

CSL / JIFSAN Symposium on Food Safety and Nutrition

Food Safety and “Nutritional Risk”: “Bioactive” Food Components

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FDA / CFSAN
June 29, 2005



Olestra as a “case study” on “bioactive” ingredients ??

This presentation focuses a good deal on FDA’s safety review of the food additive petition for the fat substitute “olestra.”

Olestra is decidedly NOT “bioactive” in the chemical sense. Yet, its safety review signals landmark issues for the evaluation of many materials that *are* the focus of this symposium, i.e., when we must expand beyond the realm of traditional toxicological endpoints into nutrition, gastrointestinal physiology, human tolerance data, etc., and also expand our reliance on clinical data, and active and passive post market surveillance. The FDA’s review of olestra brought many of these issues into sharp focus for the first time.

These facets of safety review are now commonly included in the evaluation of at least some, if not all, bioactive food ingredients, and are major attributes of the developing field of “nutritional safety assessment.”



This presentation will:

- Outline scientific principles and legal standard for safety assessment of food components; focus on the case of “olestra”
...leading to...
- Approaches for regulating food novel components, including, ultimately, “bioactive” ones...and, thereby leading to...
- ...outlining aspects of the emerging field of “Nutritional Safety Assessment”



Food Safety Decision Framework in U.S. Law

U.S. law approaches different segments or components of the food supply differently; e.g., food itself, “generally recognized as safe” food ingredients, food additives, color additives, food contact substances, pesticide residues, animal drugs, environmental contaminants of food, “prior sanctioned” food ingredients, dietary supplements, infant formula, etc.



A Core Statute for Food Ingredient Safety: Sec. 409 of the FD&C Act

- Defines “food additive” (w/ GRAS exemption)
- Requires premarket approval of new uses of food additives, if not “GRAS”
- Establishes the standard of data review
- Establishes the standard of safety
- Establishes formal rulemaking procedures for petition review
- -----since FDAMA of 1997:-----
- Defines “food contact substance” (FCS)
- Establishes a premarket notification program for food contact substances



Standard of Review

“Fair evaluation of the data . . .”



House of Representatives, Report No. 2284, “Food Additives Amendment of 1958”

Committee on Interstate & Foreign Commerce, 85th Congress, 2nd Session, July 28, 1958

“The committee feels that the Secretary’s findings of fact and orders should not be based on isolated evidence in the record, which evidence in and of itself may be considered substantial without taking account of the contradictory evidence of equal or even greater substance”



Safety Standard

“Reasonable certainty of no harm . . .”



REASONABLE CERTAINTY OF NO HARM

Legislative History of the FD&C Act

The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive.

It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

H.R. Report No. 2284, 85th Congress 1958



The RCNH Standard of Safety for Food Additives

The petitioner has the burden to demonstrate a “**reasonable certainty of no harm**” from the intended use of the additive

This requires that the FDA assess whether it has received from the petitioner adequately documented answers to appropriate questions of probative value.



Reasonable Certainty of No Harm

What does

“Reasonable Certainty of No Harm”

mean?



Reasonable Certainty of No Harm

It is not intended to ensure, nor is it possible to ensure, safety with absolute certainty:

i.e., “Reasonable Certainty of No Harm” is *not* “Certainty of No Theoretical Possibility of Harm.”



Traditional Safety Evaluation (Petitions)

- A “full blown,” exhaustive safety evaluation of all appropriate data, information and studies, with agency “ownership” of the ultimate safety decision and publication of its decision and supporting rationale in the Federal Register.



Toxicological Testing

The CFSAN “Redbook”

Minimum Toxicity Tests	Concern Levels		
	I	II	III
Short-term tests for genetic toxicity	X	X	X
Metabolism & pharmacokinetic studies		X	X
Short-term tox tests with rodents	X		
Subchronic tox tests with rodents		X	X
Subchronic tox tests with non-rodents		X	
Reproduction study w/ teratology phase		X	X
One-Yr tox tests with non-rodents			X
Carcinogenicity study with rodents			X
Chronic tox/ carcinogenicity study with rodents			X



The “Toxicological” Safety Assessment Model (Based on the Review of Toxicological Data)

- Requires defining population exposure to the additive, “Estimated Daily Intake” (or EDI), and
- Comparing that to an “Acceptable Daily Intake” (ADI) from toxicological studies



