senile Cataract	NA			1.8	1.1-3.1	0.001
				Serum Lutein (units not given), age <61	NR					3.0	1.3-7.0	0.010
				Serum Lutein (units not given), age >61	NR					1.3	0.5-3.4	NS
				Serum zeaxanthin (units not given), all ages	NR					2.2	1.3-3.7	0.05

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Serum zeaxanthin (units not given), age <61	NR					3.1	1.3-7.4	0.008
				Serum zeaxanthin (units not given), age >61	NR					1.4	0.5-3.8	NS
				Serum zeaxanthin (units not given), age <61 (adjusted for sex and season)	NR					4.11	1.22-13.8	0.02
Rodriguez-Rodriguez *et al.,* 2006	55.5%	Case-control	177 institutionalized men and women from Madrid (91 cataract cases - 31 men and 60 women - and 86 controls)	5th percentile of lutein intake (µg/day)	256	Cataracts				1	NA	0.033
				95th percentile of lutein intake (µg/day)	3290					0.086	0.007-1.084	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Taylor *et al.*, 2002 (Nutrition and Vision Project-nested in the Nurses' Health Study)[2]	77.8%	Prospective cross-sectional (13 to 15 year follow-up; FFQ administered in 1980, 1984, 1986, and 1990)	492 registered female nurses residing in the Boston area, aged 53-73, who were free of diabetes or cataracts	1st quintile of LZ intake (mg/day)	NR	Cortical lens opacities	246/492			1.0		NS
				2nd quintile of LZ intake (mg/day)	2,400					0.63	0.38-1.05	
				3rd quintile of LZ intake (mg/day)	3,300					1.30	0.78-2.15	
				4th quintile of LZ intake (mg/day)	4,300					1.02	0.62-1.67	
				5th quintile of LZ intake (mg/day)	5,600					0.86	0.52-1.44	
				1st quintile of LZ intake (mg/day)	NR	Posterior subcapsular lens opacities	86/492			1.0	NA	NS
				2nd quintile of LZ intake (mg/day)	2,400					0.61	0.30-1.25	
				3rd quintile of LZ intake (mg/day)	3,300					0.83	0.41-1.68	
				4th quintile of LZ intake (mg/day)	4,300					0.29	**0.12-0.70**	
				5th quintile of LZ intake (mg/day)	5,600					0.60	0.28-1.30	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Valero *et al.*, 2002	85.2%	Case-control	Cases: 343 patients of the CEB clinic between the ages of 55 and 74 years (43.4% male), diagnosed with nuclear (n=101), cortical (n=38), posterior subcapsular (n=63), or mixed-type (n=141) cataract Controls: 334 subjects matched for age and gender (39.9% male), with both eyes having LOCS II grading of 0 (although 8.4% had AMD)	1st quintile of lutein intake (µg/d)	≤443	Cataract	NR			1.00	NA	0.78
				2nd quintile of lutein intake (µg/d)	>443 – 699					0.88	0.54-1.42	
				3rd quintile of lutein intake (µg/d)	>699 – 993					0.98	0.61-1.56	
				4th quintile of lutein intake (µg/d)	>993 – 1383					0.69	0.40-1.09	
				5th quintile of lutein intake (µg/d)	>1383					1.00	0.64-1.64	
				1st quintile of zeaxanthin intake (µg/d)	≤39		NR			1.00	NA	0.85
				2nd quintile of zeaxanthin intake (µg/d)	>39 – 66					1.13	0.70-1.82	
				3rd quintile of zeaxanthin intake (µg/d)	>66 – 95					0.91	0.56-1.49	
				4th quintile of zeaxanthin intake (µg/d)	>95 – 142					1.06	0.66-1.71	
				5th quintile of zeaxanthin intake (µg/d)	>142					0.99	0.61-1.60	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Vu *et al.*, 2006 (Melbourne VIP)	84.0%	Cross-sectional	1955 residents of the Melbourne area 40 years of age or older	1st quintile of daily energy-adjusted LZ intake (µg)	≤472	Nuclear cataract	387 (19.8%)			1.00	NA	**0.018**
				2nd quintile of daily energy-adjusted LZ intake (µg)	472 – 639					0.90	0.59-1.39	
				3rd quintile of daily energy-adjusted LZ intake (µg)	639 – 808					0.85	0.55-1.31	
				4th quintile of daily energy-adjusted LZ intake (µg)	808 – 1037					**0.58**	**0.37-0.91**	
				5th quintile of daily energy-adjusted LZ intake (µg)	>1037					0.64	0.40-1.03	
			1950 residents of the Melbourne area 40 years of age or older	1st quintile of daily energy-adjusted LZ intake (µg)	≤472	Posterior subcapsular cataract	177 (9.1%)			1.00	NA	0.601
				2nd quintile of daily energy-adjusted LZ intake (µg)	472 – 639					1.13	0.69-1.85	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd quintile of daily energy-adjusted LZ intake (µg)	639 – 808					0.85	0.51-1.43	
				4th quintile of daily energy-adjusted LZ intake (µg)	808 – 1037					0.90	0.54-1.51	
				5th quintile of daily energy-adjusted LZ intake (µg)	>1037					0.94	0.55-1.59	
			1841 residents of the Melbourne area 40 years of age or older	1st quintile of daily energy-adjusted LZ intake (µg)	≤472	Cortical cataract	182 (9.9%)			1.00	NA	0.328
				2nd quintile of daily energy-adjusted LZ intake (µg)	472 – 639					0.85	0.52-1.40	
				3rd quintile of daily energy-adjusted LZ intake (µg)	639 – 808					0.92	0.56-1.50	
				4th quintile of daily energy-adjusted LZ intake (µg)	808 – 1037					0.61	0.35-1.03	

Table E-1 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and Cataract Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Classification	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				5th quintile of daily energy-adjusted LZ intake (µg)	>1037					0.84	0.50-1.41	

[1] Although results from the Nutritional Factors in Eye Disease Study (a cohort nested in the Beaver Dam Eye Study) were reported separately, the same cohort and study design were used in both of these studies, and the only variable that differed is that Lyle *et al.* (1999b) presented results on dietary intakes of lutein and zeaxanthin, while Lyle *et al.* (1999a) presented results on serum levels of lutein and zeaxanthin. Thus, these 2 publications were counted as 1 study.
[2] Although results from the Nutrition and Vision Project were published separately, the same cohort and study design used in both of these studies, and the only variable that differed was that Jacques *et al.* (2001) presented results on nuclear cataract, while Taylor *et al.* (2002) presented results on cortical or posterior subcapsular cataract. Thus, these two publications were considered as 1 study.

Diagnoses of Events

Chasan-Taber *et al.*, 1999 – Events were recorded as participant reporting of cataract extraction surgery (confirmed by ophthalmologist).

Talyor *et al.*, 2002 – each participant had 2 types of photographs taken for the assessment of lens opacity (one focused on the pupillary/cortical plane and one focused on the posterior/PSC lens capsule). The degree of lenticular opacification was assessed using The Lens Opacities Classification System III [the use of a slit-lamp system to assess nuclear colour, nuclear opalescence, cortical cataract, and posterior subcapsular, by comparison with a standard set of transparencies (Chylack *et al.*, 1989)]; eyes were considered to have opacities in the cortical opalescence grade was ≥0.5 or the PSC grade was ≥0.3 (these thresholds were not associated with impaired vision).

Jacques *et al.*, 2001 – Lenses were examined using a photographic slit-lamp, and were classified according to the Lens Opacity Classification System III.

Brown *et al.*, 1999 – Events were recorded as participant reporting of cataract extraction surgery (confirmed by ophthalmologist).

Lyle *et al.*, 1999b – Nuclear opacities were graded from photographs on a 5-step scale using a set of standard photographs for comparison (the Wisconsin System for Classification of Cataracts from Photographs).

Mares-Perlman *et al.*, 1995a,b – Nuclear/cortical opacities were graded from photographs on a 5-step scale using a set of standard photographs for comparison (the Wisconsin System for Classification of Cataracts from Photographs).

Gale *et al.*, 2001 – Lenses were examined using a photographic slit-lamp, and were classified according to the Lens Opacity Classification System III.

Lyle *et al.*, 1999 (p.272) – Nuclear opacities were graded from photographs on a 5-step scale using a set of standard photographs for comparison (the Wisconsin System for Classification of Cataracts from Photographs).

Valero *et al.*, 2002 – Cases were defined as those subjects with a grade of ≥1 (LOCS II) in at least one eye.

Vu *et al.*, 2006 – Cortical cataract was defined as opacity of 4/16 or greater of the pupil circumference; posterior subcapsular cataract was defined as opacity of 1 mm^2 or greater; nuclear cataract was defined as opacity ≥ 2.0 (as compared to a set of standard cataract photographs according to the Wilmer standard cataract grading method; West *et al.*, 1988)

Hammond *et al.*, 1997 – The density of the ocular media was measured by comparing the scotopic sensitivity curve (obtained far enough from the fovea to avoid absorbance by the MP) to the rhodopsin spectrum.

Cuilla and Hammond, 2004 – Subjects waiting to undergo cataract surgery were defined as having severe cataracts (sufficient to interfere with the activities of daily living).

Delcourt *et al.*, 2006 – Cataracts were graded according to the LOCS III criteria.

Christen *et al.*, 2008 – Incident cataracts were reported by the study participants and verified by their ophthalmologists.

Jacques *et al.*, 2005 – The degree of nuclear lens opacity (density) was assessed using computer-assisted image analysis of digital lens images, and was measured as a function of a standard gray scale ranging from 0 (clear) to 255 (black), and reported as pixel density units.

Moeller *et al.*, 2008 – The optical density of nuclear opacities was graded against a series of 7 standard photographs producing continuous scores on a decimal scale that ranged from 0.0 to 7.1 (cataract was defined as a score of ≥4 or a history of cataract extraction)

Dherani *et al.*, 2008 – Cataracts were graded according to the LOCS II criteria.

