Lessons for GM foods

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Absorption of Fats Decreases as Number of Fatty Acid Ester Groups Increase

Glycerol (3)
Erythritol (4)
Xylitol (5)
Sucrose (8)

Percent Absorption

Mattson FH, Volpenhein RA, J Nutr 102: 1972
Triglycerides Readily Absorbed
Sucrose Octa-Ester Resistant to Pancreatic Lipases and Bacterial Metabolism
1971 Proctor and Gamble first meets with U.S. Food and Drug Administration

1987 Proctor and Gamble applies for market approval as general purpose fat substitute

1990 Proctor and Gamble narrows application to savory snacks

1995 Congressional sub-committee holds hearings on FDA food additive petitions

1995 Regulatory decision team votes 17-5 for approval

1996 Approval, conditional upon Post-Marketing Surveillance
The Procter and Gamble Co. has made a commitment to the agency that it will conduct the studies outlined in the letter to FDA...

If Procter and Gamble does not conduct the identified studies ...., FDA will consider the approval set forth in this document to be void...
It is the agency’s responsibility….to review and evaluate the data generated by Procter and Gamble’s studies, as well as any new data that bear on the safety of olestra (such as data and information on the health significance of carotenoids) to determine whether there continues to be a basis for a reasonable certainty that the use of olestra in savory snacks is not harmful.
Olestra lowers absorption of β-carotene and vitamins E, D and K in humans.

Schlagheck, J Nutr 1997
Olestra Substantially Decreases Serum Carotenoid Concentrations

Only Co-Consumption of Olestra with Food Reduces Serum Vitamins

![Bar chart showing the effect of Olestra feeding on serum concentrations of vitamins. The chart compares control, mixed in food, and chips as snack conditions for α-tocopherol, retinol, and 25(OH)D2.](chart.png)

Schlagheck, J Nutr 1997
Olestra Increases Frequency of Gastrointestinal Symptoms

Schlagheck, J Nutr 1997
1. Olestra intake

2. Changes in food consumption patterns

3. Changes in nutritional status

Gastrointestinal symptoms were evaluated in randomized clinical trials
No Difference in Gastrointestinal Symptoms Olestra vs. Triglyceride Chips at Single Occasion

Double-Blinded, Ad Libitum Consumption

- Olestra (N=563)
- Triglyceride (N=529)

Cheskin et al, JAMA, 1998
No Difference in Gastrointestinal Symptoms
Olestra vs. Triglyceride Chips for 6-Weeks

Double-Blinded, *Ad Libitum* Consumption

- **Olestra (N=1620)**
- **Triglyceride (N=1561)**

Three Specific Aims

1. Monitor adoption and patterns of use in the US population

2. Assess associations between introduction of olestra-containing foods and serum micronutrients in the US population (80% to detect 10% reduction)

3. Assess associations of long-term, heavy olestra consumption with changes in serum micronutrients (80% to detect 10% reduction)
Aim 1. Monitor Adoption and Use

**DESIGN**

- Random digit dial telephone surveys (Express mail letter with $10 bill enclosed)
- Baseline survey completed before introduction of olestra-containing foods
- Repeated surveys Years 1, 2 and 3
Aim 2. Olestra and Serum Micronutrients in U.S. Population

DESIGN

- Telephone-survey participants invited to clinic ($100 individual, $200 with child)
- Baseline completed before introduction of olestra-containing foods
- Repeated cross-sectional samples Years 1, 2 and 3
Aim 3. Long-Term, Heavy Olestra Consumption and Serum Micronutrients

**DESIGN**

- Baseline clinic cross-section participants followed every 4 months by phone for olestra use
- Olestra users (80%) and non-users (20%) invited to repeat clinic visits Years 1, 2 and 3 ($100 individual, $200 with child)
Sentinal* Site Design

Olestra Entered Sentinel Market
Feb 1997

Baseline

Follow-up
Sept 1998 – Jan 1999

Telephone Survey

Clinic Cross Section

Clinic Cohort

2,173
Adult=1,069
Child=210

1,538
Adult=948
Child=231

365
Adult=218
Child=41

Adult=419
Child=74

Adult=386
Child=67

*Indianapolis, IN
National Site Design

Olestra Entered National Market
May 1998

Baseline
Oct 1997 – April 1998

Follow-up

Telephone Survey

Clinic Cross Section

Clinic Cohort

5,586

1,212

1,220

Adult=2,887
Child=625

Adult=659
Child=138

Adult=1,401
Child=298

Adult=623
Child=153

Adult=1,324
Child=283

*San Diego CA; Minneapolis MN; Baltimore MD
Aim 1. Monitor Adoption and Use

CONTENT

1. Diet-related psychosocial constructs

2. Usual consumption of savory snacks, fruits and vegetables over past month

3. Savory snack, fruit and vegetable consumption over past 24-hours

4. Demographic characteristics
Aim 1. Monitor Adoption and Use

METHODS

• “Usual” food consumption in past month
  • Standard 5-item fruit and vegetable questionnaire
  • Developed “snack” questionnaire