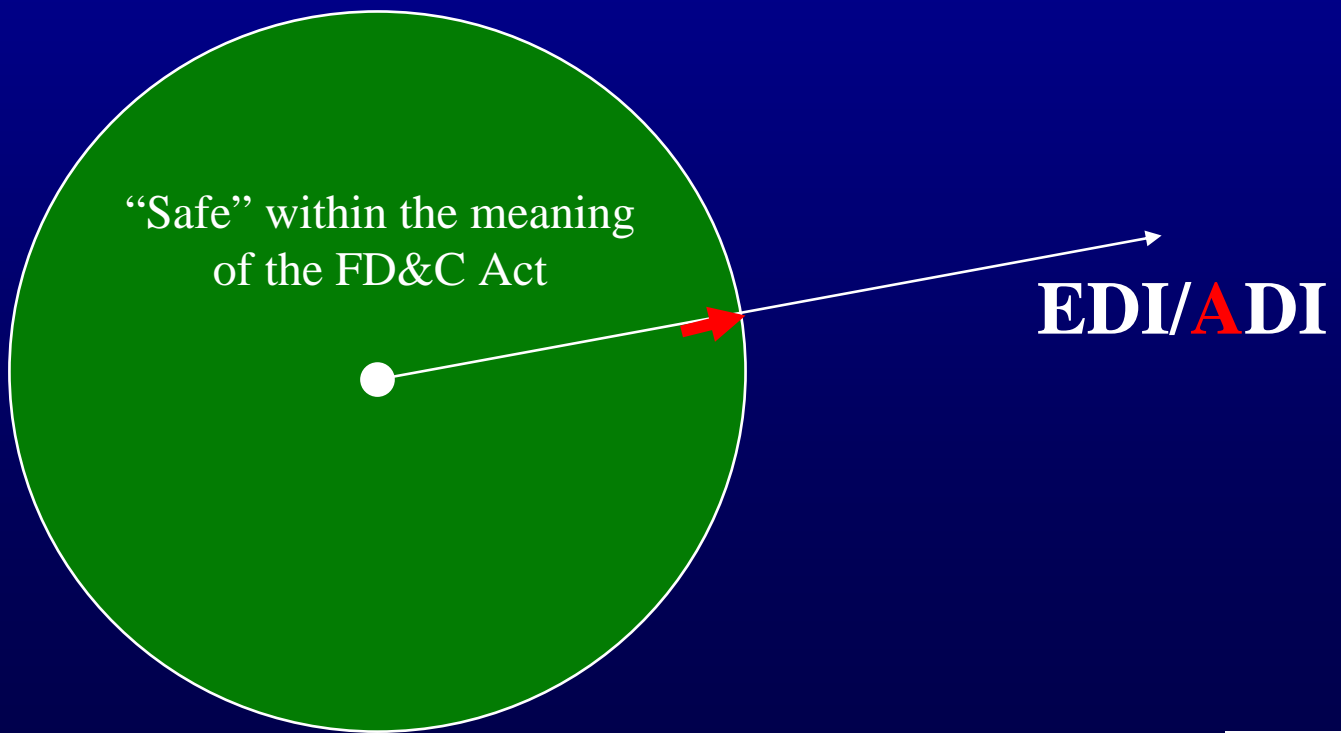
The “Toxicological” Safety Assessment Model (Based on the Review of Toxicological Data)

- Lifetime-average, “high eaters only” **EDI**
- **HNEL** from lifetime animal studies
- Threshold behavior for toxic effects
- Application of appropriate safety (uncertainty) factors (e.g., 10x and 10x)
- Acceptable Daily Intake or **ADI**
- Comparison of the **EDI** to the **ADI**
- **No effects** at estimated consumption levels



The “Circle” of Reasonable Certainty of No Harm

As a metaphor for the process, think of the goal as: “being within a circle of unit radius” as defined below:



Beyond the Traditional Toxicology Framework

The Case of the Food Additive
OLESTRA



“Olestra”

a macronutrient substitute for fat

- Under the FD&C Act, olestra was a *new food additive* use...
- 1987 Petition from P&G for olestra use as a fat substitute (later only for use in “savory snacks”)
- ...requiring FDA premarket safety evaluation.
- This, in turn, required the review of data on likely human exposure, toxicological properties and, as it turns out, effects on human physiology and nutrition, as well.