Confounding factors adjusted/ accounted for

Chasan-Taber *et al.*, 1999 – Age, gender, cancer diagnosis, cigarette smoking, BMI, diabetes, energy intake, area of residence in 1976 (used as a measure of sunlight exposure), aspirin use, number of visits to a physician in 1978, alcohol intake, time period (2-year intervals), and the presence of eye disease at baseline.

Talyor *et al.*, 2002 – Age, gender, area of residence, history of diabetes and hypertension, cigarette smoking, summertime sunlight exposure, alcohol use, BMI, the date of examination, and the presence of eye disease at baseline.

Morris *et al.*, 2007 – Age, gender, energy intake, smoking, dietary fat, hard liquor and wine consumption, hypertension, sun exposure, BMI, the use of hormone replacement therapy, and the presence of eye disease at baseline.

Jacques *et al.*, 2001 – Age, gender, the presence of cataracts at baseline, alcohol intake, BMI at baseline, smoking, sunlight exposure, hypertension, use of vitamin C, E, or multivitamin supplements, and diabetes.

Brown *et al.*, 1999 – Age, gender, the presence of eye disease at baseline, time period (2-year intervals), diabetes, smoking, BMI, area of residence in 1986 (used as a measure of sunlight exposure), aspirin use, energy intake, physical activity, alcohol intake, routine eye exams, and profession.

Lyle *et al.*, 1999 – Age, gender, BMI, hypertension, diabetes, energy intake, smoking, alcohol intake, and the presence of cataracts at baseline.

Robman *et al.*, 2007 – Age, menopausal status, BMI, smoking, family history of AMD, source study, duration of follow-up, and presence of eye disease at baseline.

Mares-Perlman *et al.*, 1996 – Age and gender.

Vandenlangenberg *et al.*, 1998 – Age, gender, total daily calories, pack-years smoked, beer intake, history of cardiovascular disease, and history of diabetes.

Mares-Perlman *et al.*, 1995b – Age, gender, smoking, alcohol intake, sunlight exposure, diabetes, and hypercholesterolemia.

Mares-Perlman *et al.*, 1995a – Age, gender, BMI, hematocrit, education, smoking, alcohol intake, energy intake, supplementation, and antioxidant nutrient index (combined intakes of carotenoids, vitamin C, and vitamin E).

Gale *et al.*, 2001 – Age, gender, social class, BMI, glycosylated haemoglobin, serum cholesterol, pack-years of smoking, use of steroids in previous 5 years, and alcohol intake.

Cho *et al.*, 2004 – Age, calendar year, smoking, BMI, energy intake, alcohol intake, fish intake, physical activity, history of hypertension and hypercholesterolemia, post-menopausal hormone use (women), and occupation (men).

Lyle *et al.*, 1999 (p.272) – Age, sex, smoking, alcohol intake, BMI, haemoglobin and glycosylated haemoglobin, hypertension, and use of hypertensive medications.

Mares-Perlman *et al.*, 2001 – Age, gender, alcohol intake, hypertension, smoking, BMI (eye colour, diabetes, cardiovascular disease, and postmenopausal hormone use were found to not affect the OR more than 10% and therefore were not included in the final model).

Moeller *et al.*, 2006 – OR for intermediate AMD are adjusted for age, smoking, diabetes, family history of AMD, blue iris colour, cardiovascular disease, and hormone replacement therapy. OR for advanced AMD are adjusted for age, smoking, family history of AMD, blood pressure, cardiovascular disease, and hormone replacement therapy.

Valero *et al.*, 2002 – OR were adjusted for gender, age, and energy intake.

Vu *et al.*, 2006 – Fat intake, age, gender, iris colour, arthritis, diabetes > 5 years, gout >10 years, use of beta-blockers > 10 years, ACE inhibitors, loop diuretics, acetaminophen, thiazide diuretics, or vitamin A or E supplements, UV-B exposure, myopia ≥ 1D, AMD, and smoking >30 years.

Hammond *et al.*, 1997 – Age, gender, smoking, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, and the presence of eye disease at baseline.

Cuilla and Hammond, 2004 – Age, hypertension, diabetes, and the presence of eye disease at baseline were accounted for, but statistics were not adjusted.

Delcourt *et al.*, 2006 – Age, gender, BMI, smoking, iris colour, sunlight exposure, use of oral corticosteroids, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, the presence of eye disease at baseline, education level, plasma glutathione peroxidise and transthyretin, cardiovascular disease, cancer, asthma, and use of sunglasses.

Christen *et al.*, 2008 – Age, randomized treatment assignment, smoking, alcohol use, BMI, exercise, postmenopausal hormone use, history of hypertension, hypercholesterolemia, or diabetes mellitus, family history of myocardial infarction before age 60, and history of eye examination in the past 2 years.

Jacques *et al.*, 2005 – Age, smoking, BMI, sunlight exposure, alcohol intake, baseline nuclear density value, diabetes, the presence of eye disease at baseline, and length of follow-up

Moeller *et al.*, 2008 – Age, family history of cataract, sunlight exposure, use of nutritional supplements, iris colour, education, smoking, physical activity, height, weight, hormone replacement therapy, alcohol use, pulse pressure, diabetes, hypertension, and cardiovascular disease.

Dherani *et al.*, 2008 – Age, gender, smoking, alcohol intake, sunlight exposure, current and past jobs, literacy, household cooking practices, land-holding, BMI, and systolic blood pressure.

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Bernstein *et al.*, 2002	58.3%	Case-control	52 control subjects (73 eyes) without AMD	MPOD [resonance Raman carotenoid signal intensity at 1525 cm-1 (mean counts ± SD)]	219 ± 134	AMD	52/114					NA
			15 AMD patients (25 eyes) using high-dose lutein suppl. (≥4 mg/day)	MPOD [resonance Raman carotenoid signal intensity at 1525 cm-1 (mean counts ± SD)]	212 ± 169		15/114					**0.038** (*vs.* AMD cases not using suppl.)
			48 AMD patients (68 eyes) using low dose (≤0.275 mg/day) or no lutein suppl.	MPOD [resonance Raman carotenoid signal intensity at 1525 cm-1 (mean counts ± SD)]	148 ± 147		48/115					**0.01**(*vs.* controls) 0.038 (*vs.* AMD cases using suppl.)

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Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Cardinault *et al.*, 2005	62.5%	Case-control	37 males and females aged 74.7 ± 1.2 years with early or late ARM	Serum lutein (µM; mean, SEM)	0.178 (0.013)	ARM	37/61					NS
				Serum zeaxanthin (µM; mean, SEM)	0.044 (0.004)							
			24 controls matched for age, gender, smoking status, and serum cholesterol, triglycerides, and phospholipids	Serum lutein (µM; mean, SEM)	0.187 (0.023)		24/61					
				Serum zeaxanthin (µM; mean, SEM)	0.058 (0.009)							
Cho *et al.*, 2004	75.0%	Prospective cohorts (12 years of follow-up for males and 18 years for females)	77,562 females and 40,866 males aged ≥50 years without ARM or cancer at baseline Female subjects only	1st quintile of LZ intake (median; µg/day)	1455 for women and 1426 for men	Early ARM	464 (329 female and 135 male)/ 118428		1.00		NA	0.74
				2nd quintile of LZ intake (median; µg/day)	NR				1.03		0.75-1.43	
				3rd quintile of LZ intake (median; µg/day)	NR				1.36		0.79-2.34	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				4th quintile of LZ intake (median; µg/day)	NR				1.17		0.54-2.51	
				5th quintile of LZ intake (median; µg/day)	6160 for women and 6612 for men				1.22		0.54-2.74	
				1st quintile of LZ intake (median; µg/day)	1455 for women and 1426 for men	Neovascular ARM	316 (217 female and 99 male)/ 118428		1.00		NA	0.56
				2nd quintile of LZ intake (median; µg/day)	NR				1.16		0.79-1.71	
				3rd quintile of LZ intake (median; µg/day)	NR				1.12		0.76-1.66	
				4th quintile of LZ intake (median; µg/day)	NR				1.15		0.77-1.71	
				5th quintile of LZ intake (median; µg/day)	6160 for women and 6612 for men				1.17		0.78-1.76	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			Female subjects only	1st quintile of LZ intake (median; µg/day)	1455	Early ARM	329/ 11562		1.00		NR	0.27
				2nd quintile of LZ intake (median; µg/day)	NR				0.94		NR	
				3rd quintile of LZ intake (median; µg/day)	NR				1.08		NR	
				4th quintile of LZ intake (median; µg/day)	NR				0.82		NR	
				5th quintile of LZ intake (median; µg/day)	6160				0.83		NR	
				1st quintile of LZ intake (median; µg/day)	1455	Neovascular ARM	217/ 77562		1.00		NR	0.37
				2nd quintile of LZ intake (median; µg/day)	NR				1.10		NR	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd quintile of LZ intake (median; µg/day)	NR				1.16		NR	
				4th quintile of LZ intake (median; µg/day)	NR				1.17		NR	
				5th quintile of LZ intake (median; µg/day)	6160				1.26		NR	
			Male subjects only	1st quintile of LZ intake (median; µg/day)	1426	Early ARM	135/ 40866		1.00		NR	**0.05**
				2nd quintile of LZ intake (median; µg/day)	NR				1.33		NR	
				3rd quintile of LZ intake (median; µg/day)	NR				1.89		NR	
				4th quintile of LZ intake (median; µg/day)	NR				1.79		NR	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				5th quintile of LZ intake (median; µg/day)	6612				1.91		NR	
				1st quintile of LZ intake (median; µg/day)	1426	Neovascular ARM	99/ 40866		1.00		NR	0.87
				2nd quintile of LZ intake (median; µg/day)	NR				1.27		NR	
				3rd quintile of LZ intake (median; µg/day)	NR				1.06		NR	
				4th quintile of LZ intake (median; µg/day)	NR				1.10		NR	
				5th quintile of LZ intake (median; µg/day)	6612				1.03		NR	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Ciulla and Hammond, 2004	40.0%	Cross-sectional	59 men and women, aged 64-80, with non-exudative AMD, all with visual acuity of 20/30 or better	Average MPOD	0.26 ± 0.21	Non-exudative AMD	59/59					NS
			29 'normal' (relatively healthy and without retinal disease, but with varying levels of lenticular opacities) men and women, aged 64-80, all with visual acuity of 20/30 or better	Average MPOD	0.28 ± 0.21		0/29					
Dasch *et al.*, 2005 (MARS)	64.0%	Case-control	182 males and females with normal maculae and not using LZ suppl. (controls)	Mean serum lutein (µg/mL; SE)	124 (0.06)	NA	182/770					NA
				Mean serum zeaxanthin (µg/mL; SE)	0.019 (0.0012)							NA
			372 subjects with early ARM and not using LZ suppl.	Mean serum lutein (µg/mL; SE)	0.112 (0.004)	Early AMD	372/770					0.38 (*vs.* controls)

