

# Procter & Gamble

The Procter & Gamble Company  
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March 3, 2000

Docket Management Office  
5630 Fisher's Lane  
Rockville, MD 20852

Dear Madam:

We wish to submit the enclosed report and cover letter entitled "Vitamin Advisory Panel Chicago, December 4 and 5, 1997, Report of Proceedings" to the olestra docket #00F-0792 so that it is publicly available. All of this material has been previously submitted to Mary Ditto of FDA's Office of Pre-market Approval.

Please let me know if you have any questions (513-634-6808).

Thank you.

Sincerely,

THE PROCTER & GAMBLE COMPANY



Greg Allgood, Ph.D.  
Associate Director  
Regulatory & Clinical Development

Enclosure

00F-0792

RPT2

**Vitamin Advisory Panel  
Chicago,  
December 4<sup>th</sup> and 5<sup>th</sup> 1997**

**Report of proceedings**

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## LIST OF ATTENDEES

### *Chairman*

Dr. John Suttie, University of Wisconsin, Madison, WI

### *Consultants*

Dr. Tammy Bray, The Ohio State University, Columbus, OH  
Dr. Gail Harrison, UCLA School of Public Health, Los Angeles, CA  
Dr. Robert Sandler, University of North Carolina at Chapel Hill, Chapel Hill, NC  
Dr. A. Catharine Ross, The Pennsylvania State University, University Park, PA  
Dr. Khursheed Jeejeebhoy, University of Toronto, Toronto, Canada  
Dr. Mark Thornquist, Fred Hutchinson Cancer Research Center, Seattle, WA  
Dr. James Olson, Iowa State University, Ames, IA  
Dr. Anthony Diplock, Guys Hospital, London, UK  
Dr. Robert Greenberg, Norris Cotton Cancer Center, Lebanon, NH  
Dr. Stephen Kritchevsky, University of Tennessee, Memphis, TN  
Dr. Frank Meyskens, UC Irvine, Orange, CA  
Dr. Steve Schwartz, The Ohio State University, Columbus, OH

**EXECUTIVE SUMMARY  
AND OVERVIEW OF THE REPORT  
FROM THE  
VITAMIN ADVISORY PANEL  
CHICAGO, DECEMBER 4<sup>TH</sup> & 5<sup>TH</sup> 1997**

## EXECUTIVE SUMMARY

This expert Vitamin Panel was convened to review the current state of the science concerning the hypotheses regarding carotenoids and disease prevention and the health significance of the micronutrient effects of the sucrose polyester, olestra. The panel was comprised of leading experts in the fields of nutrition, medicine, biochemistry, public health, epidemiology and food science. The meeting was convened independently by Strategic Consultants International (SCI), UK; who took responsibility for the development of the agenda, summarizing and distributing the olestra data, briefing the panelists and the preparation of this report. Procter and Gamble funded the meeting and attended as observers. At no time did they materially influence the format, content or consensus reached at the meeting.

The meeting agenda was developed by SCI in collaboration with Dr. John Suttie, the Chairman of the panel, as a series of questions. Each question addressed a specific point either directly regarding the effects of olestra e.g. what are the dose-related effects of olestra on the absorption of fat-soluble vitamins; or indirectly of relevance to olestra e.g. is there conclusive evidence that carotenoids prevent cancer? These questions were then assigned to the most appropriate member of the expert panel. Procter and Gamble provided information concerning olestra on these agenda items and the relevant documentation was sent to the experts by SCI in order that they could review the original data in detail. The experts were asked to base their introductory presentations on this data, but to include any other relevant information that they wished to present. These initial presentations were followed by a thorough discussion, moderated by Dr. John Suttie, and involving all members of the panel. At the conclusion of each discussion period, the panel agreed to a consensus statement which summarized the conclusions reached.

SCI have based this report on the content of the audio-tapes recorded at the time of the meeting. The document has been reviewed by the panellists and their comments have been incorporated. Their signatures approving the report are included.

The overall, final conclusions of the panel were: -

- When consumed as a fat substitute in savory snacks, vitamin-supplemented olestra is likely to produce negligible changes in fat soluble vitamin concentrations.
- Many factors affect the absorption of carotenoids from food. The effect of olestra on carotenoid absorption, when consumed as a fat substitute in savory snacks, is likely to be slight.
- Serum carotenoids reflect the intake of certain fruits and vegetables, and in people who consume them, serum levels are associated with a decreased risk of cancer and cardiovascular disease. There is no conclusive evidence that carotenoids themselves prevent cancer or cardiovascular disease.
- When consumed as a fat substitute in savory snacks, olestra's effects on the concentration of fat soluble vitamins and carotenoids pose no apparent health risks.

## OVERVIEW OF THE REPORT

### 1.1 Introduction to olestra. *(Dr. Tammy Bray)*

#### *Summary of presentation*

Olestra is a sucrose polyester with 6 – 8 fatty acid side chains and similar physical properties to soybean oil. Radio-label studies show virtually no absorption from the gut.

Olestra can reduce the absorption of certain highly lipophilic micronutrients, due to partitioning of the substance between olestra and other gut contents and subsequent excretion of the substance with olestra in the feces.

The timing of the ingestion of a lipophilic substance relative to olestra ingestion significantly affects the degree by which olestra reduces the absorption of the lipophile. The greatest reduction in absorption is seen when olestra is mixed in the diet, e.g. in the pig studies<sup>(1)</sup>, and the least reduction is seen when olestra is consumed some time after or before the ingestion of a lipophilic compound.

#### *Consensus Statement*

- Based on its chemical structure and experimental data, olestra can reduce the absorption of highly lipophilic compounds.
- The inhibition of absorption of lipophilic substances is greatest when olestra is ingested simultaneously.

### 1.2 What are the estimated consumption levels and eating patterns of olestra in savory snacks, with special reference to intake with meals? How does this compare with the protocols in clinical trials and the active surveillance program *(Dr. Gail Harrison)*

#### *Summary of presentation*

The Market Research Corporation of America (MRCA) menu census survey was used to estimate potential olestra intake from savory snacks. This database compares favorably with other databases such as the Nationwide Food Consumption Survey (NFCS) and the Continuing Survey of Food Intake by Individuals (CSFII). Conservative assumptions were used, i.e. all fat from all savory snacks was assumed to be replaced with olestra, and then estimated intake was increased by 10%. These assumptions are likely to give exaggerated estimates of consumption.

Reference <sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional Effects of Olestra, a non absorbed fat replacement. Introduction and overview. J. Nutr 127: 15935-15485, 1997

These figures showed an estimated mean chronic intake for savory snack consumers of 3.1 grams of olestra per day, and an estimated intake for the 90<sup>th</sup> centile eaters of 6.9 grams per day. These estimates show that the design of olestra human and pig studies<sup>(1)</sup> are likely to have further exaggerated olestra effects, as up to 32 grams per day were consumed by humans and up to 163 grams per day by pigs. Furthermore, all subjects ate olestra every day, and no nutrients were consumed without olestra. This does not equate with the snack eating pattern shown in the MRCA survey.

### ***Consensus Statement***

- With currently approved snack products, few people (<10%) will consume more than 1 oz of chips per day over time (which equates to a maximum of 8 grams per day of olestra).
- Most meals are not taken with snacks, and not all snacks will contain olestra.
- The studies to date provide an upper boundary to the olestra effects, considering the likelihood that olestra will not always be consumed with meals under normal free living conditions.

### **1.3 What is the experience to date with olestra? (Dr. Robert Sandler)**

#### ***Summary of presentation***

Dr Sandler presented the conclusions of the GI advisory panel held on September 30<sup>th</sup> and October 1<sup>st</sup> 1996, and a summary of the GI post-marketing surveillance committee findings. This presentation was provided for background information to the vitamin panel, and was not intended as a basis for the vitamin panel to draw conclusions.

### **1.4 What are the dose related effects of olestra (in the pig and human studies) on the absorption of: water soluble vitamins, essential minerals and fat soluble vitamins. How do the dose-response effects differ in clinical trials stipulating olestra intake with meals, compared with free living studies? How do the effects under free-living conditions compare with nutrient bioavailability effects which occur as a result of some other dietary constituents (fiber, milk, fatty acids, pectin etc.)? (Dr. A. Catharine Ross)**

#### ***Summary of presentation***

Dose ranging studies for the effects of olestra on nutrition in the pig were performed with up to 5.5% olestra mixed in the diet and for up to 39 weeks in duration. The equivalent consumption level compared to the estimated chronic consumption for the 90<sup>th</sup> centile consumers of savory snacks (6.9 grams/day) is in the range of 0.25-0.5% olestra in the pig diet. Olestra showed a dose-related decrease in vitamin A, D and E status. No effects were seen in functional vitamin K status, or general health, growth, feed efficiency, Ca, Fe, Zn, folate or vitamin B<sub>12</sub>.