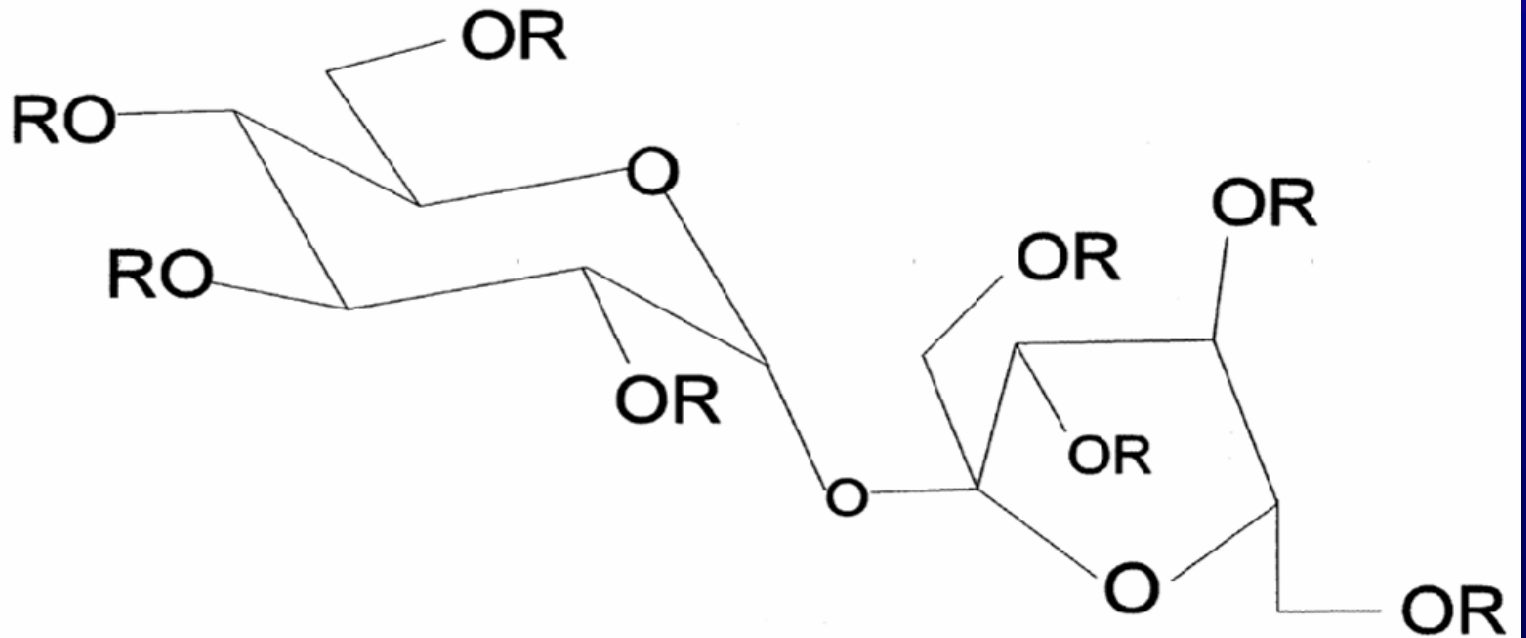


Olestra... What is it?