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Mean serum zeaxanthin (µg/mL; SE)	0.020 (0.0008)							0.41 (*vs.* controls)
			216 subjects with late ARM and not using LZ suppl.	Mean serum lutein (µg/mL; SE)	0.131 (0.006)	Late AMD	216/770					0.39 (*vs.* controls)
				Mean serum zeaxanthin (µg/mL; SE)	0.022 (0.0011)							0.08 (*vs.* controls)
Delcourt *et al.*, 2006 (POLA Study)	73.9%	Cross-sectional	640 males and females aged ≥60 years and residing in Sète (southern France)	1st tertile of plasma lutein (µM)	<0.18	Early and late AMD	41/640			1.0	NA	**0.04**
				2nd tertile of plasma lutein (µM)	0.18-0.41					0.40	0.18-0.89	
				3rd tertile of plasma lutein (µM)	≥0.41					0.31	0.09-1.07	
				1st tertile of plasma zeaxanthin (µM)	<0.04					1.0	NA	**0.005**
				2nd tertile of plasma zeaxanthin (µM)	0.04-0.09					0.74	0.35-1.59	
				3rd tertile of plasma zeaxanthin (µM)	≥0.09					0.07	0.01-0.58	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st tertile of plasma LZ (μM)	<0.25					1.0	NA	**0.01**
				2nd tertile of plasma LZ (μM)	0.25-0.56					0.45	0.20-1.01	
				3rd tertile of plasma LZ (μM)	≥0.56					0.21	0.05-0.79	
Gale *et al.*, 2003	63.6%	Cross-sectional	380 (207 Men and 173 women) born and currently residing in Sheffield, England, aged 66-75	1st tertile of plasma zeaxanthin (nmol/L)	≤ 26.5	AMD	33			2.0	1.0-4.1	**0.046**
				2nd tertile of plasma zeaxanthin (nmol/L)	26.6 – 46.3		27			1.7	0.8-3.4	
				3rd tertile of plasma zeaxanthin (nmol/L)	>46.3		17			1.0	NA	
				1st tertile of plasma lutein (nmol/L)	≤ 140.9		32			1.7	0.9-3.2	0.120
				2nd tertile of plasma lutein (nmol/L)	141.0 – 206.8		23			1.0	0.5-1.9	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd tertile of plasma lutein (nmol/L)	>206.8		22			1.0	NA	
				1st tertile of plasma lutein + zeaxanthin (nmol/L)	≤ 172.1		31			1.9	0.9-3.5	0.090
				2nd tertile of plasma lutein + zeaxanthin (nmol/L)	172.2 – 247.9		26			1.4	0.7-2.7	
				3rd tertile of plasma lutein + zeaxanthin (nmol/L)	>247.9		20			1.0	NA	
LaRowe *et al.*, 2008 (CAREDS/ WHI)	91.6%	Cross-sectional	1698 women aged 50-79 years (in 1994-1998) participating in the WHI study, with dietary LZ intakes either > the 78th or < the 28th percentile	1st quintile of MPOD (median and range; n=340)	0.08 (0-0.16)	Overall intermediate AMD	305/1670 at risk			1.00	NA	0.16
				2nd quintile of MPOD (median and range; n=340)	0.24 (0.17-0.30)					1.2	0.8-1.8	
				3rd quintile of MPOD (median and range; n=339)	0.36 (0.31-0.42)					1.1	0.7-1.6	
				4th quintile of MPOD (median and range; n=340)	0.48 (0.42-0.55)					1.2	0.8-1.8	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				5th quintile of MPOD (median and range; n=339)	0.63 (0.55-1.0)					1.4	0.9-2.1	
			Subjects aged <70 years	1st quintile of MPOD (median and range)	0.08 (0-0.16)		98/857 at risk			1.00	NA	0.89
				2nd quintile of MPOD (median and range)	0.24 (0.17-0.30)					0.6	0.3-1.2	
				3rd quintile of MPOD (median and range)	0.36 (0.31-0.42)					0.8	0.4-1.6	
				4th quintile of MPOD (median and range)	0.48 (0.42-0.55)					1.0	0.5-1.9	
				5th quintile of MPOD (median and range)	0.63 (0.55-1.0)					0.9	0.4-1.7	
			Subjects aged ≥ 70 years	1st quintile of MPOD (median and range)	0.08 (0-0.16)		201/813 at risk			1.00	NA	0.11

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				2nd quintile of MPOD (median and range)	0.24 (0.17-0.30)					1.6	1.0-2.8	
				3rd quintile of MPOD (median and range)	0.36 (0.31-0.42)					1.3	0.8-2.3	
				4th quintile of MPOD (median and range)	0.48 (0.42-0.55)					1.3	0.8-2.2	
				5th quintile of MPOD (median and range)	0.63 (0.55-1.0)					1.8	1.1-3.0	
			All subjects (aged 50-79 years)	1st quintile of MPOD (median and range; n=340)	0.08 (0-0.16)	Large Drusen	233/1598 at risk			1.00	NA	0.38
				2nd quintile of MPOD (median and range; n=340)	0.24 (0.17-0.30)					1.2	0.8-2.0	
				3rd quintile of MPOD (median and range; n=339)	0.36 (0.31-0.42)					1.1	0.7-1.7	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				4th quintile of MPOD (median and range; n=340)	0.48 (0.42-0.55)					1.1	0.7-1.7	
				5th quintile of MPOD (median and range; n=339)	0.63 (0.55-1.0)					1.3	0.9-2.1	
			Subjects aged <70 years	1st quintile of MPOD (median and range)	0.08 (0-0.16)		71/830 at risk			1.00	NA	0.88
				2nd quintile of MPOD (median and range)	0.24 (0.17-0.30)					0.6	0.3-1.4	
				3rd quintile of MPOD (median and range)	0.36 (0.31-0.42)					0.9	0.4-1.9	
				4th quintile of MPOD (median and range)	0.48 (0.42-0.55)					0.9	0.4-2.1	
				5th quintile of MPOD (median and range)	0.63 (0.55-1.0)					1.0	0.4-2.0	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			Subjects ≥70 years	1st quintile of MPOD (median and range)	0.08 (0-0.16)		162/768 at risk			1.00	NA	0.33
				2nd quintile of MPOD (median and range)	0.24 (0.17-0.30)					1.7	1.0-3.0	
				3rd quintile of MPOD (median and range)	0.36 (0.31-0.42)					1.3	0.7-2.3	
				4th quintile of MPOD (median and range)	0.48 (0.42-0.55)					1.1	0.6-2.0	
				5th quintile of MPOD (median and range)	0.63 (0.55-1.0)					1.7	1.0-3.0	
			All subjects (aged 50-79 years)	1st quintile of MPOD (median and range; n=340)	0.08 (0-0.16)	Pigmentary Abnormalities	157/1522 at risk			1.00	NA	**0.03**
				2nd quintile of MPOD (median and range; n=340)	0.24 (0.17-0.30)					1.4	0.8-2.4	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd quintile of MPOD (median and range; n=339)	0.36 (0.31-0.42)					1.3	0.8-2.3	
				4th quintile of MPOD (median and range; n=340)	0.48 (0.42-0.55)					1.6	1.0-2.9	
				5th quintile of MPOD (median and range; n=339)	0.63 (0.55-1.0)					1.8	1.0-3.1	
			Subjects aged <70 years	1st quintile of MPOD (median and range)	0.08 (0-0.16)		50/809 at risk			1.00	NA	0.71
				2nd quintile of MPOD (median and range)	0.24 (0.17-0.30)					0.7	0.3-1.9	
				3rd quintile of MPOD (median and range)	0.36 (0.31-0.42)					0.9	0.3-2.2	
				4th quintile of MPOD (median and range)	0.48 (0.42-0.55)					1.1	0.5-2.7	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				5th quintile of MPOD (median and range)	0.63 (0.55-1.0)					1.0	0.4-2.4	
			Subjects aged ≥70 years	1st quintile of MPOD (median and range)	0.08 (0-0.16)		107/713 at risk			1.00	NA	**0.03**
				2nd quintile of MPOD (median and range)	0.24 (0.17-0.30)					1.9	0.9-4.0	
				3rd quintile of MPOD (median and range)	0.36 (0.31-0.42)					1.8	0.9-3.8	
				4th quintile of MPOD (median and range)	0.48 (0.42-0.55)					2.1	1.0-4.2	
				5th quintile of MPOD (median and range)	0.63 (0.55-1.0)					2.4	1.2-4.8	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Mares-Perlman *et al.*, 1995c	72.0%	Nested case-control	127 cases with retinal pigment abnormalities or soft drusen; 9 cases with late ARMD (geographic atrophy); 31 cases with neovascular and exudative macular degeneration	Serum lutein (nmol/L; mean, SD)	204 (181)	AMD	127/294					NS
				Serum zeaxanthin (nmol/L; mean, SD)	55 (32)							NS
				Serum LZ (nmol/L; mean, SD)	294 (128)							**<0.05** (cases *vs.* controls)
			167 controls matched for age, sex, and smoking status	Serum lutein (nmol/L; mean, SD)	201 (103)							NS
				Serum zeaxanthin (nmol/L; mean, SD)	51 (28)							NS
				Serum LZ (nmol/L; mean, SD)	291 (138)							**<0.05** (cases *vs.* controls)