Reference <sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional Effects of Olestra, a non absorbed fat replacement: Introduction and overview. J. Nutr 127: 15935-15485, 1997

Human dose ranging studies investigated the effects of up to 32 grams per day of olestra taken as savory snacks with controlled meals in studies for up to 8 weeks, and taken as part of a self selected diet (not necessarily with meals) for up to 16 weeks. Predictable dose-related decreases were seen on serum vitamin A, D, E and K concentrations. No effects were seen on functional vitamin K status, general health, folate, vitamin B<sub>12</sub>, Ca, Fe or Zn. The effects seen with a self-selected diet were less than in the controlled diet studies.

**Consensus Statement**

- The pig and human studies<sup>(1)</sup> confirm that the dietary effects of olestra are seen only on highly lipophilic micronutrients.
- Dose related and predictable effects on serum vitamin A, D and E concentrations were observed in the pig studies.
- The human studies confirm the findings of the pig studies with regard to decreases in serum vitamins A and E (with unsupplemented olestra)
- The effects of unsupplemented olestra on serum fat soluble vitamin concentrations observed with clinical studies were greater than observed in studies under free-living conditions

**1.5 What are the data supporting the FDA’s agreed levels of supplementation with vitamins? (Dr. Khursheed Jeejeebhoy)**

**Summary of presentation**

Vitamin replacement studies were performed in the pig and human to assess the level of vitamin supplementation required to offset the effects of olestra. The following table summarizes the levels of vitamin supplementation agreed with the FDA, and the basis for these levels:

FDA agreed supplementation level	Basis for supplementation level
1.9 milligrams α-tocopheryl equivalents per gram olestra (i.e. 2.07 mg d-α-tocopheryl acetate)	8 week human and 26 week pig vitamin replacement studies
51 retinol equivalents per gram olestra (as retinyl acetate or retinyl palmitate) i.e. 93 μg retinyl palmitate	26 week pig vitamin replacement study
12 IU vitamin D per gram olestra (i.e. 300 ng vitamin D)	8 week human and 12 week pig vitamin replacement studies
8 micrograms vitamin K per gram olestra	8 week dose ranging study

The requirement for vitamin D addition can be questioned, as dietary vitamin D provides such a small component of total vitamin D in humans.

Reference <sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional Effects of Olestra, a non absorbed fat replacement: Summary. J. Nutr 127: 17195-17285, 1997

### ***Consensus Statement***

- The levels of fat soluble vitamin supplementation in savory snacks agreed with the FDA are likely to correct any reduction in concentrations due to olestra consumption.
- Toxic levels of vitamins A, D, E and K are such that there is no medical concern regarding the levels of vitamin added to olestra.
- Although the possible impact of olestra snack consumption on coumadin therapy has not been established empirically, the normal daily vitamin K intake is known to be extremely variable, and the routine monitoring of this therapy by the attending physician provides an adequate measure of safety.

### **1.6 Summary of results to date from the active surveillance program (Dr. Mark Thornquist)**

#### ***Summary of presentation***

Subjects eating low-fat or non-fat snacks are much more likely to eat olestra snacks than subjects eating standard-fat snacks or no snacks at baseline. The 90<sup>th</sup> centile consumption of olestra snacks observed in the active surveillance program, 2 grams per day, is much lower than the estimate of 6.9 grams per day from the MRCA menu census survey. Only 10% of snack eaters consume snacks and carotenoid containing foods at the same time, and of these only a small percentage will be taking olestra-containing snacks.

### ***Consensus Statement***

- In the entire test market population, only 10% consumed olestra-containing snacks. In the olestra snack eating population, olestra snack consumption was only 3-4 eating occasions per month.

### **1.7 In humans, what are the dose related effects of olestra on the absorption of carotenoids and other phytochemicals? (Dr. James Olson)**

#### ***Summary of presentation***

Dr Olson reviewed the mechanisms by which olestra reduces the absorption of lipophilic micronutrients including carotenoids, and hypothesised that this may be due, in part, to interference with the interaction of carotenoids with bile acids. The effect is dose dependent and requires concomitant presence of olestra and carotenoids in the gut. The reduction in serum carotenoids in subjects ingesting olestra plateaued at 4 weeks in the 16-week free-living study, whereas serum carotenoids continued to fall at least 9 weeks in subjects ingesting a carotenoid-free diet without olestra. Dr Olsen hypothesised that this plateau effect may be due to adaptive mechanisms within the body.

### ***Consensus Statement***

- Olestra may inhibit to varying degrees (depending on the lipophilicity of individual carotenoids) the absorption of carotenoids from the intestine.
- The effects of olestra are dependent on dose and on concomitant presence of carotenoids in the GI tract.
- Under estimated 90th centile usage regimens, carotenoid absorption should only be slightly reduced (less than 10%).

**1.8 What are the proposed pathophysiological mechanisms by which carotenoids may prevent (or exacerbate) disease? What are the data regarding the plausibility of any of these hypotheses. (Dr. Anthony Diplock)**

### ***Summary of presentation***

A number of mechanisms have been proposed by which carotenoids may prevent disease. The established mechanism is as a provitamin A. Other mechanisms proposed for carotenoids include an effect on gene expression, and as an antioxidant.

The hypothesis that carotenoids may have an effect on gene expression independent of their provitamin A activity rests on structural similarities between the two molecules. It is not known if this hypothesis is viable. Antioxidant and pro-oxidant effects have been shown in vitro, but not in vivo or in ex-vivo models.

### ***Consensus Statement***

- The only established mechanism by which carotenoids affect disease is through their pro-vitamin A activity.
- Anti-oxidant and pro-oxidant activity has been shown in vitro, but not in in-vivo or ex-vivo models.

**1.9 Is there conclusive evidence that carotenoids ( $\beta$ -carotene,  $\alpha$ -carotene, lycopene, lutein/zeaxanthin) prevent disease:**

**1.9.1 Weighing the evidence from carotenoid studies and cancer: particularly lung and prostate. (Dr. Robert Greenberg)**

### ***Summary of presentation***

Epidemiological studies have shown a mixed picture in terms of a statistically significant inverse association between  $\beta$ -carotene and the incidence of cancer. This association has been shown most consistently with lung cancer. Prospective  $\beta$ -carotene supplementation studies have failed to show an inverse association. Greenberg et al<sup>(1)</sup> showed an inverse correlation between  $\beta$ -carotene (as measured at baseline) and mortality but failed to show a protective effect in the group allocated to  $\beta$ -carotene therapy when compared to placebo.

Reference <sup>(1)</sup> Greenberg ER et al, Mortality associated with hour plasma concentration of Beta Carotene and the effect of oral supplementation. The Journal of The American Medical Association, March 6<sup>th</sup>, Volume 675.

### 1.9.2 Heart disease (*Dr. Stephen Kritchevsky*)

#### *Summary of presentation*

Five out of five case-control studies showed an inverse association between carotenoids and heart disease, but it depends which carotenoid is examined, and there were differing endpoints. Two of three studies showed a strong protective effect for disease only in smokers.

The randomized clinical trials of  $\beta$ -carotene supplementation showed a possible increase in death due to cardiovascular disease in the treated group, and certainly no protective effect. Analysis of the baseline blood samples has shown a significant inverse correlation between  $\beta$ -carotene and CVD death (Greenberg et al, JAMA March 6, 1996).

Data from the cholestyramine group of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) shows that prospectively reducing serum carotenoids does not offset the disease reducing benefit of reducing total cholesterol, as would be predicted if serum carotenoids were protective against heart disease.

### 1.9.3 Might serum carotenoids be serving as biomarkers for a healthy life style and for the intake of green vegetables and fruit etc., rather than conferring any direct effect? (*Dr. Frank Meyskens*)

#### *Summary of presentation*

Diets high in fruits and vegetables are recognized in observational clinical trials to provide a health benefit. However, this does not establish a cause and effect health role for carotenoids themselves. There are other explanations for the health benefit of diets high in fruit and vegetables: i.e. such a diet is low in fat, iron and calories, high in vitamin C, E and fiber, and may be associated with regular exercise and a lack of smoking.

Previous expert committees that have published their findings have not come to a consensus that carotenoids do in fact prevent chronic disease.

#### *Consensus Statement on the evidence regarding a role for carotenoids ( $\beta$ -carotene, $\alpha$ -carotene, lycopene, lutein/zeaxanthin) in disease prevention*

- Serum carotenoid concentrations are indicators of the intake of certain fruits and vegetables.
- There is no consensus that carotenoids themselves play a preventative role against cancer and cardiovascular disease.
- Case-control and cohort studies have shown that there may be an association between diets high in  $\beta$ -carotene and a reduced incidence of cancer and heart disease.