• Food consumption in past 24-hours
  • Developed and validated “focused” 24-hr dietary recall
  • At each eating occasion, assessed specific types and amounts of savory snacks, fruits and vegetables, and foods made with high-carotenoid ingredients
Aim 1. Monitor Adoption and Use

ANALYSES

• Each observation weighted for sampling probability and population age/sex distribution

• Total and age/sex specific distributions of consumption of savory snacks

• Associations of demographic characteristics and psychosocial constructs with snack and fruit and vegetable consumption

• Frequency of co-consumption of high-carotenoid and olestra-containing foods
Olestra Consumption was Very Low

<table>
<thead>
<tr>
<th>Snack Type</th>
<th>Mean (svgs/m)</th>
<th>Eating ≥ 1/m (%)</th>
<th>Mean among Eaters (svgs/m)</th>
<th>90%tile (svgs/m)</th>
<th>95%tile (svgs/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10.9</td>
<td>95.2</td>
<td>13.0</td>
<td>39.0</td>
<td>53.3</td>
</tr>
<tr>
<td>Regular Fat</td>
<td>3.8</td>
<td>75.1</td>
<td>6.0</td>
<td>29.2</td>
<td>40.1</td>
</tr>
<tr>
<td>Reduced, Fat Non-Fat</td>
<td>4.1</td>
<td>79.7</td>
<td>6.3</td>
<td>23.9</td>
<td>30.6</td>
</tr>
<tr>
<td>Olestra</td>
<td>0.3</td>
<td>15.5</td>
<td>3.6</td>
<td>10.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Olestra (g/d)</td>
<td>0.1</td>
<td></td>
<td>1.1</td>
<td>4.0</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Olestra Consumption Differs by Demographic Characteristics

Neumark-Stainer, et. al., J Am Diet Assoc, 2000
Olestra Consumption Differs by Health Conditions

Neumark-Stainer, et. al., J Am Diet Assoc, 2000
Importance of Eating Low Fat Diet
Relationship between Diet and Disease
Nutrition Salience

Neumark-Stainer, et. al., J Am Diet Assoc, 2000
Consumption of Savory Snacks with High-Carotenoid Foods is Rare

<table>
<thead>
<tr>
<th>Meal</th>
<th>Eating (%)</th>
<th>Fruit or Vegetable (%)</th>
<th>High-Carotenoid Fruit or Vegetable (%)</th>
<th>Savory Snack (%)</th>
<th>Savory Snack with Fruit or Vegetable (%)</th>
<th>Savory Snack with High-Carotenoid Fruit or Vegetable (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>69.9</td>
<td>68.9</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-Morning</td>
<td>23.2</td>
<td>40.5</td>
<td>4.6</td>
<td>35.6</td>
<td>11.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Lunch</td>
<td>79.3</td>
<td>61.5</td>
<td>38.6</td>
<td>23.6</td>
<td>14.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Mid-Afternoon</td>
<td>35.2</td>
<td>40.5</td>
<td>4.1</td>
<td>36.2</td>
<td>12.2</td>
<td>1.2</td>
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<tr>
<td>Dinner</td>
<td>92.4</td>
<td>73.2</td>
<td>42.8</td>
<td>13.3</td>
<td>8.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Late Night</td>
<td>41.0</td>
<td>35.1</td>
<td>2.7</td>
<td>24.2</td>
<td>7.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Very Little Carotenoid “At –Risk” of Poor Absorption
Aim 2. Olestra and Serum Micronutrients in U.S. Population

METHODS

• 1 ½ hour clinic visit

• Fasting blood draw for serum micronutrients and carotenoids

• Diet (FFQ, Snack Foods and Focused Recall) Supplement use Dietary micronutrients and carotenoids Sun exposure, physical activity BMI, smoking, etc.
Aim 2. Olestra and Serum Micronutrients in U.S. Population

ANALYSES

- Each observation weighted for sampling probability and population age/sex distribution

- Using baseline data, fit models predicting Vit E, D and K and carotenoids from diet, supplements and covariates

- Using Year 1 data, replicate baseline models with the addition of olestra consumption
Olestra was Not Associated with Population-Level Serum Micronutrients