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Mares-Perlman *et al.*, 1996 (nested in Beaver Dam Eye Study)	66.7%	Retrospective longitudinal (FFQ for habits 10 years previous administered at baseline)	1968 male and female subjects aged 43 to 86 and living in south-central Wisconsin (predominately Caucasian; 55% female)	Lowest quintile of LZ intake (µg/4200 kJ)	17-204	Early ARM	314			1.0	0.7-1.5	0.78
				Highest quintile of LZ intake (µg/4200 kJ)	621-10700							
				Lowest quintile of LZ intake (µg/4200 kJ)	17-204	Late ARM	30			1.6	0.5-5.5	0.32
				Highest quintile of LZ intake (µg/4200 kJ)	621-10700							
Mares-Perlman *et al.*, 2001 (NHANES III)	Diet: 75.0% Serum: 71.4%	Cross-sectional (8222 American men and women aged ≥40 years)	Non-Hispanic White, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.61	Soft Drusen	64/1568			0.9	0.3-2.3	NS
				Lowest quintile of serum LZ (µmol/L)	0.19							
				Highest quintile of dietary LZ (µg/d)	4287		64/1608			0.9	0.4-2.0	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of dietary LZ (µg/d)	315							
			Non-Hispanic White, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.64		248/1692			1.3	0.8-2.0	NS
				Lowest quintile of serum LZ (µmol/L)	0.19							
				Highest quintile of dietary LZ (µg/d)	4905		260/1745			1.2	0.8-1.7	NS
				Lowest quintile of dietary LZ (µg/d)	389							
			Non-Hispanic White, aged ≥80 years	Highest quintile of serum LZ (µmol/L)	0.69		177/623			1.4	0.8-2.4	NS
				Lowest quintile of serum LZ (µmol/L)	0.20							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Highest quintile of dietary LZ (µg/d)	4730		186/653			2.1	1.2-3.7	**<0.05**
				Lowest quintile of dietary LZ (µg/d)	382							
			Non-Hispanic Black, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.64		56/1021			1.5	0.7-3.5	NS
				Lowest quintile of serum LZ (µmol/L)	0.21							
				Highest quintile of dietary LZ (µg/d)	8532		63/1098			1.0	0.5-2.3	NS
				Lowest quintile of dietary LZ (µg/d)	699							
			Non-Hispanic Black, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.79		69/655			0.6	0.3-1.5	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of serum LZ (µmol/L)	0.24							
				Highest quintile of dietary LZ (µg/d)	7915		80/712			1.2	0.6-2.4	NS
				Lowest quintile of dietary LZ (µg/d)	872							
			Mexican American, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.69		50/910			1.3	0.5-3.6	NS
				Lowest quintile of serum LZ (µmol/L)	0.23							
				Highest quintile of dietary LZ (µg/d)	3400		50/939			1.4	0.5-3.6	NS
				Lowest quintile of dietary LZ (µg/d)	459							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			Mexican American, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.68		98/693			1.1	0.5-2.1	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							
				Highest quintile of dietary LZ (µg/d)	3445		105/718			1.1	0.5-2.2	NS
				Lowest quintile of dietary LZ (µg/d)	452							
			All races, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.67		190/3662			0.7	0.3-1.7	NS
				Lowest quintile of serum LZ (µmol/L)	0.21							
				Highest quintile of dietary LZ (µg/d)	5554		197/3816			1.2	0.6-2.3	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of dietary LZ (µg/d)	394							
			All races, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.72		430/3139			1.1	0.6-1.9	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							
				Highest quintile of dietary LZ (µg/d)	5973		461/3278			1.3	0.9-1.9	NS
				Lowest quintile of dietary LZ (µg/d)	441							
			All races, aged ≥80 years	Highest quintile of serum LZ (µmol/L)	0.77		197/758			1.4	0.7-2.7	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Highest quintile of dietary LZ (µg/d)	5601		210/803			2.4	1.3-4.4	**<0.05**
				Lowest quintile of dietary LZ (µg/d)	382							
			Non-Hispanic White, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.61	Pigmentary Abnormalities	21/1570			0.7	0.2-3.0	NS
				Lowest quintile of serum LZ (µmol/L)	0.19							
				Highest quintile of dietary LZ (µg/d)	4287		22/1610			0.3	0.1-0.3	**<0.05**
				Lowest quintile of dietary LZ (µg/d)	315							
			Non-Hispanic White, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.64		61/1716			0.7	0.3-1.7	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of serum LZ (µmol/L)	0.19							
				Highest quintile of dietary LZ (µg/d)	4905		62/1769			0.9	0.4-2.0	NS
				Lowest quintile of dietary LZ (µg/d)	389							
			Non-Hispanic White, aged ≥80 years	Highest quintile of serum LZ (µmol/L)	0.69		69/648			0.8	0.4-1.7	NS
				Lowest quintile of serum LZ (µmol/L)	0.20							
				Highest quintile of dietary LZ (µg/d)	4730		71/680			1.3	0.6-2.8	NS
				Lowest quintile of dietary LZ (µg/d)	382							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			Non-Hispanic Black, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.64		12/1028			2.7	0.3-2.7	NS
				Lowest quintile of serum LZ (µmol/L)	0.21							
				Highest quintile of dietary LZ (µg/d)	8532		13/731			1.2	0.2-6.4	NS
				Lowest quintile of dietary LZ (µg/d)	699							
			Non-Hispanic Black, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.79		11/671			NR	NR	NA
				Lowest quintile of serum LZ (µmol/L)	0.24							
				Highest quintile of dietary LZ (µg/d)	7915		12/?			NR	NR	NA

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of dietary LZ (µg/d)	872							
			Mexican American, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.69		13/914			NR	NR	NA
				Lowest quintile of serum LZ (µmol/L)	0.23							
				Highest quintile of dietary LZ (µg/d)	3400		13/943			0.5	0.0-5.1	NS
				Lowest quintile of dietary LZ (µg/d)	459							
			Mexican American, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.68		13/715			4.8	0.5-47.0	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Highest quintile of dietary LZ (µg/d)	3445		14/740			NR	NR	NA
				Lowest quintile of dietary LZ (µg/d)	452							
			All races, aged 40-59 years	Highest quintile of serum LZ (µmol/L)	0.67		49/3675			0.5	0.1-1.7	NS
				Lowest quintile of serum LZ (µmol/L)	0.21							
				Highest quintile of dietary LZ (µg/d)	5554		51/3829			0.1	0.1-0.3	**<0.05**
				Lowest quintile of dietary LZ (µg/d)	394							
			All races, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.72		87/3202			1.4	0.6-3.4	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of serum LZ (µmol/L)	0.22							
				Highest quintile of dietary LZ (µg/d)	5973		90/3344			1.1	0.5-2.4	NS
				Lowest quintile of dietary LZ (µg/d)	441							
			All races, aged ≥80 years	Highest quintile of serum LZ (µmol/L)	0.77		74/792			0.9	0.4-2.0	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							
				Highest quintile of dietary LZ (µg/d)	5601		77/839			1.0	0.4-2.4	NS
				Lowest quintile of dietary LZ (µg/d)	382							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			All races, aged ≤60 years	Highest quintile of serum LZ (µmol/L)	0.67	Late ARM	45/3685			0.6	0.2-1.9	NS
				Lowest quintile of serum LZ (µmol/L)	0.21							
				Highest quintile of dietary LZ (µg/d)	5554		47/3857			0.5	0.1-1.6	NS
				Lowest quintile of dietary LZ (µg/d)	394							
			All races, aged 60-79 years	Highest quintile of serum LZ (µmol/L)	0.72		15/3012			0.5	0.1-5.1	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							
				Highest quintile of dietary LZ (µg/d)	5973		16/3143			0.1	0.0-0.9	**<0.05**

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Lowest quintile of dietary LZ (µg/d)	441							
			All races, aged ≥80 years	Highest quintile of serum LZ (µmol/L)	0.77		30/673			0.8	0.3-2.4	NS
				Lowest quintile of serum LZ (µmol/L)	0.22							
				Highest quintile of dietary LZ (µg/d)	5601		31/714			0.6	0.2-2.7	NS
				Lowest quintile of dietary LZ (µg/d)	382							