- Randomized controlled clinical studies of  $\beta$ -carotene supplementation have not shown any benefit in lung cancer and coronary artery disease. Benefits of other carotenoids have not been ruled out.
- $\beta$ -carotene supplementation may increase the risk of mortality from lung cancer and ischemic heart disease in smokers.

#### **1.10 What factors can affect carotenoid stability, bioavailability, absorption and utilization? (Dr. Steve Schwarz)**

##### ***Summary of presentation***

Factors affecting the absorption and utilization of carotenoids from foods include the level of intake (inversely related to efficiency), dietary fat, dietary fiber, type of carotenoid and interaction amongst carotenoids. Also, the food matrix containing the carotenoid, host-related factors and drug interactions are important. Factors affecting the carotenoid content in foods include the quality of fruit and vegetables, storage conditions, food processing and preparation and the influence of other ingredients.

##### ***Consensus Statement***

- Olestra consumption is one of the many factors which can potentially influence carotenoid absorption from the diet.

# INTRODUCTION

## 2. INTRODUCTION

- **Dr. John Suttie, Chairman of the panel, introduced the meeting and described the format of the proceedings. He explained that the aim was to review the data pertaining to the current state of the science concerning the hypotheses regarding carotenoids and disease prevention and the health significance of the micronutrient effects of the sucrose polyester, olestra.**
- **The agenda was constructed as a series of questions, each addressing a different aspect of the data with regard to the current state of the science concerning the hypotheses regarding carotenoids and disease prevention and the clinical significance of the micronutrient effects of the sucrose polyester, olestra. The questions were assigned to members of the consultant panel with particular expertise in the area. At the meeting the reviewers were asked to present the relevant data and to summarize their views on the particular questions.**
- **Following each presentation there was a discussion, moderated by Dr. John Suttie, involving all the members of the panel.**
- **At the conclusion of the discussion period the panel agreed a consensus statement which summarized the conclusions.**
- **This report summarizes the information presented by the members of the panel and the points that were made during the ensuing discussion. It also reports the consensus statements to which they agreed at the conclusion of each discussion period.**
- **This meeting was funded by Procter & Gamble, but was independently convened and arranged by Strategic Consultants International, UK. At no time did Procter & Gamble staff materially influence the format, content or consensus reached at the meeting.**

# REPORT

### 3. THE REPORT

#### 3.1 Introduction to olestra

*Presentation from Dr. Tammy Bray, The Ohio State University, Columbus, Ohio*

##### *Summary*

Olestra is a sucrose polyester with 6 – 8 fatty acid side chains and similar physical properties to soybean oil. Radio-label studies show virtually no absorption from the gut.

##### **Radio-label absorption studies**

	<u>Absorbed Fraction</u>
• Highly saturated	<0.000004
• Highly unsaturated	<0.000003
• Short chain/low ester	<0.000010
• Heat-abused	<0.000012
• Model of children	<0.000005
• Compromised GI model	<0.000001

Olestra can reduce the absorption of certain highly lipophilic micronutrients, due to partitioning of the substance between olestra and other gut contents and subsequent excretion of the substance with olestra in the feces.

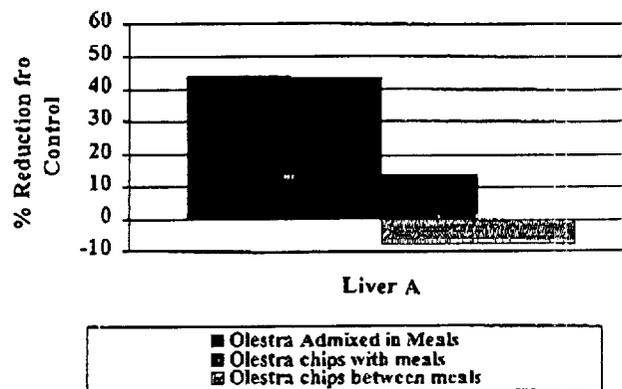
##### **Effect of olestra ingestion on substances with log oil/water partition coefficient ( $\text{LogPC}_{ow}$ ) > 3.5**

<u>Compound</u>	<u>LogPC<sub>ow</sub></u>	<u>Does Olestra Reduce Absorption?</u>	
		<u>Humans</u>	<u>Animals</u>
$\beta$ -carotene	17.6	+	+
$\alpha$ -tocopherol	12.2	+	+
Phylloquinone	11.7	+	+
Cholecalciferol	10.2	+	+
Cholesterol	8.7	+	+
Oleic acid	7.7	+/-	
Retinol	7.6	+/-	+
DDT	6.8		+
DDE	6.0		+
Lithocholic acid	4.6	-	-
Ethynyl estradiol	3.7	-	-
Deoxycholic acid	3.6	-	-

\* at high levels mixed directly into diet

The amount of olestra ingested (see dose ranging studies section 3.4 of this report) and the timing of the ingestion of a lipophilic substance relative to olestra ingestion significantly affect the degree by which olestra reduces the absorption of the lipophile. The greatest reduction in absorption is seen when olestra is mixed in the diet, e.g. in the pig studies<sup>(1)</sup>, and the least reduction is seen when olestra is consumed some time after or before the ingestion of a lipophilic compound.

### Effect of Olestra Admixed in \*Diet vs. as Chips on Liver Vitamin A Concentration



\*vitamin A in diet provided as 75:25 mixture of retinyl palmitate:  $\beta$ -carotene

#### Points raised in the discussion

- Olestra has been shown to not interfere with triglyceride absorption.
- Triglyceride increases gastric emptying time but olestra does not. This means that olestra is present in the stomach for a shorter time than an equivalent fat meal, and so the opportunity for partitioning of lipophilic substances into olestra in the stomach is reduced.

#### Consensus Statement

- Based on its chemical structure and experimental data, olestra is likely to reduce the absorption of highly lipophilic compounds.
- A lipophilic substance and olestra must be present at the same time in the gut to influence absorption.

Reference <sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional effects of olestra, a non absorbed fat replacement: Introduction and Overview. J. Nutri 127: 15935-15485,1997.

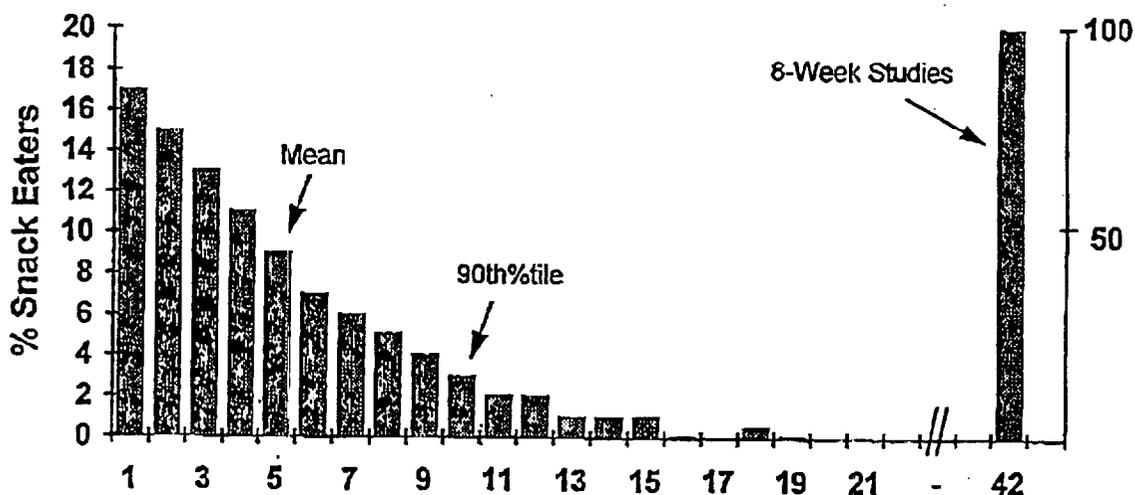
**3.2 What are the estimated consumption levels and eating patterns of savory snacks; with special reference to intake with meals? How does this compare with the protocols in clinical trials and data from the active surveillance program?**

*Presentation from Dr. Gail Harrison, UCLA School of Medicine, Los Angeles, CA*

**Summary**

The Market Research Corporation of America (MRCA) menu census survey was used to estimate potential olestra intake from savory snacks. This database compares favorably with other databases such as the Nationwide Food Consumption Survey (NFCS) and the Continuing Survey of Food Intake by Individuals (CSFII). Conservative assumptions were used i.e. all fat from all savory snacks was assumed to be replaced with olestra, then estimated intake was increased by 10% to allow for a rise due to the knowledge that olestra snacks are less calorific than full fat snacks. These assumptions are likely to give exaggerated estimates of consumption.