Olestra g/day
- None (n=714)
- >0 - <0.4 (n=129)
- ≥0.4 - <2.0 (n=62)
- ≥2.0 (n=26)

Thornquist et al, J Nutr, 2000, Sentinel Site, n=931
Aim 3. Long-Term, Heavy Olestra Consumption and Serum Micronutrients

METHODS

• 1 ½ hour clinic visit

• Fasting blood draw for serum micronutrients and carotenoids

• Diet (FFQ, Snack Foods and Focused Recall) Supplement use
  Dietary micronutrients and carotenoids
  Sun exposure, physical activity
  BMI, smoking, etc.
Aim 3. Long-Term, Heavy Olestra Consumption and Serum Micronutrients

ANALYSES

• Fit models predicting change in Vit E, D and K and carotenoids associated with Olestra consumption
Olestra was Not Associated with Changes in Serum Micronutrients

Olestra g/day

- None (n=261)
- >0 - <0.4 (n=71)
- ≥0.4 - <2.0 (46)
- ≥2.0 (n=20)

Thornquist et al, J Nutr, 2000, Sentinel Site, n=398
Olestra was Associated with Weight Loss and Reduced Serum Lipids

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Total Cholesterol (mmol/L)</th>
<th>LDL Cholesterol (mmol/L)</th>
<th>HDL Cholesterol (mmol/L)</th>
<th>Triglycerides (mmol/L)</th>
</tr>
</thead>
</table>

Olestra g/day
- None (n=261)
- >0 - <0.4 (n=71)
- ≥0.4 - <2.0 (n=46)
- ≥2.0 (n=20)

Patterson et. al., Arch Intern Med 2000, Sentinel Site, n=326
Based on Sentinel Site Results, FDA Continued Approval in 1999
Olestra Sales were Poor

- **Wow Lays + Ruffles**
- **Fat-Free Pringles**
- **Wow Doritos + Tostitos**

Volume Sales

- June 1998
- Oct 1998
- Feb 1999
- June 1999
- Oct 1999
- Feb 2000
- June 2000
- Oct 2000
Proctor and Gamble Ended Post-Marketing Surveillance Activities Abruptly in April of 2000

Sentinel site closed at end of Year 2

National sites closed mid way through Year 2

Funding for all activities ended

Publication of results delayed until 2006
Olestra was Associated with Small Changes in Serum Micronutrients

Olestra was Not Associated with Weight Loss and Reduced Serum Lipids

Olestra g/day

- None (n=877)
- >0 - <0.4 (n=152)
- ≥0.4 - <2.0 (n=122)
- ≥2.0 (n=27)

Satia-Abouta et. al., Nutrition, 2003, National Sites, n=1,178
Post-Marketing Surveillance was Expensive

<table>
<thead>
<tr>
<th></th>
<th>1997</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8,172,420</td>
<td>6,389,784</td>
<td>6,377,996</td>
<td>6,229,151</td>
<td>27,169,351</td>
</tr>
</tbody>
</table>

Budget in US Dollars
Scientific Challenges in Olestra Post-Marketing Surveillance

- Complex research design and protocols
- Blinding
- Low exposure
- High participant burden
- High costs
- Measurement:
  - Micronutrient and carotenoid intake
  - Snack food
  - Co-consumption of olestra and carotenoids
- Analysis using data from incomplete study
Lesions for GM Post-Marketing Surveillance

- **Design**
  - Hypothesis driven
    - *Criterion for statistical test*
  - Accurate exposure assessment
    - *Notoriously difficult*
  - Well-defined, unbiased, feasible outcomes
    - *Cannot detect chronic disease risk*
  - Adequately powered
    - *Detect biologically meaningful effect*

- **Funding**
  - Industry
  - Government
  - Foundation/NGO
Lesions for GM Post-Marketing Surveillance

- Regulatory
  - Data collection and analysis not standardized
    - *Exclusion based on influence statistic*
  - Interpretation subject to judgment
    - *Dose-response, threshold, non-linear*
  - Data documentation and verification unrealistic
    - *Cannot meet FDA requirements based on drugs*
  - Analyses well outside of agency expertise
    - *Covariates, parameterization of statistical model*
Lesions for GM Post-Marketing Surveillance

- Distortion of Research Findings
  - Anecdote
    - “I took one bite and had headaches and diarrhea for 3 days”
  - Attribution bias
    - Common symptoms attributed to salient exposure
- Ideology
  - Natural and organic
- Media
  - Sensational sells

- Limitations of Observational Epidemiology
  - Reproducibility
  - Generalizability
  - Measurement error
  - Bias and confounding