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Moeller *et al.*, 2006	83.3%	Retrospective[2] (Associations with MPOD were cross-sectional)	1,787 women aged 50-79 years residing in Iowa, Wisconsin, and Oregon with lutein and zeaxanthin intakes above the 78th and below the 28th percentile at baseline in the WHI Observational Study were recruited 4-7 years later into the CAREDS	1st quintile of median serum LZ (range; µM)	0.153 (0.043-0.192)	Intermediate AMD	NR			1.00	NA	0.84
				2nd quintile of median serum LZ (range; µM)	0.222 (0.192-0.254)					0.98	0.66-1.44	
				3rd quintile of median serum LZ (range; µM)	0.289 (0.254-0.327)					1.03	0.77-1.53	
				4th quintile of median serum LZ (range; µM)	0.372 (0.328-0.416)					0.86	0.58-1.28	
				5th quintile of median serum LZ (range; µM)	0.503 (0.417-1.692)					1.01	0.68-1.49	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Any intermediate AMD	327/1753			0.98	0.77-1.26	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Large drusen	250/1676			0.91	0.69-1.21	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Pigmentary abnormalities	167/1593			1.10	0.79-1.54	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Advanced AMD	34/1787			0.89	0.43-1.81	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
			Subjects <75 years of age	High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Any intermediate AMD	190/1313			0.83	0.60-1.14	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Large drusen	136/1259			0.74	0.51-1.07	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Pigmentary abnormalities	97/1220			0.93	0.60-1.42	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Advanced AMD	12/1325			0.41	0.11-1.53	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
			Subjects ≥75 years of age	High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Any intermediate AMD	137/440			1.31	0.85-2.00	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Large drusen	114/417			1.26	0.80-1.99	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Pigmentary abnormalities	70/373			1.40	0.80-2.43	NS
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
				High dietary LZ (µg/1000 kcal/day)	1627 ± 797	Advanced AMD	22/462			1.37	0.54-3.47	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Low dietary LZ (µg/1000 kcal/day)	646 ± 214					1.00	NA	
Morris *et al.*, 2007 (Nutrition and Vision Project-nested in the Nurses' Health Study)	81.8%	Cross-sectional[2] (FFQ administered 1980, 1984, 1986, and 1990)	398 registered female nurses residing in the Boston area, aged 53-73, who were free of diabetes, diagnosed cancer, and had both lenses intact	1st quartile of LZ intake (µg/day)	<2536	ARM-related drusen	36/110			1.0	NA	0.38
				2nd quartile of LZ intake (µg/day)	2536-3397		46/112			1.4	0.8-2.7	
				3rd quartile of LZ intake (µg/day)	3398-5048		48/112			1.6	0.8-2.9	
				4th quartile of LZ intake (µg/day)	≥5049		51/112			1.5	0.8-2.8	
				1st quartile of LZ intake (µg/day)	<2357	Pigmentary abnormalities	16/92			1.0	NA	0.31
				2nd quartile of LZ intake (µg/day)	2357-3404		11/89			0.7	0.2-1.8	
				3rd quartile of LZ intake (µg/day)	3405-5004		20/89			1.3	0.5-2.9	
				4th quartile of LZ intake (µg/day)	≥5005		22/90			1.2	0.5-2.8	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Nolan *et al.*, 2007	76.2%	Cross-sectional	625 males and females with no known family history of ARM (controls)	MPOD	0.322 ± 0.166	NA	NA					NA
				Dietary lutein (mg/day; mean ± SD)	1.37 ± 0.95							NA
				Dietary zeaxanthin (mg/day; mean ± SD)	0.198 ± 0.118							NA
				Serum lutein (µg/mL; mean ± SD)	0.084 ± 0.040							NA
				Serum zeaxanthin (µg/mL; mean ± SD)	0.026 ± 0.016							NA
			175 males and females with family history of early ARM, GA, and CNV	MPOD	0.219 ± 0.15	NA	NA					**0.01** (*vs.* controls)
				Dietary lutein (mg/day; mean ± SD)	1.50 ± 1.08							NS
				Dietary zeaxanthin (mg/day; mean ± SD)	0.203 ± 0.117							NS
				Serum lutein (µg/mL; mean ± SD)	0.095 ± 0.047							**0.01** (*vs.* controls)

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Serum zeaxanthin (µg/mL; mean ± SD)	0.027 ± 0.015							NS
			41 males and females with family history of early ARM	MPOD	0.237 ± 0.12	NA	NA					**0.01** (*vs.* controls)
				Dietary lutein (mg/day; mean ± SD)	1.61 ± 0.99							NS
				Dietary zeaxanthin (mg/day; mean ± SD)	0.235 ± 0.144							NS
				Serum lutein (µg/mL; mean ± SD)	0.086 ± 0.050							**0.01** (*vs.* controls)
				Serum zeaxanthin (µg/mL; mean ± SD)	0.026 ± 0.013							NS
			55 males and females with family history of GA	MPOD	0.214 ± 0.18	NA	NA					0.01 (*vs.* controls)
				Dietary lutein (mg/day; mean ± SD)	1.53 ± 0.90							NS
				Dietary zeaxanthin (mg/day; mean ± SD)	0.195 ± 0.095							NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				Serum lutein (µg/mL; mean ± SD)	0.098 ± 0.040							**0.01** (*vs.* controls)
				Serum zeaxanthin (µg/mL; mean ± SD)	0.027 ± 0.013							NS
			79 males and females with family history of CNV	MPOD	0.207 ± 0.16	NA	NA					**0.01** (*vs.* controls)
				Dietary lutein (mg/day; mean ± SD)	1.39 ± 1.11							NS
				Dietary zeaxanthin (mg/day; mean ± SD)	0.187 ± 0.109							NS
				Serum lutein (µg/mL; mean ± SD)	0.099 ± 0.050							**0.01** (*vs.* controls)
				Serum zeaxanthin (µg/mL; mean ± SD)	0.029 ± 0.013							NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Obana *et al*., 2008	40.0%	Case-control	Controls: 10 male and 10 female Japanese subjects with no history of diabetes or heart/ liver dysfunction, aged 60 to 80 years	MPOD (measured in counts by Raman Spectroscopy) (n=20 eyes)	~1125	ARM	n/a					n/a
			Cases: 97 Japanese male and female patients recruited from hospital, with early (n=68; 51 M and 17 F) or late (n=73; 57 M and 16 F) ARM; aged 50 to 85 years	MPOD (measured in counts by Raman Spectroscopy) in eyes with no signs of ARM (n=13 eyes)	~525		13/13					<0.001 (vs. controls)

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				MPOD (measured in counts by Raman Spectroscopy) in eyes with early ARM (n=81 eyes)	~535		81/81					<0.001 (vs. controls)
				MPOD (measured in counts by Raman Spectroscopy) in eyes with late ARM (n=86 eyes)	~490		86/86					<0.001 (vs. controls) <0.001 (vs. eyes with early ARM)
				MPOD (measured in counts by Raman Spectroscopy) in cases with AREDS grade 1 ARM	~600	ARM	All					NS
				MPOD (measured in counts by Raman Spectroscopy) in cases with AREDS grade 2 ARM	~595							NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				MPOD (measured in counts by Raman Spectroscopy) in cases with AREDS grade 3 ARM	~625							NS
				MPOD (measured in counts by Raman Spectroscopy) in cases with AREDS grade 4 ARM	~600							NS
Robman *et al.*, 2007 (Cardiovascular Health and Age-Related Maculopathy Study)	46.2%	Retrospective[2] (mean 7 year follow-up; FFQ administered at baseline only)	254 subjects aged 51-89 with early AMD in at least 1 eye (levels 2 to 4) at baseline	1st quintile of LZ intake (µg/day)	≤520	Interlevel AMD progression	NR			1.00	NA	NR
				2nd quintile of LZ intake (µg/day)	520-702					1.59	0.54-4.70	
				3rd quintile of LZ intake (µg/day)	702-880					1.56	0.52-4.67	
				4th quintile of Z intake (µg/day)	880-1072					3.30	1.18-9.22	
				5th quintile of LZ intake (µg/day)	≤1072					2.51	0.85-7.42	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				1st quintile of LZ intake (µg/day)	≤520	Inter- and Intra-level AMD progression	NR			1.00	NA	NR
				2nd quintile of LZ intake (µg/day)	520-702					0.83	0.32-2.15	
				3rd quintile of LZ intake (µg/day)	702-880					1.18	0.46-3.00	
				4th quintile of LZ intake (µg/day)	880-1072					2.06	0.84-5.05	
				5th quintile of LZ intake (µg/day)	≤1072					1.51	0.59-3.88	
				1st quintile of LZ intake (µg/day)	≤520	Side-by-side AMD progression	NR			1.00	NA	NR
				2nd quintile of LZ intake (µg/day)	520-702					0.91	0.35-2.38	
				3rd quintile of LZ intake (µg/day)	702-880					2.06	0.82-5.17	
				4th quintile of LZ intake (µg/day)	880-1072					2.09	0.85-5.18	
				5th quintile of LZ intake (µg/day)	≤1072					1.84	0.64-4.23	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
SanGiovanni *et al.*, 2007 (AREDS)	80.0%	Case-control	3,403 males and females with varying severity of ARM/ARMD and 1,115 matched controls, aged >60 years	1st quintile of LZ intake (median; µg)	521	Neovascular AMD	174/178			1.0	NA	0.08
				2nd quintile of LZ intake (median; µg)	763		138/219			0.74	0.53-1.04	
				3rd quintile of LZ intake (median; µg)	1000		112/237			0.54	0.38-0.76	
				4th quintile of LZ intake (median; µg)	1333		116/233			0.68	0.48-0.97	
				5th quintile of LZ intake (median; µg)	2095		117/248			0.65	0.45-0.93	
				1st quintile of LZ intake (median; µg)	521	Geographic atrophy	34/178			1.0	NA	**0.03**
				2nd quintile of LZ intake (median; µg)	763		25/219			0.61	0.34-1.11	
				3rd quintile of LZ intake (median; µg)	1000		24/237			0.59	0.33-1.07	
				4th quintile of daily LZ intake (median; µg)	1333		17/233			0.50	0.26-0.95	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				5th quintile of LZ intake (median; µg)	2095		18/248			0.45	0.24-0.86	
				1st *vs*. 5th quintile of LZ intake	(521 *vs*. 2095 µg/day)	Stage 2: Extensive small or non-extensive intermediate drusen	1060 cases			0.9	0.7-1.2	NS
				1st *vs*. 5th quintile of LZ intake	(521 *vs*. 2095 µg/day)	Stage 3: Extensive intermediate or large drusen	1568 cases			0.7	0.6-1.0	**<0.05**
				1st *vs*. 5th quintile of LZ intake	(521 *vs*. 2095 µg/day)	Stage 4: Geographic atrophy	118 cases			0.5	0.2-0.9	**<0.05**
				1st *vs*. 5th quintile of LZ intake	(521 *vs*. 2095 µg/day)	Stage 5: Neovascular AMD	658 cases			0.6	0.4-0.8	**<0.05**
Seddon *et al.*, 1994	70.4 %	Case-control	356 cases aged 55-80 years diagnosed with neovascular ARMD within 1 year prior to enrolment and 520 matched controls	1st quintile of LZ intake (median; IU)	560.8	Exudative AMD	356/876			1.0	NA	**<0.001**
				2nd quintile of LZ intake (median; IU)	1211					1.14	0.7-1.8	
				3rd quintile of LZ intake (median; IU)	1708					0.84	0.5-1.3	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				4th quintile of LZ intake (median; IU)	2487					0.77	0.5-1.2	
				5th quintile of LZ intake (median; IU)	5757					0.43	0.2-0.7	
				1st quintile of LZ intake (median; IU)[1]	560.8	Exudative AMD	356/876			1.0	NA	**0.008**
				2nd quintile of LZ intake (median; IU)[1]	1211					1.16	0.7-1.8	
				3rd quintile of LZ intake (median; IU)[1]	1708					0.85	0.5-1.4	
				4th quintile of LZ intake (median; IU)[1]	2487					0.77	0.5-1.3	
				5th quintile of LZ intake (median; IU)[1]	5757					0.44	0.2-0.8	
Simonelli *et al.*, 2002	61.5%	Case-control	Cases: 19 Italian men and women with early ARM, mean age 66 years	Mean serum LZ/cholesterol (ng/mg)	92.1 ± 35.0	Early or late ARM	19/96					NS (*vs.* any other group)