**Estimated Frequency of Olestra Snack consumption (all ages)**



The 14-day average calculated intake of olestra was taken as an estimate of the likely chronic consumption level.

**Olestra 14-Day Average Intake (grams/day)**

Group	Savory Snack Eaters	
	Mean	90 <sup>th</sup> centile
Total Population of Eaters	3.1	6.9
2-5 year old (males and females)	3.0	6.4
13-17 year old (males)	4.7	10.9
≥ 65 year old (males)	2.4	5.4

These estimates show that the design of olestra human and pig studies<sup>(1)</sup> are likely to have further exaggerated olestra effects, as up to 32 grams per day were consumed by humans and up to 163 grams per day by pigs. Furthermore, in the dose ranging studies all subjects ate olestra every day with all main meals, and no nutrients were consumed without olestra. This does not equate with the snack eating pattern shown in the MRCA survey.

### ***Points raised in the discussion***

- The database has not been analysed to show any difference amongst groups in the proportion of savory snacks consumed with meals.
- Fat intake as a percentage of dietary energy has fallen recently, and is now around 34%. There appear to be small regional differences, with the Mid West and South having higher percentage fat intakes than the Pacific and North East. The actual fat intake has not changed, but the total calories have gone up, reducing the percentage from fat.

#### **Consensus Statement**

- With currently approved snack products, few people (<10%) will consume more than 1 oz of chips per day over time (which equates to a maximum of 8 grams per day of olestra).
- Most meals are not taken with snacks, and not all snacks will contain olestra.
- The studies to date provide an upper boundary to the olestra effects, considering the likelihood that olestra will not be consumed with meals under normal free living conditions.

Reference <sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional Effects of Olestra, a non absorbed fat replacement: Introduction and overview. J. Nutr 127: 1593S-1548S, 1997

### **3.3 What is the experience to date with olestra?**

***Presentation from Dr. Robert Sandler, University of North Carolina at Chapel Hill, Chapel Hill, NC***

#### ***Summary***

Dr Sandler presented the conclusions of the GI advisory panel held on September 30<sup>th</sup> and October 1<sup>st</sup> 1996, and a summary of the GI post-marketing surveillance committee findings.

## GI Advisory Panel Conclusions

- No effect on gastric emptying or intestinal motility.
- No change in GI flora; no metabolism by flora.
- No effect on bile acid pool or absorption of CHO, fat, protein.
- No light microscopic changes in intestinal mucosa.
- Increase in stool weight at higher doses, but no change in stool water, electrolytes or pH.
- Severity of GI symptoms at higher doses not greater than placebo and not clinically significant.
- During 5-month home test no difference in reports of common GI symptoms.
- No excess GI symptoms in children, diabetics, IBD patients.
- Postmarketing surveillance reports susceptible to publicity.

### Summary of GI post-marketing surveillance committee findings

- High background rate of symptoms in National Survey complicates interpretation of spontaneous reports.
- Rechallenge study in “sensitive” individuals shows no evidence of effect.
- There is no association between dose, age, and time of onset of symptoms.
- No “probable” adverse events have been identified.

This presentation was provided for background information to the vitamin panel, and was not intended as a basis for the vitamin panel to draw conclusions.

### 3.4 What are the dose related effects of olestra (in the pig and human studies) on the absorption of: water soluble vitamins, essential minerals, fat soluble vitamins?

*Presentation from Dr. A. Catharine Ross, The Pennsylvania State University, University Park, PA*

#### *Summary*

Dose ranging studies for the effects of olestra on nutrition in the pig were performed with up to 5.5% olestra mixed in the diet and for up to 39 weeks in duration. The equivalent consumption level compared to the estimated chronic consumption for the 90<sup>th</sup> centile consumers of savory snacks (6.9 grams/day) is in the range of 0.25-0.5% olestra in the pig diet. Olestra consumption was associated with a dose-related decrease in vitamin A, D and E status.

**Effect of Olestra on Vitamin E  
Status in 26-week study**

<u>% Olestra</u>	<u>Week 26</u> <u>% Reduction in Vitamin E</u>		
	<u>Serum</u>	<u>Liver</u>	<u>Adipose</u>
1.1	51	53	51
3.3	75	71	68
5.5	77	75	74

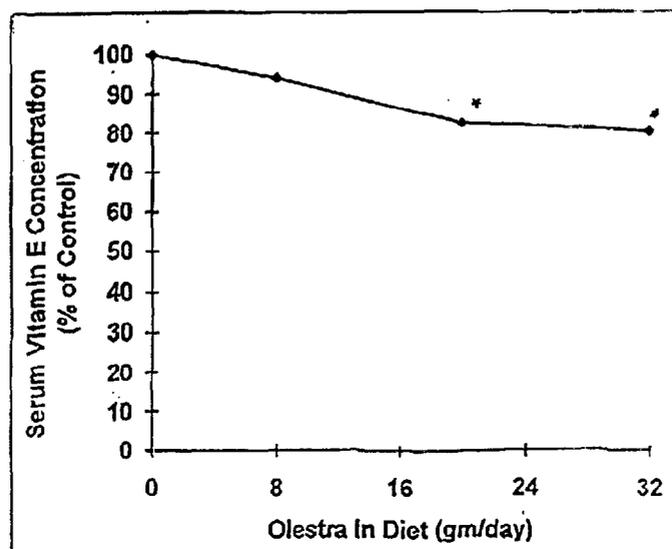
No effects were seen in functional vitamin K status, or general health, growth, feed efficiency, Ca, Fe, Zn, folate or vitamin B<sub>12</sub>.

**Effect of Olestra on Prothrombin Time in 26-week study  
(Week 26)**

<u>Olestra Dose (%)</u>	<u>Males</u>	<u>Females</u>
	Seconds ( $\pm$ SD)	
0	10.8 $\pm$ 0.2	10.7 $\pm$ 0.4
0.25	10.8 $\pm$ 0.3	11.1 $\pm$ 0.4
0.50	11.1 $\pm$ 0.1	10.5 $\pm$ 0.2
1.1	10.7 $\pm$ 0.3	10.6 $\pm$ 0.9
3.3	10.9 $\pm$ 0.5	11.2 $\pm$ 0.3
5.5	11.1 $\pm$ 0.5	11.1 $\pm$ 0.5

Human dose ranging studies investigated the effects of up to 32 grams per day of olestra taken as savory snacks with controlled meals in studies for up to 8 weeks, and taken as part of a self selected diet (not necessarily with meals) for up to 16 weeks. Predictable dose-related decreases were seen on serum vitamin A, D, E and K concentrations.

**Dose Response of Olestra on Human Serum Vitamin E Concentrations  
in 8 Week Dose Response Study**



\* Significantly different from control ( $p < 0.05$ )

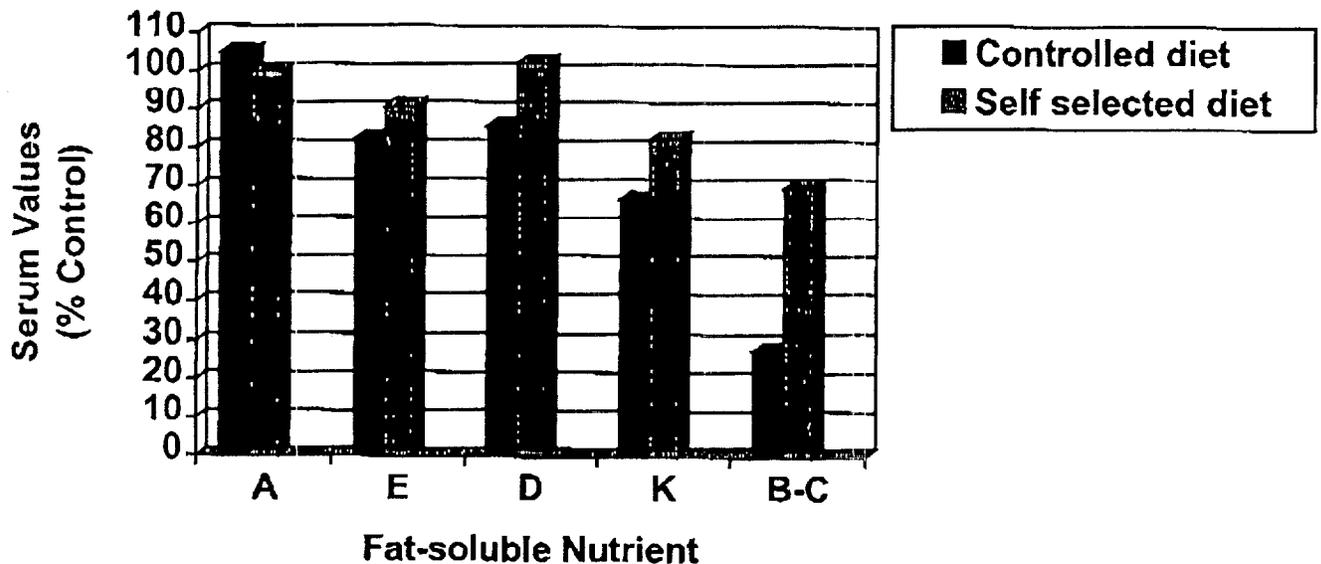
No effects were seen on functional vitamin K status, general health, folate, vitamin B<sub>12</sub>, Ca, Fe or Zn.