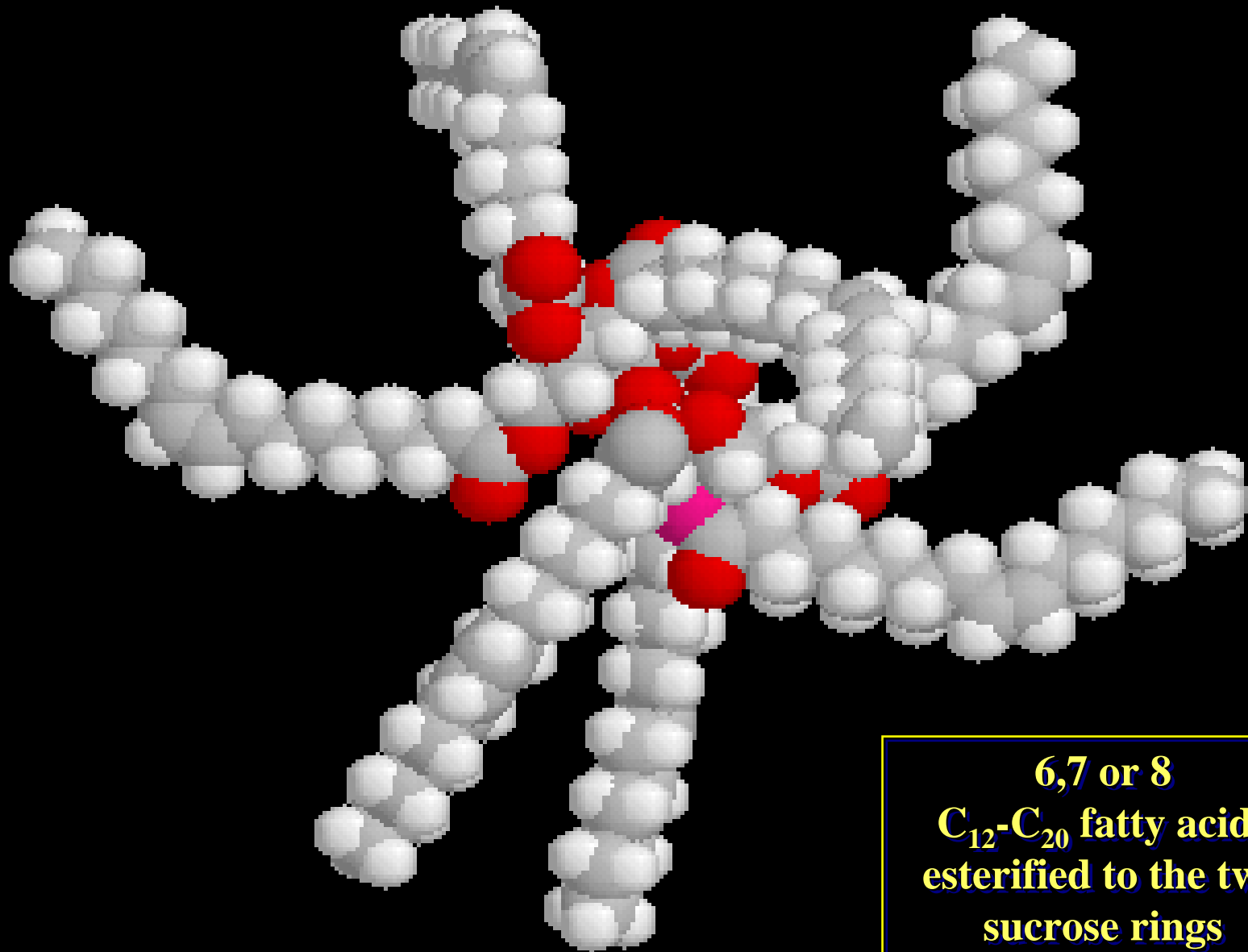
- Olestra is a Sucrose Polyester, a mixture of substances formed by chemical combination of sucrose with 6, 7, or 8 fatty acids.
- It has many of the *physical* properties of natural fats, and therefore can technologically substitute for fat in food manufacture.



Olestra: Molecular Structure



R = Fatty Acids (C12 - C20)



6,7 or 8
 C_{12} - C_{20} fatty acids
esterified to the two
sucrose rings

THE TAX CUTS
What You'd Save

TIME

Fat-Free Fat?

These munchies taste great. But they have no fat calories, thanks to a synthetic oil called olestra. The FDA must now rule if they're safe. The inside story of a decision that will affect dieters everywhere.