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			Cases: 29 Italian men and women with late ARM, mean age 66 years	Mean serum LZ/cholesterol (ng/mg)	84.5 ± 34.3		29/96					NS (*vs.* any other group)
			Controls: 46 Italian men and women with no eye disease that could cause loss of visual acuity, mean age 68 years	Mean serum LZ/cholesterol (ng/mg)	96.8 ± 46.0		0/96					NS (*vs.* any other group)
Tan *et al.*, 2008 (Blue Mountains Eye Study)	70.4%	Prospective cohort (up to 5-year follow-up; FFQ administered at baseline)	2083 Caucasian residents of Australia, aged ≥ 49 years, free of the indicated endpoint at baseline	1st tertile of daily LZ intake	Amount NR	Late AMD	19/673 at risk		1.00		NA	0.36
				2nd tertile of daily LZ intake	Amount NR		23/682 at risk		1.11		0.58-2.13	
				3rd tertile of daily LZ intake	≥942 µg/day		17/680 at risk		0.72		0.34-1.50	
				1st tertile of daily LZ intake	Amount NR	Neovascular AMD	13/675 at risk		1.00		NA	0.061
				2nd tertile of daily LZ intake	Amount NR		16/684 at risk		1.12		0.52-2.41	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
				3rd tertile of daily LZ intake	≥942 µg/day		9/681 at risk		0.37		0.13-1.05	
Van Leeuwen *et al.*, 2005 (The Rotterdam Study)	70.4%	Prospective cohort (0.3 to 13.9 years of follow-up; FFQ administered at baseline only)	4170 non-institutionalized men and women with normal cognition, aged ≥55 years, with no AMD in either eye at baseline	1st quartile of LZ intake (range; mg/day)	≤1.8	ARMD	560/4170	1.0				0.65
				2nd quartile of LZ intake (range; mg/day)	>1.8 - ≤ 2.2			~ 0.9				
				3rd quartile of LZ intake (range; mg/day)	>2.2 - ≤ 2.8			~ 1.25				
				4th quartile of LZ intake (range; mg/day)	>2.8			~ 1.0				
				HR per 1-SD increase above mean dietary intake	Mean dietary intake = 2.37 ±1.08			1.01			0.93-1.09	NS

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
Vandenlangenberg *et al.*, 1998 (Beaver Dam Eye Study)	66.7%	Prospective cross-sectional (FFQ for current and past habits administered at baseline)	1361 male and female subjects aged 43 to 86 and living in south-central Wisconsin (predominately Caucasian; 55% female), and free of large drusen and RP abnormalities at baseline	1st quintile of LZ intake (µg/1000 kcal; median past intake)	294	Large Drusen (using past intake data)	114/1361			1.0	NA	0.86
				2nd quintile of LZ intake (µg/1000 kcal; median past intake)	421					0.76	0.4-1.5	
				3rd quintile of LZ intake (µg/1000 kcal; median past intake)	537					0.76	0.4-1.5	
				4th quintile of LZ intake (µg/1000 kcal; median past intake)	691					0.93	0.5-1.7	
				5th quintile of LZ intake (µg/1000 kcal; median past intake)	1006					0.93	0.5-1.8	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			1405 male and female subjects aged 43 to 86 and living in south-central Wisconsin (predominately Caucasian; 55% female), and free of large drusen and RP abnormalities at baseline	1st quintile of LZ intake (µg/1000 kcal; median past intake)	294	Pigmentary abnormalities (using past intake data)	63/1405			1.0	NA	0.68
				2nd quintile of LZ intake (µg/1000 kcal; median past intake)	421					1.38	0.6-3.1	
				3rd quintile of LZ intake (µg/1000 kcal; median past intake)	537					1.06	0.4-2.6	
				4th quintile of LZ intake (µg/1000 kcal; median past intake)	691					0.53	0.2-1.5	
				5th quintile of LZ intake (µg/1000 kcal; median past intake)	1006					1.48	0.6-3.5	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			1361 male and female subjects aged 43 to 86 and living in south-central Wisconsin (predominately Caucasian; 55% female), and free of large drusen and RP abnormalities at baseline	1st quintile of LZ intake (µg/1000 kcal; median past intake)	294	Large drusen (using baseline intake data)	114/1361			1.0	NA	0.87
				2nd quintile of LZ intake (µg/1000 kcal; median past intake)	421					0.66	0.3-1.3	
				3rd quintile of LZ intake (µg/1000 kcal; median past intake)	537					1.04	0.6-1.9	
				4th quintile of LZ intake (µg/1000 kcal; median past intake)	691					0.92	0.5-1.8	
				5th quintile of LZ intake (µg/1000 kcal; median past intake)	1006					0.93	0.5-1.8	

Table E-2 Tabulation of Data from Observational Studies in which Associations Between Lutein/Zeaxanthin and AMD Risk were Evaluated

Reference	Quality Score	Study Design	Population and Final Sample Size	Subject Class.	Lutein/ Zeaxanthin Intake/ Status	Events		Significance/ Risk Ratios (between groups)				
						Event Recorded	Incidence	HR	RR	OR	95% CI	P for trend
			1405 male and female subjects aged 43 to 86 and living in south-central Wisconsin (predominately Caucasian; 55% female), and free of large drusen and RP abnormalities at baseline	1st quintile of LZ intake (µg/1000 kcal; median past intake)	294	Pigmentary abnormalities (using baseline intake data)	63/1405			1.0	NA	0.87
				2nd quintile of LZ intake (µg/1000 kcal; median past intake)	421					0.82	0.3-2.0	
				3rd quintile of LZ intake (µg/1000 kcal; median past intake)	537					0.92	0.4-2.1	
				4th quintile of LZ intake (µg/1000 kcal; median past intake)	691					1.13	0.5-2.6	
				5th quintile of LZ intake (µg/1000 kcal; median past intake)	1006					0.84	0.3-2.0	

NA = Not applicable.
[1] multivariate model adjusted for intake of beta carotene
[2] Although study designs were retrospective, intake data were collected prospectively.

Diagnoses of Events
Chasan-Taber *et al.*, 1999 – Events were recorded as participant reporting of cataract extraction surgery (confirmed by ophthalmologist).
Morris *et al.*, 2007 – Retinas were photographed and graded according to the Wisconsin Age-related Maculopathy Grading System (ASGP, 2000)