### Olestra Effect on Urinary Gla and PIVKA-II

<u>Olestra Intake</u> (grams/day)	<u>Urinary Gla</u> (nmoles Gla/mg creatinine)		<u>PIVKA-II</u> (% of total prothrombin)	
	<u>Baseline</u>	<u>Day 56</u>	<u>Baseline</u>	<u>Day 56</u>
	0	20.6	23.3	1.0
8	21.6	21.3	1.1	1.0
20	21.9	23.6	1.1	0.9
32	23.4	23.2	1.2	1.0

The effects seen on fat-soluble vitamin status with a self selected diet were less than in the controlled diet studies.

### The effect of self selected diet containing olestra vs. controlled diet containing olestra



Many interactions take place during normal food consumption, and this should be borne in mind when the effects of olestra on fat-soluble vitamins is considered.

### Some Factors Effecting Uptake of Dietary Components

<u>Interaction</u>	<u>% Reduction at a Meal</u>
Fat-free meal and $\beta$ -carotene	>90
Fiber and $\beta$ -carotene	58
$\beta$ -carotene supplement and lutein	50
Cholesterol-lowering agents	30-70
Milk or cheese and iron	50
Tea or red wine and iron	60
Calcium supplement and zinc	85

#### *Points raised in the discussion*

These are contained within the consensus statement for this section of the meeting.

#### **Consensus Statement**

- The pig and human studies<sup>(1)</sup> confirm that the dietary effects of olestra are seen only on highly lipophilic micronutrients.
- Dose related and predictable effects on serum vitamin A, D and E concentrations were observed in the pig studies.
- The human studies confirm the findings of the pig studies with regard to decreases in serum vitamins A and E (with unsupplemented olestra)
- The effects of unsupplemented olestra on serum fat soluble vitamin concentrations observed with clinical studies were greater than observed in studies under free living conditions

Reference<sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional Effects of Olestra, a non absorbed fat replacement: Introduction and overview. J. Nutr 127: 1539S-1546S, 1997

#### **3.5 What are the data supporting the FDA's agreed levels of supplementation with vitamins?**

*Presentation from Dr. Khurshed Jeejeebhoy, University of Toronto, Toronto, Canada*

#### **Summary**

Vitamin replacement studies were performed in the pig and human to assess the level of vitamin supplementation required to offset the effects of olestra. These studies showed that the effects of olestra on vitamins A, D and E can be reliably and predictably offset by increasing their concentration in the diet.

The vitamin D restoration level was dissimilar between the pig and human studies. A value of 0.33 µg/g olestra was calculated from the pig 12 week study, however a restoration value of 0.07 µg/g was calculated from the 8 week supplementation study.

No effects were seen on functional vitamin K status in either pig or human studies. However, as an effect was shown on serum vitamin K levels it was decided, following discussion with the FDA, to add 80 µg vitamin K per gram of olestra. This level of supplementation will provide 1 RDA (Recommended Daily allowance) per 10 oz serving of potato chips containing olestra.

The following table summarises the levels of vitamin supplementation agreed with the FDA, and the basis for these levels:

FDA agreed supplementation level	Basis for supplementation level
1.9 milligrams α-tocopheryl equivalents per gram olestra (i.e. 2.07 mg d-α-tocopheryl acetate)	8 week human and 26 week pig vitamin replacement studies
51 retinol equivalents per gram olestra (as retinyl acetate or retinyl palmitate) i.e. 93 µg retinyl palmitate	26 week pig vitamin replacement study
12 IU vitamin D per gram olestra (i.e. 300 ng vitamin D)	8 week human and 12 week pig vitamin replacement studies
8 micrograms vitamin K per gram olestra	8 week dose ranging study

The requirement for vitamin D addition can be questioned, as dietary vitamin D provides such a small component of total vitamin D in humans.

#### ***Points raised in the discussion***

- It is highly unlikely that even a high consumption of olestra would lead to excessive vitamin D intake.
- In the supplementation studies, vitamins were added in the way they would be added in the marketed product, i.e. the vitamin E was added to the olestra, and the other vitamins added to the finished product, for instance as a top dressing to potato chips.

### Consensus Statement

- The levels of fat soluble vitamin supplementation in savory snacks agreed with the FDA are likely to correct any reduction in concentrations due to olestra consumption.
- Toxic levels of vitamins A,D,E and K are such that there is no medical concern regarding the levels of vitamin added to olestra.
- Although the possible impact of olestra snack consumption on coumadin therapy has not been established empirically, the normal daily vitamin K intake is known to be extremely variable, and the routine monitoring of this therapy by the attending physician provides an adequate measure of safety.

Reference <sup>(1)</sup> John C Peters, Kenneth D. Lawson, Suzette J. Middleton and Keith C. Treibwasser. Assessment of the Nutritional Effects of Olestra, a non absorbed fat replacement: Summary. J. Nutr 127: 1719S-1728S, 1997

### 3.6 Summary of results to date from the active surveillance program

*Presentation from Dr. Mark Thornquist, Fred Hutchinson Cancer Research Center, Seattle, WA*

#### *Summary*

1,069 adults and 210 children from the Indianapolis area, which is a test market site for olestra, attended an initial baseline visit in the Fall and early Winter of 1996. Data regarding diet and frequency of olestra snack consumption were collected, and blood taken for analysis.

The adults were subsequently followed-up with repeat telephone calls, and 500 have been selected for repeat visits over the next several years. Median reported olestra snack eating occasions were higher on the second call than the first, although the mean numbers of occasions were the same, and maximum occasions less.

#### **Olestra Snack Eating Occasions on the First and Second Follow-up Calls**

	<b>First Call (n =1030)</b>	<b>(Second Call (n = 694)</b>
Median eating occasions in users	2 per month	3 per month
Mean eating occasions in users	1.2 per week	1.2 per week
Maximum occasions	6 per day	10 per week

Subjects eating low-fat or non-fat snacks are much more likely to eat olestra snacks than are subjects eating standard-fat snacks or no snacks at baseline. Twice as many overweight and obese people ate olestra snacks regularly than those with a normal body mass index; those subjects who exercised regularly were more likely to take olestra-containing snacks.

### Type of Olestra Snack Consumed

	Percent
Potato chips	75.1
Tortilla chips	12.5
Crackers	5.9
Other	6.6

The 90<sup>th</sup> centile consumption of olestra snacks observed in the active surveillance program, 2 grams per day, is much lower than the estimate of 6.9 grams per day from the MRCA menu census survey.

### Olestra Consumption by Fruit and Vegetable Intake

Servings of Fruit and Vegetables Per Day	n	Olestra Eating Occasions per Month (% of eaters)		
		0	1-2	>2
≤ 2	555	68.3	15.7	16.0
3-4	326	69.6	17.2	13.2
≥ 5	128	70.3	17.2	12.5

The most frequent meal eaten with olestra was lunch. No one ate an olestra snack with breakfast. Only 10% of snack eaters consume snacks and carotenoid containing foods at the same time, and of these only a small percentage will be taking olestra-containing snacks.

#### *Points raised in the discussion*

- The availability and marketing of olestra containing snacks in the Indianapolis test area is representative of its future availability when marketed nation-wide.
- The Active Surveillance Study collects data over the previous month using an adapted Food Frequency Questionnaire, and then a 24-hour dietary recall. Subjects are told that it is a diet and health study, and the researchers do not make direct reference to olestra.
- The pattern of use of olestra in the test market is probably at steady state, according to traditional market history patterns.

#### **Consensus Statement**

- In the entire test market population, only 10% consumed olestra-containing snacks. In the olestra snack eating population, olestra snack consumption was only 3-4 eating occasions per week.

**3.7 What are the dose related effects of olestra in humans on the absorption of carotenoids and other phytochemicals?**

*Presentation from Dr. Olson, Iowa State University, Ames, Iowa*

**Summary**

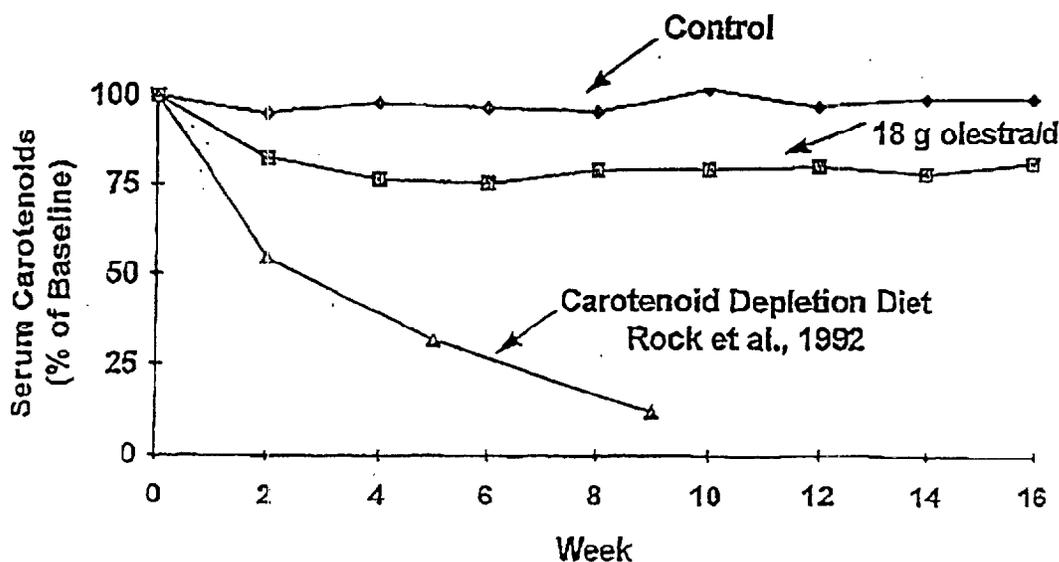
Dr Olson reviewed the mechanisms by which olestra reduces the absorption of lipophilic micronutrients including carotenoids, and hypothesised that this may be due, in part, to interference with the binding of carotenoids with bile acids. The effect is dose dependent and requires concomitant presence of olestra and carotenoids in the gut. The effects of olestra on  $\beta$ -carotene ingestion can be estimated from the MRCA menu census survey.

**Estimated Real-Life Effects of Olestra Ingestion on  $\beta$ -carotene Absorption**

Chronic intake (90 <sup>th</sup> Percentile)	7 grams/day
Meals including snacks in 14 days	52
Carotenoid meals	36 (70%)
Olestra meals	10 (19%)
Concomitant olestra/carotenoid meals	5 (10%)
Estimated effect on carotenoid absorption	6%

The reduction in serum carotenoids in subjects ingesting olestra plateaus at 4 weeks in the 16-week free-living study, whereas serum carotenoids continue to fall for at least 9 weeks in subjects ingesting a carotenoid-free diet without olestra. Dr Olson hypothesised that this plateau effect may be due to adaptive mechanisms within the body, thereby reaching a new equilibrium.

**The Effect of Olestra on Serum Carotenoids**  
 16-week free living placebo controlled study vs. carotenoid depleted diet



Plasma carotenoid content reflects only a small proportion of total body content, and so a significant reduction in plasma concentration may not necessarily imply a significant reduction in total body content.

### Body Distribution of Carotenoids<sup>(1)</sup>

Total Body Content: 65 Micromoles (100%)  
(Excludes GI Tract and Skeleton)

Adipose	65%
Liver	12%
Skin	7%
Plasma	7%
Muscle	3%
Others	6%

#### *Points raised in the discussion*

- An alternative hypothesis to explain the plateau effect of olestra on carotenoid plasma levels seen in the 16 week free-living study is that only a certain percentage of carotenoid containing foods are eaten with olestra, therefore, the effect levels out at a new steady state. Furthermore, the inhibition of carotenoid absorption by olestra is limited, even when olestra and carotenoids are taken together, and so is not representative of a carotenoid depletion diet.

#### **Consensus Statement**

- Olestra may inhibit to varying degrees (depending on the lipophilicity of individual carotenoids) the absorption of carotenoids from the intestine.
- The effects of olestra are dependent on dose and on concomitant presence of carotenoids in the GI tract.
- Under estimated 90th centile usage regimens, carotenoid absorption should only be slightly depressed (less than 10%).

Reference<sup>(1)</sup>: Olson JA Carotenoids. In: Shils M, Olson JA, Shike M, Ross AC (eds) Modern Nutrition in Health and Disease, 9<sup>th</sup> ed., Baltimore: Williams and Wilkins, in press.

**3.8 What are the proposed pathophysiological mechanisms by which carotenoids may prevent (or exacerbate) disease? What are the data regarding the plausibility of any of these hypotheses?**

*Presentation from Dr. Anthony Diplock, Guy's Hospital, London, UK*

*Summary*

A number of mechanisms have been proposed by which carotenoids may prevent disease. The established mechanism is as a provitamin A. Other mechanisms proposed for carotenoids include an effect on gene expression, and as an antioxidant.

**Proposed Mechanisms of Biological Effectiveness of Carotenoids**

- Vitamin A (retinoic acid) has a well-documented and established role in modulating gene expression.
- Carotenoids, as provitamin A, may be considered to have a similar function.
- Structural similarities between carotenoids and retinoic acid may allow a direct effect of some carotenoids on gene expression, independent of their provitamin A role.
- Carotenoids are taken up from the human gastrointestinal tract and carried unchanged, in significant quantities, to peripheral tissues where they could exert a role in gene expression modulation.

The hypothesis that carotenoids may have an effect on gene expression independent of their provitamin A activity rests on structural similarities between the two molecules. It is not known if this hypothesis is viable. Antioxidant activity has been shown *in vitro*, but not *in vivo* or in *ex-vivo* models.

**Antioxidant *in vitro* data**

- In oil emulsion all carotenoids are antioxidant with no relation to chemical structure
- In phosphatidyl choline liposomes antioxidant activities can be explained by chemical structure
- Presence of conjugated ring ketogroups enhances antioxidant activity

***In vivo/ex vivo* studies with human LDL**

- A number of human studies have investigated the enhancement of resistance to LDL oxidation by dietary supplements of  $\beta$ -carotene.
- In the LDL particle carotenoids are probably located in the inner (cholesterol ester) core;  $\alpha$ -tocopherol is located in the outer phospholipid monolayer.
- Many human studies show that vitamin E supplements protect isolated LDL against oxidative modification in the range of intake 46-1600IU per day.
- $\beta$ -carotene supplementation does not apparently alter the susceptibility of LDL to oxidation.

**Points raised in the discussion**

- In vitro studies which have shown a *pro*-oxidant effect of carotenoids tended to be done at very high oxygen tensions which are not achieved in vivo.
- There is no evidence to support the gene expression theory regarding the mechanism by which carotenoids may prevent disease.

**Consensus Statement**

- The only established mechanism by which carotenoids affect disease is through their pro-vitamin A activity.
- Antioxidant and pro-oxidant effects have been shown in vitro, but not in in-vivo or ex-vivo models.

3.9 Is there conclusive evidence that carotenoids ( $\beta$  carotene,  $\alpha$  carotene, lycopene, lutein/zeaxanthin) prevent disease: Weighing the evidence from carotenoids studies, cancer: particularly lung and prostate.

*Presentation from Dr. Greenberg, Norris Cotton Cancer Center, Lebanon, NH*

**Summary**

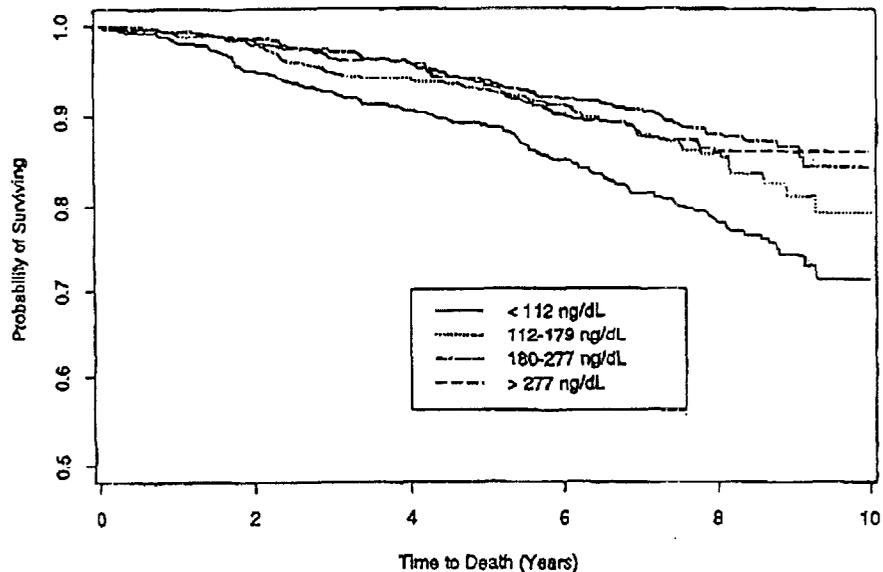
Epidemiological studies have shown a mixed picture in terms of a statistically significant inverse association between  $\beta$ -carotene and the incidence of cancer. This association has been shown most consistently with lung cancer.