Robman *et al.*, 2007 – AMD status at baseline and follow-up was graded according to a 6-point scale (1, no drusen or hard drusen only; 2, intermediate drusen or hyperpigmentation without hypopigmentation; 3, soft distinct or indistinct drusen or hypopigmentation, with or without hyperpigmentation; 4, soft distinct or indistinct drusen and pigmentary abnormalities; 5, geographic atrophy; 6, neovascular AMD). Interlevel progression is defined as an increase of one or more levels in the worse affected eye (the greatest change); interlevel and intralevel progression is defined as cases showing an increase of one or more levels in either eye together with cases in which there was an increase of 2 or more levels in the specific grades of size, total number, area occupied by a lesion, and spread to a more central location within a level; side-by-side progression is defined as the assessment of progression by a masked, side-by-side comparison of the baseline and follow-up macular photographs, and assessed using a criteria of 'better', 'worse', or 'same'.
Mares-Perlman *et al.*, 1996 – ARM status was assessed using fundus photography, and photos were graded according to a standard protocol using the standard criteria: drusen type (hard indistinct, hard distinct, soft indistinct, soft distinct, and reticular), size, uniformity, and sharpness, presence of retinal pigment epithelium degeneration (based on the appearance of greyish yellow or pinkish yellow areas in the plane of the retinal pigment epithelium), and increased retinal pigment (based on the presence of granules or clumps of grey or black pigment in or beneath the retina). Each condition was divided into 2 categories: none or questionable, and present. Late ARM was defined as the presence of pure geographic atrophy or exudative AMD (RPE or serous detachment of the sensory retina, subretinal or sub-RPE haemorrhage, or subretinal fibrous scars). Early ARM was defined as the presence of soft indistinct or reticular drusen or the presence of any drusen type with RPE degeneration or increased retinal pigment in the macular area, in the absence of any signs of late AMD.
Vandenlangenberg *et al.*, 1998 – Large drusen was defined as that with diameter >125 µm, and retinal pigment abnormalities were defined as increased retinal pigment and/or depigmentation. Together, large drusen and retinal pigment abnormalities were referred to as Early ARM Lesions.
Mares-Perlman *et al.*, 2001 – AMD was graded according to The Wisconsin Age-Related Maculopathy grading system
Gale *et al.*, 2003 – The Wisconsin Age-Related Maculopathy grading system was used to assess macular changes.
Tan *et al.*, 2008 – The Wisconsin Age-Related Maculopathy grading system was used to assess macular changes
Delcourt *et al.*, 2006 – The assessment scheme presented by Bird *et al.* (1995) was used to assess and grade AMD.
Moeller *et al.*, 2006 – Assessment of fundus photographs was based on that used by the AREDS group.
SanGiovanni *et al.*, 2007 – Group 1 (controls) had no or non-extensive small drusen (<63µm); group 2 had at least one eye with ≥1 intermediate drusen (63-124 µm), extensive small drusen, or pigmentary abnormalities; group 3 had at least one eye with ≥1 large drusen (≥125 µm) or extensive intermediate drusen; group 4 had at least 1 eye with definite geographic atrophy within 3000 mm of the fovea; group 5 had evidence suggesting choroidal neovascularisation or retinal detachment (non-drusenoid RPE detachment, serous sensory or hemorrhagic retinal detachment, subretinal haemorrhage, subretinal pigment epithelium haemorrhage, or subretinal fibrosis) in one eye or scars of photocoagulation for AMD.
Cho *et al.*, 2004 – ARM diagnosis was self-reported and confirmed by the subjects' ophthalmologists
Seddon *et al.*, 1994 – Cases were diagnosed by medical professionals (at any of the 5 ophthalmology centres used for recruitment). diagnostic criteria for advanced/exudative/neovascular AMD were visual acuity of less than 20/20, drusen in either eye, and at least one of: macular fibrous scar, subretinal haemorrhage or fluorescein angiographic signs of neovascularisation, and at least one of: a neurosensory macular detachment, macular lipid deposits, gray subretinal membrane, or RPE detachment.
Mares-Perlman *et al.*, 1995c – Cases were defined according to the Wisconsin Age-Related Maculopathy grading system.
Dasch *et al.*, 2005 – ARM stages were classified according to the Rotterdam Classification System. Stage 0: no sign of ARM at all, or hard drusen (≤63µm) only; stage 1: soft distinct drusen only (≤63µm), or pigment epithelial changes only, no soft drusen (≤63µm); stage 2: soft indistinct drusen (≥125µm) or reticular drusen only, or soft distinct drusen (≤63µm) with pigment epithelium changes; stage 3: soft indistinct drusen (≥125µm) or reticular drusen with pigment epithelium changes; stage 4: atrophic or neovascular (late) AMD.
Cardinault *et al.*, 2005 – AMD was diagnosed by a physician, and defined by the presence of soft drusen and/or pigmentary abnormalities (early AMD) or geographic atrophy/signs of exudative ARM degeneration (late AMD)
Nolan *et al.*, 2007 – NA
LaRowe *et al.*, 2008 – AMD was graded according to The Wisconsin Age-Related Maculopathy grading system
Bernstein *et al.*, 2002 – Subjects were diagnosed by a physician (diagnosis was confirmed by authors)
Simonelli *et al.*, 2002 – The assessment scheme presented by Bird *et al.* (1995) was used to assess and grade AMD
Van Leeuwen *et al.*, 2005 – The assessment scheme presented by Bird *et al.* (1995) was used to assess and grade AMD

Obana *et al.*, 2008 – Incidence of ARM was assessed by the scheme presented by Bird *et al.* (1995); severity of ARM was assessed using the AREDS grading system.

Confounding factors adjusted/ accounted for

Chasan-Taber *et al.*, 1999 – Age, gender, cancer diagnosis, cigarette smoking, BMI, diabetes, energy intake, area of residence in 1976 (used as a measure of sunlight exposure), aspirin use, number of visits to a physician in 1978, alcohol intake, time period (2-year intervals), and the presence of eye disease at baseline.
Morris *et al.*, 2007 – Age, gender, energy intake, smoking, dietary fat, hard liquor and wine consumption, hypertension, sun exposure, BMI, the use of hormone replacement therapy, and the presence of eye disease at baseline.
Jacques *et al.*, 2001 – Age, gender, the presence of cataracts at baseline, alcohol intake, BMI at baseline, smoking, sunlight exposure, hypertension, use of vitamin C, E, or multivitamin supplements, and diabetes.
Lyle *et al.*, 1999 – Age, gender, BMI, hypertension, diabetes, energy intake, smoking, alcohol intake, and the presence of cataracts at baseline.
Robman *et al.*, 2007 – Age, menopausal status, BMI, smoking, family history of AMD, source study, duration of follow-up, and presence of eye disease at baseline.
Mares-Perlman *et al.*, 1996 – Age and gender.
Vandenlangenberg *et al.*, 1998 – Age, gender, total daily calories, pack-years smoked, beer intake, history of cardiovascular disease, and history of diabetes.
Gale *et al.*, 2001 – Age, gender, social class, BMI, glycosylated haemoglobin, serum cholesterol, pack-years of smoking, use of steroids in previous 5 years, and alcohol intake.
Mares-Perlman *et al.*, 2001 – Age, gender, BMI, smoking, alcohol intake, iris colour, medication use, diabetes, and hyperlipidemia/hypercholesterolemia
Gale *et al.*, 2003 – Age, smoking, serum cholesterol, beer consumption, history of angioplasty or coronary bypass grafting, hypermetropic refractive error, BMI, and diabetes.
Tan *et al.*, 2008 – Age, family history, medication use, diabetes, cardiovascular events, smoking, white blood cell count, and occupation
Delcourt *et al.*, 2006 – Age, gender, smoking, lipid-standardized alpha-tocopherol, HDL, BMI, iris colour, sunlight exposure, medication use, hypertension, diabetes, and the presence of eye disease at baseline.
Moeller *et al.*, 2006 – Age, BMI, smoking, alcohol intake, iris colour, sunlight exposure, medication use, hypertension, diabetes, family history of eye disease, and the presence of eye disease at baseline.
SanGiovanni *et al.*, 2007 – Age, sex, total energy intake, angina, arthritis, use of hydrochlorothiazide, education, refractive error, race, smoking, hypertension, anti-hypertensive medication, lens opacity, use of antacids and thyroid hormones, BMI, the presence of eye disease at baseline, and quintiles of n-3 long-chain PUFA and arachidonic acid.
Cho *et al.*, 2004 – Age, gender, calendar time, smoking, BMI, energy, alcohol, and fish intake, physical activity, history of hypertension and high blood cholesterol, post-menopausal hormone use (women), and occupation (men)
Seddon *et al.*, 1994 – Age, gender, clinic (recruitment), education, systolic blood pressure, physical activity, alcohol intake, BMI, and smoking status
Mares-Perlman *et al.*, 1995c – Age, gender, smoking, beer drinking, supplement use, sunlight exposure, hyperlipidemia/hypercholesterolemia, and the presence of eye disease at baseline.
Dasch *et al.*, 2005 – Age, gender, smoking, BMI, hyperlipidemia/hypercholesterolemia, iris colour, ethnicity, and the presence of eye disease at baseline.
Cardinault *et al.*, 2005 – Age, gender, smoking status, medication use, hypertension, the presence of eye disease at baseline, and serum cholesterol, triglycerides, and phospholipids.
Nolan *et al.*, 2007 – Age, gender, smoking, family history of ARM, BMI, alcohol intake, iris colour, cholesterol levels, blood pressure, and visual acuity.
LaRowe *et al.*, 2008 – Age, diabetes, BMI, smoking, family history of AMD, the presence of AMD at baseline, hypertension, cardiovascular disease, use of cholesterol-lowering medications or hormone replacement therapy, intake of energy, fat, and fibre, and supplementation with high-dose antioxidants.
Bernstein *et al.*, 2002 – Age, gender, race, smoking, phakic/pseudophakic eyes, iris colour, pupil size, and visual acuity.
Simonelli *et al.*, 2002 – Age, gender, smoking, alcohol intake, sunlight exposure, hypertension, diabetes, hyperlipidemia/hypercholesterolemia, cardiovascular diseases, and the presence of eye disease at baseline.

Van Leeuwen *et al.*, 2005 – Age, gender, BMI, smoking, alcohol intake, hypertension, hyperlipidemia/hypercholesterolemia, atherosclerosis composite score, and the presence of eye disease at baseline.
Obana *et al.*, 2008 – Age, gender, diabetes, and the presence of eye disease at baseline were accounted for, although statistical analyses were not adjusted.