**Lung Cancer Studies**

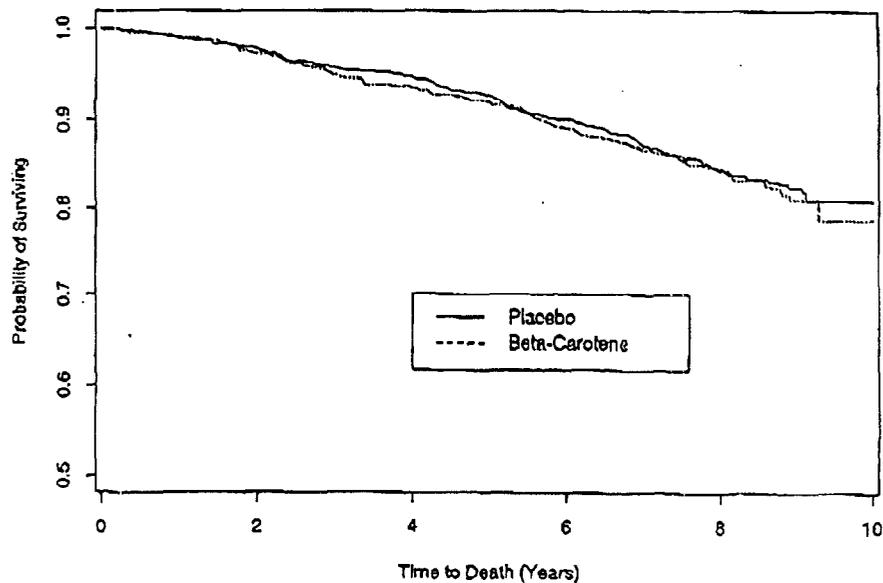
	# Cases	# Reports	#Protection	# p<0.05
Case-Control	6057	14	14	10
Cohort Diet	547	5	3	2
Cohort Blood	584	7	6	6

Prospective  $\beta$ -carotene supplementation studies have failed to show an inverse association. Greenberg et al<sup>(1)</sup> showed an inverse correlation between  $\beta$ -carotene (as measured at baseline) and mortality but failed to show a protective effect in the group allocated to  $\beta$ -carotene therapy when compared to placebo.

### Mortality According to Initial Plasma Beta-Carotene Concentration



### Mortality According to Treatment Group (Beta-Carotene or Placebo)



Reference <sup>(1)</sup>: Greenberg ER et al, Mortality associated with Low Plasma Concentration of Beta Carotene and the Effect of Oral Supplementation, The Journal of the American Medical Association, March 6, Volume 275.

### 3.10 Heart disease

*Presentation from Dr. Stephen Kritchevsky, University of Tennessee, Memphis, TN*

#### *Summary*

The diet based epidemiological studies have mostly looked at pro-vitamin A carotenoids, and most have looked at coronary heart disease mortality. Out of the seven cohort studies:

- 6 of 7 show a benefit of dietary carotenoids
- 2 of 7 demonstrate statistical significance but
  - 1 is for smokers only (Rimm et al, 1993)
  - 1 is for consumption of high carotenoid foods (Gaziano et al, 1995)
- 2 studies find stronger or as strong relationships with vegetable intake (Sahyoun et al, 1996; Knekt et al, 1994)
- The largest study of women shows no effect (Kushi et al, 1996)

Flavonols have been studied with mixed results.

In the blood sample based epidemiological studies, 5 out of 5 case-control studies from 4 independent study groups showed an inverse association between carotenoids and heart disease, but it depends which carotenoid is examined:

$\beta$ -carotene (3 of 4)  
 $\alpha$ -carotene (0 of 2)  
Lycopene (3 of 3)  
Lutein/zeaxanthin (2 of 2)

There were also differing endpoints, i.e. intimal medial thickness, angina, non-fatal myocardial infarction, ischemic heart disease.). Two of 3 studies showed a strong protective effect for disease only in smokers. The 2 largest of the 3 cohort blood studies found significant inverse association of similar magnitude with relative risks of 0.64.

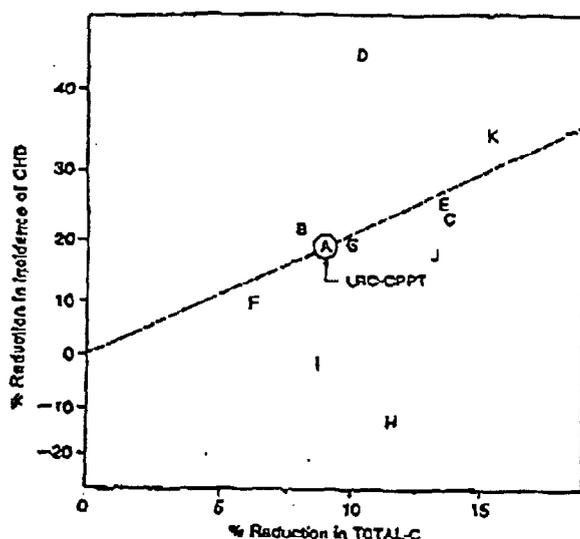
The 4 randomized clinical trials of  $\beta$ -carotene supplementation in a total of 71,238 subjects showed a possible increase in death due to cardiovascular disease in the treated group, and certainly no protective effect.

Analysis of the baseline blood samples has shown a significant inverse correlation between  $\beta$ -carotene and CVD death. <sup>(1)</sup>

Reference <sup>(1)</sup>: Greenberg ER et al, Mortality associated with Low Plasma Concentration of Beta Carotene and the Effect of Oral Supplementation, The Journal of the American Medical Association, March 6, Volume 275.

Data from the cholestyramine group of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) shows that the cholestyramine group experienced a 38 $\mu$ /dl decrease (about 25%) in circulating carotenoid levels which is on the order of that seen in free-living studies of olestra. However, the reduction in incidence of coronary heart disease was exactly as predicted from the decrease in cholesterol levels. This implies that prospectively reducing carotenoid levels does not have a deleterious effect on the incidence of coronary heart disease.

**Comparison of Results of 11 Cholesterol-Lowering Trials with the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) Cholestyramine Group.**



**3.11 Might serum carotenoids be serving as biomarkers for a healthy life style and for the intake of green vegetables and fruit etc., rather than conferring any direct effect?**

*Presentation from Dr. Frank Meyskens, UC Irvine, Orange, CA*

**Summary**

Diets high in fruits and vegetables are recognized in observational clinical trials to provide a health benefit. However, this does not establish a cause and effect health role for carotenoids themselves. There are other explanations for the health benefit of diets high in fruit and vegetables: i.e. such a diet is low in fat, iron and calories, high in vitamin C, E and fiber, and may be associated with regular exercise and a lack of smoking.

Previous expert committees that have published their findings have not come to a consensus that carotenoids do in fact prevent chronic disease.

### **Previous International Expert Committees to have considered the Role of Carotenoids in the Prevention of Disease**

- 1987 UK Committee on Medical Aspects of Food Policy.
- 1993 "Role of Antioxidants on Health," the International Life Science Institute.
- 1993 "Antioxidant Nutrients and Cancer and Cardiovascular Disease," FDA Conference.
- 1994 "Antioxidant Vitamins and  $\beta$ -Carotene in Disease Prevention," Sponsors include the National Cancer Institute and the National Heart, Lung and Blood Institute.

Rock et al <sup>(1)</sup> recently published a study looking at the correlation of vegetable intake with nutrients and other factors. This 12 month controlled study in 79 women with prior breast cancer demonstrated that vegetable intake correlated with lutein,  $\alpha$ - and  $\beta$ - carotene, lycopene and retinol, but not with  $\alpha$ -tocopherol or  $\beta$ -cryptoxanthin.

Reference<sup>(1)</sup>: Rock CL et al, Responsiveness of Carotenoids to a High Vegetable Diet Intervention Designed to Prevent Breast Cancer Recurrence. *Cancer Epidemiology, Biomarkers&Prevention*, Vol 6, 617-623, August 1997

#### ***Points raised in the discussion of the evidence regarding a role for carotenoids ( $\beta$ -carotene, $\alpha$ -carotene, lycopene, lutein/zeaxanthin) in disease prevention the last 3 presentations***

- The slight excess in colonic cancer in the cholestyramine group of the LRC-CPPT may have been due to a local effect of cholestyramine on the colonic mucosa.
- Epidemiological studies, especially diet studies are problematic. It is difficult to measure diet with a high degree of confidence and there are errors in any diet assessment. Furthermore those studies were mostly not designed to look at cardiovascular endpoints and that weakness is reflected in the reliance on mortality rather than incidence.
- The term "biomarkers" was queried. It was felt that the term "indicators" more accurately reflected the intended hypothesis regarding the relationship between carotenoids and fruit and vegetable intake.
- A meta-analysis of the data looking at different types of fruits and vegetables and their correlation with various serum carotenoids might be useful.
- Intervention studies that look at the effect of increasing fruit and vegetable consumption tend to aim at targets that are way above the usual intake. It is necessary to get to a level several times above the general population mean intake to begin to demonstrate increases in tissue concentrations on specific carotenoids.

### Consensus Statement

- Serum carotenoid concentrations are indicators of the intake of certain fruits and vegetables.
- There is no consensus that carotenoids themselves play a preventative role against cancer and cardiovascular disease.
- Case-control and cohort studies have shown that there may be an association between diets high in  $\beta$ -carotene and a reduced incidence of cancer and heart disease.
- Randomized controlled clinical studies of  $\beta$ -carotene supplementation have not shown any benefit in lung cancer and coronary artery disease. Benefits of other carotenoids have not been ruled out.
- $\beta$ -carotene supplementation may increase the risk of mortality from lung cancer and ischemic heart disease in smokers.

### 3.12 What factors can affect carotenoid stability, bioavailability, absorption and utilization?

*Presentation from Dr. Steve Schwartz, The Ohio State University, Columbus, OH*

#### *Summary*

Many factors affect the absorption and utilization of carotenoids from foods.

#### **Factors Affecting Absorption and Utilization**

- Efficiency – inversely related to uptake
- Dietary fat is the most critical factor;  $\beta$ -carotene absorption was greatly decreased when consumed in the absence of fat.
- Type of carotenoids (xanthophylls vs. carotenes)
- Interaction amongst carotenoids
- Food matrix
  - Particle size
  - Digestibility
- Host-related factors
  - Nutrient status
  - Genetic factors
  - Disease state (e.g. malabsorption, intestinal parasites)
- Drug interactions
  - Ethanol
  - p450 inducers
  - Cholestyramine

Factors affecting the carotenoid content in foods include the quality of fruit and vegetables, storage conditions, food processing and preparation and the influence of other ingredients.

For instance, when a single dose of 23 mg lycopene was administered in fresh tomatoes or tomato paste together with 15 grams of corn oil, the tomato paste yielded 2.5 fold higher chylomicron lycopene concentration than the fresh tomatoes.<sup>(1)</sup> Chylomicron concentration is more indicative of direct absorption kinetics than an overall plasma response.

#### *Points raised in the discussion*

- The metabolic dynamics of the carotenoid *cis* isomers are different from that of the *trans* isomers. There is very little *cis* isomer of beta-carotene for example in the plasma after administration. There is no known biological function of the *cis* isomer.

#### Consensus Statement

- Olestra consumption is one of the many factors which can potentially influence carotenoid absorption from the diet.

Reference <sup>(1)</sup>: Gartner et al, Amer J Clin Nutri, 56:116, 1997.

#### 4 FINAL CONCLUDING STATEMENT

The panel agreed the following consensus statements:

- When consumed as a fat substitute in savory snacks, vitamin-supplemented olestra is likely to produce negligible changes in fat soluble vitamin concentrations.
- Many factors affect the absorption of carotenoids from food. The effect of olestra on carotenoid absorption, when consumed as a fat substitute in savory snacks, is likely to be slight.
- Serum carotenoids reflect the intake of certain fruits and vegetables, and in people who consume them, serum levels are associated with a decreased risk of cancer and cardiovascular disease. There is no conclusive evidence that carotenoids themselves prevent cancer or cardiovascular disease.
- When consumed as a fat substitute in savory snacks, olestra's effects on the concentration of fat soluble vitamins and carotenoids pose no apparent health risks.

**SIGNED APPROVAL FORMS FROM  
PANELLISTS**

VITAMIN ADVISORY PANEL

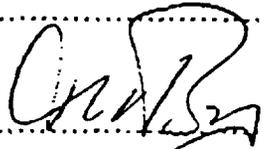
Date: 19 February, 1998

Code: vitaaccept.doc

Having attended the Vitamin Advisory Panel held on December 4<sup>th</sup>/5<sup>th</sup> 1997, and based on the evidence available at that time, I approve the contents of this report and the consensus statements therein.

Name: Tammy M. Bray

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The Ohio State Univ.  
1987 Neil Ave  
Columbus, OH 43210-1295

Signed: 

Date: March 1, 98

Please fax this form to Ms. Alison Howe at  
Strategic Consultants International  
Fax: 011-44-1442-210169

**VITAMIN ADVISORY PANEL**

Date: 19 February, 1998

Code: vitaaccept.doc

Having attended the Vitamin Advisory Panel held on December 4<sup>th</sup>/5<sup>th</sup> 1997, and based on the evidence available at that time, I approve the contents of this report and the consensus statements therein.

Name: Gail G. Harrison

Address: UCLA School of Public Health

10833 Le Conte Avenue

Los Angeles, California 90095-1772

Signed:



Date:

2/2/98

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Strategic Consultants International  
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VITAMIN ADVISORY PANEL

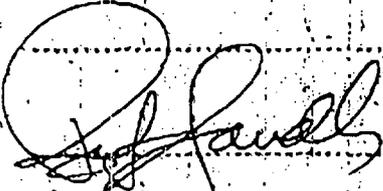
Date: 19 February, 1998

Code: vitaaccept.doc

Having attended the Vitamin Advisory Panel held on December 4<sup>th</sup>/5<sup>th</sup> 1997, and based on the evidence available at that time, I approve the contents of this report and the consensus statements therein.

Name: ROBERT SANDUER

Address: UNIVERSITY OF NORTH CAROLINA

Signed: 

Date: 2/29/98

Please fax this form to Ms. Allison Howe at  
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Fax: 011-44-1442-210169

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Name: ..... *A. Catharine Ross* .....

Address: ..... *Penn State University* .....  
..... *115 Henning Bldg.* .....  
..... *University Park, PA 16802* .....  
.....  
.....

Signed: ..... *A. Catharine Ross* .....

Date: ..... *3/2/98* .....

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Name: Dr K. W. JEE JEEBHOY

Address: 3-035 Queen Wing  
St Michael Hospital  
30 Bond St  
TORONTO

Signed: [Signature]

Date: 25/2/98

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Name: Professor A.T. Diplock

Address: International Antioxidant Research Centre,  
University of London  
Guy's Hospital  
London SE1 9RT

Signed: Anthony Diplock

Date: 27 February 1998

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Fax: 011-44-1442-210169

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Name: E R Greenberg

Address: Norris Cotton Casco Center  
Lebanon NH  
03756

Signed: [Signature]

Date: 2/27/98

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VITAMIN ADVISORY PANEL

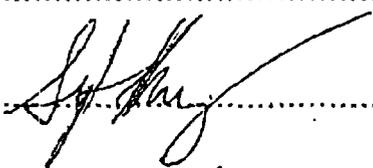
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Name: Stephen B. Kritchevsky, PhD

Address: Department of Preventive Medicine  
UT, Memphis  
66 N. Pauline, Ste 633  
Memphis, TN 38105  
USA

Signed: 

Date: 2/26/98

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Name: Frank L. Mayskens Jr

Address: Chao Family Comprehensive Cancer Ctr  
101 The City Drive  
Bldg 23, 4th Floor  
Orange, Ca 92868

Signed: Frank L. Mayskens Jr

Date: 2-23-98

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Fax: 011-44-1442-210169

VITAMIN ADVISORY PANEL

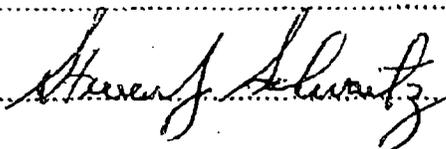
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Name: ..... Steven J. Schwartz, Ph.D. ....

Address: ..... Food Science and Technology .....  
..... 144 Howlett Hall .....  
..... 2001 Fyffe Court .....  
..... Columbus, OH 43210 .....

Signed: .....  .....

Date: ..... 2-27-98 .....

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