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
Kvansakul *et al.*, 2006[a,b]		Lutein (10 mg/day for 6 months, then 20 mg/day for 6 months)	Not described	6 months at 10 mg/day, followed by 6 months at 20 mg/day	3 healthy male subjects with no ocular abnormalities enrolled in the Lutein ZeaXanthin Eye Accumulation (LUXEA) trial	MPOD (measured at the fovea)				Not determined	Not reported	Not reported
						Not determined	0.52 (at end of phase 2)	Not determined	Not determined			
						Contrast acuity[c]				Not determined	P<0.001	Not reported
						Not reported	Not reported	-5	-25			
						Wavefront aberration (*rms*)				Not determined	NS	Not reported
						Not reported	Not reported	-0.05	-14%			
						Light scatter[d]				Not determined	NS	Not reported
						Not reported	Not reported	0.2	-20%			
		Zeaxanthin (10 mg/day for 6 months, then 20 mg/day for 6 months)	Not described	6 months at 10 mg/day, followed by 6 months at 20 mg/day	5 healthy male subjects with no ocular abnormalities enrolled in the Lutein ZeaXanthin Eye Accumulation (LUXEA) trial	MPOD (measured at the fovea)				Not determined	Not reported	Not reported
						Not determined	0.51	Not determined	Not determined			
						Contrast acuity[c]				Not determined	NS	Not reported
						Not reported	Not reported	-3	-14			
						Wavefront aberration (*rms*)				Not determined	NS	Not reported
						Not reported	Not reported	-0.05	-12%			
						Light scatter[d]				Not determined	NS	Not reported
						Not reported	Not reported	-0.3	-25%			

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
		Lutein+Zeaxanthin (10 mg each/day for 6 months, then 20 mg each/day for 6 months)	Not described	6 months at 10 mg each/day, followed by 6 months at 20 mg each/day	5 healthy male subjects with no ocular abnormalities enrolled in the Lutein ZeaXanthin Eye Accumulation (LUXEA) trial	MPOD (measured at the fovea)				Not determined	Not reported	Not reported
						Not determined	0.53	Not determined	Not determined			
						Contrast acuity[c]				Not determined	NS	Not reported
						Not reported	Not reported	-2	-14%			
						Wavefront aberration (*rms*)				Not determined	NS	Not reported
						Not reported	Not reported	.02	-1%			
						Light scatter[d]				Not determined	NS	Not reported
						Not reported	Not reported	0.4	-15%			
		Placebo (20 mg/day for 6 months)	Not described	6 months at 20 mg/day	4 healthy male subjects with no ocular abnormalities enrolled in the Lutein ZeaXanthin Eye Accumulation (LUXEA) trial	MPOD (measured at the fovea)				Not determined	Not applicable	Not applicable
						Not determined	0.37	Not determined	Not applicable			
						Contrast acuity[c]				Not determined	Not applicable	Not applicable
						Not reported	Not reported	4	Not applicable			
						Wavefront aberration (*rms*)				Not determined	Not applicable	Not applicable
						Not reported	Not reported	2	Not applicable			
						Light scatter[d]				Not determined	Not applicable	Not applicable
						Not reported	Not reported	1	Not applicable			

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
Olmedilla *et al.*, 2001		Lutein, approximately 7 mg/day (12 mg all-*trans*-lutein, 3 mg 13/15-*cis*-lutein, and 3.3 mg α-tocopherol 3 days per week)	Capsule	Average of 13 months (range 4-20 months)	5 subjects (females aged 55-73 years) with cataracts	Visual acuity (Snellen decimal notation)				Not determined	Not determined	Not determined
						0.59 ± 0.17	0.97 ± 0.04	0.38	Not applicable			
						Glare sensitivity – low threshold				Not determined	Not determined	Not determined
						0.6-0.9	0.9-1.1	Not applicable	Not applicable			
						Glare sensitivity – medium threshold				Not determined	Not determined	Not determined
						0.4-0.9	0.9-1.1	Not applicable	Not applicable			
						Glare sensitivity – high threshold				Not determined	Not determined	Not determined
						0.3-0.9	0.9-1.2	Not applicable	Not applicable			
			Capsule	Average of 26 months (range 16-36 months)	5 subjects (3 men and 2 women, aged 69-75 years) with age-related macular degeneration	Visual acuity – right eye (Snellen decimal notation)				Not determined	Not determined	Not determined
						<0.03-0.8	<0.3-0.8	Not applicable	Not applicable			
						Visual acuity – left eye (Snellen decimal notation)				Not determined	Not determined	Not determined
						<0.03-0.5	0.03-0.15	Not applicable	Not applicable			
Olmedilla *et al.*, 2003		Lutein, approximately 7 mg/day (12 mg all-*trans*-lutein, 3 mg 13/15-*cis*-lutein, and 3.3 mg α-tocopherol 3 days per week)	Capsule	24 months	5 subjects (females aged 55-73 years) with cataracts	Visual acuity (Snellen decimal notation)				P<0.005	Not reported	Not reported
						0.59 ± 0.17	0.96 ± 0.08	0.37	0.32			
						Glare sensitivity – low threshold				Not reported	Not reported	Not reported
						0.6-0.9	0.9-1.1	Not applicable	Not applicable			

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
						Glare sensitivity – medium threshold				Not reported	Not reported	Not reported
						0.4-0.9	0.9-1.1	Not applicable	Not applicable			
						Glare sensitivity – high threshold				Not reported	Not reported	Not reported
						0.3-0.9	0.9-1.2	Not applicable	Not applicable			
		Placebo (corn oil) 3 days per week	Capsule	24 months	5 subjects (3 males and 2 females aged 55-73 years) with cataracts	Visual acuity (Snellen decimal notation)				Not applicable	Not applicable	Not applicable
						0.43 ± 0.14	0.48 ± 0.08					
						Glare sensitivity – low threshold				Not applicable	Not applicable	Not applicable
						0.4-0.6	0.4-0.6					
						Glare sensitivity – medium threshold				Not applicable	Not applicable	Not applicable
						0.4-0.6	0.5					
						Glare sensitivity – high threshold				Not applicable	Not applicable	Not applicable
						0.4-0.6	0.5					
Richer *et al.*, 2004[e]		Lutein (10 mg/day)	Capsule	12 months	29 subjects (27 male, 2 female) with age-related macular degeneration	MPOD – right eye				P=0.03	NS	Not reported
						0.23	0.31	0.08	0.11			
						MPOD – left eye				P=0.01	NS	Not reported
						0.24	0.33	0.09	0.13			
						Near visual acuity[f]				Not reported	Not reported	Not reported
						Not reported	Not reported	5.4	5.6			
						Glare recovery (seconds; average of both eyes)				Not reported	Not reported	Not reported
						Not reported	Not reported	23.7	1.0			

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
						Contrast sensitivity – right eye (Log[Contrast Step] at 3 cc/degree)				P=0.04	Not reported	Not reported
						1.55	Not reported	0.14	0.11			
						Contrast sensitivity – right eye (Log[Contrast Step] at 6 cc/degree)				NS (P=0.07)	Not reported	Not reported
						1.56	Not reported	0.15	0.09			
						Contrast sensitivity – right eye (Log[Contrast Step] at 12 cc/degree)				P=0.01	Not reported	Not reported
						1.10	Not reported	0.21	0.19			
		Placebo (10 mg maltodextrin/day)	Capsule	12 months	31 subjects (30 male, 1 female) with age-related macular degeneration	MPOD – right eye				NS	Not applicable	Not applicable
						0.23	0.20	-0.03				
						MPOD – left eye				NS	Not applicable	Not applicable
						0.24	0.20	-0.04				
						Near visual acuity[f]				Not reported	Not applicable	Not applicable
						Not reported	Not reported	-0.2				
						Glare recovery (seconds; average of both eyes)				Not reported	Not applicable	Not applicable
						Not reported	Not reported	22.7				
						Contrast sensitivity – right eye (Log[Contrast Step] at 3 cc/degree)				NS	Not applicable	Not applicable
						1.62	Not reported	0.03				

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
						Contrast sensitivity – right eye (Log[Contrast Step] at 6 cc/degree)				NS	Not applicable	Not applicable
						1.65	Not reported	0.06				
						Contrast sensitivity – right eye (Log[Contrast Step] at 12 cc/degree)				NS	Not applicable	Not applicable
						1.20	Not reported	0.02				
Rosenthal *et al.*, 2006		Lutein, 2.5 mg/day	Tablet	6 months	15 subjects (females, average age 71.4 years) with various severities of ARMD	Visual acuity (letters)				Not reported	Not reported	NS
						75.5	Not reported	0.5	Not applicable			
		Lutein, 5 mg/day	Tablet	6 months	15 subjects (females, average age 70.5 years) with various severities of ARMD	Visual acuity (letters)				Not reported	Not reported	NS
						68.7	Not reported	0.9	Not applicable			
		Lutein, 10 mg/day	Tablet	6 months	15 subjects (females, average age 71.5 years) with various severities of ARMD	Visual acuity (letters)				Not reported	Not reported	NS
						70.6	Not reported	1.7	Not applicable			

Table E-3 Tabulation of Data from Human Intervention Studies

Reference	Quality Score	Daily Dose	Matrix	Duration	Population and Final Sample Size	Endpoint				Significance		
						Baseline	End of Treatment	Change from Baseline	Change from Baseline Adjusted for Placebo Effect	Within Groups	Between Groups (End of Treatment)	Between Groups (Change from Baseline)
Stringham and Hammond, 2008		Lutein and zeaxanthin (10 mg/day and 2 mg/day, respectively)	Tablet	6 months	40 healthy subjects (17 males and 23 females, aged 17 to 41 years) with no history of visual pathology	MPOD (measured at 50' eccentricity)				P=0.003	Not applicable	Not applicable
						0.41	0.57	0.16	Not applicable			
						Glare sensitivity (glare disability, seconds)				P<0.0001	Not applicable	Not applicable
						Not reported	Not reported	15.7	Not applicable			
						Glare sensitivity (photostress recovery, seconds)				P=0.0003	Not applicable	Not applicable
						Not reported	Not reported	12.06	Not applicable			

Abbreviations: ARMD, age-related macular degeneration; MPOD, macular pigment optical density; NS, not significant.
[a] True "baseline" measurements (*i.e.* prior to intervention) were not included in this study; the baseline data presented were collected after the first 6 months of intervention (with 10 mg or lutein and/or zeaxanthin) and the end of treatment data were collected after the second 6 months of intervention (with 20 mg lutein and/or zeaxanthin).
[b] No correlation was observed between MPOD and visual acuity or light scatter in this study.
[c] Assessment test thresholds; measured at the fovea.
[d] Change in *k´*, proportional to total amount of light scattered by the eye.
[e] Constrast sensitivity was determined for the right and left eyes at various special frequencies. Only statistically significant data for the lutein group and comparable data for the placebo group are presented.
[f] Snellen letter equivalent improvement; average of both eyes.

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NA- Not applicable