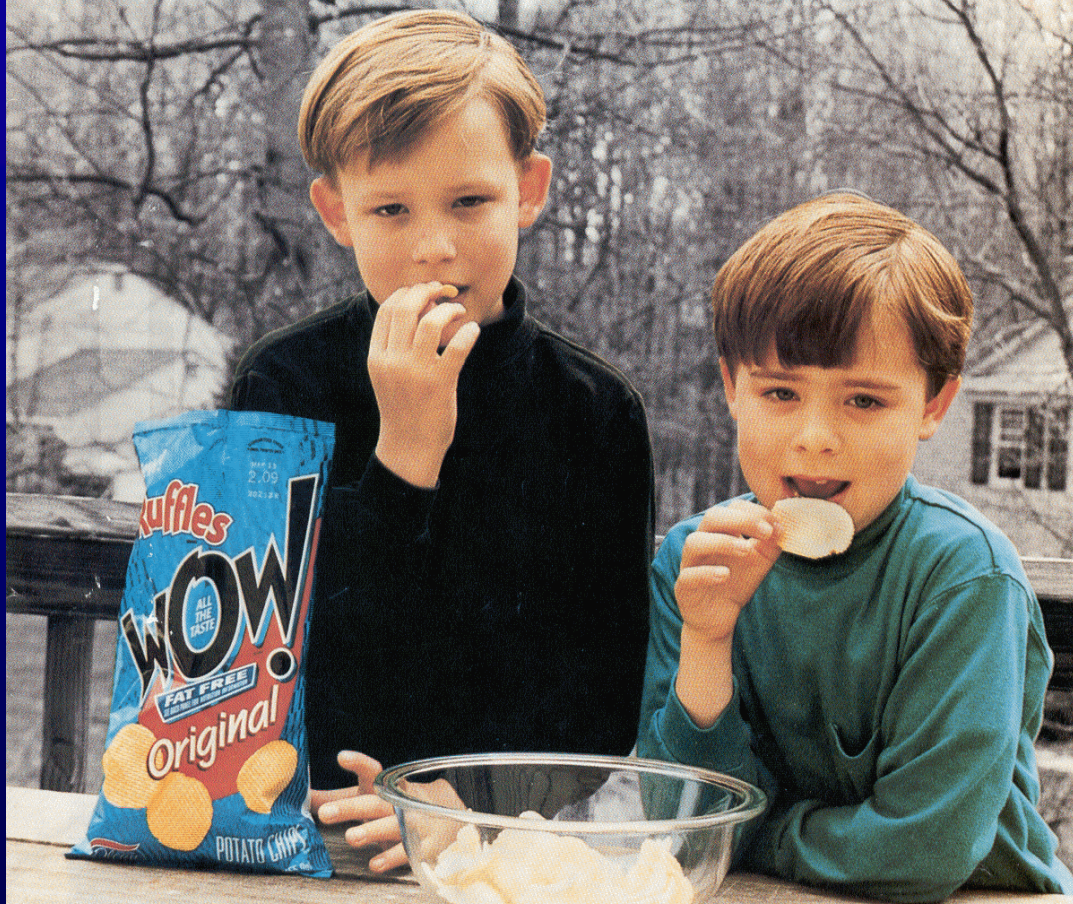
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APRIL 21, 1997

CHEMICAL & ENGINEERING NEWS

Cutbacks Shake
German Science
Page 42



Food Additives
Fat Replacements Stir Market - Page 19

GOVERNMENT INSIGHTS

Olestra and the importance of FDA

Business leaders in the pharmaceutical and food industries calling for "reforms" that involve the agency's authority should be...

additive, FDA Commissioner David A. Kessler called olestra "probably one of the most extensively studied food substances to date." The conclusion that research is straightforward to eat. Its one...

Fat Substitute Moves Closer To Final Approval From FDA

By John Schwartz
Washington Post Staff Writer

Olestra, a fat substitute developed by Procter & Gamble that promises guilt-free

age. (The more solid, or "stiffer," formulations reduce the incidence of this side effect.)

"In our deliberations we have covered the alimentary canal from the beginning to the

THURSDAY, JULY 25, 1996 / PAGE A1

The Washington Times

Who is trying to kill olestra? And why?

By Henry I. Miller

Government agencies ranging from the Federal Aviation Administration to the Food and Drug Administration (FDA) often seek the advice of independent advisers to critique and improve their deci-

delay). Olestra is a potential boon to public health in the United States, where one person in three is obese, diets are dominated by fat, and most people die from fat-related diseases. Since the FDA's approval, CSJ abandoned objectivity and common sense in an all-out war on olestra. Its executive

"to be more direct by removing weasel words" —qualifiers such as "suggests" — and "maybe." What Mr. Jacobson derides as a "weasel word" was in fact...

JONATHAN YARDLEY

Olestra: Snacking on Snake Oil

Speaking as we were the other day of the federal government's loony efforts to steer Americans toward what it regards as proper eating habits, what are we to make of its latest initiative in that regard? Did you read last week's news about Olestra? Was that or was that not

into the sack with the very forces it's been fighting all along.

Olestra. Roll that one around on your tongue awhile. It sounds less like a food substance than a subcompact automobile of Asian manufacture: "The 1996 Banzai Olestra. Never buy fuel again—it makes its own gas." But as the

having been chosen by the Higher Powers for a special place in the sun but also to our enthusiasm for the most bizarre eating habits on the planet. We worship the youthful and the thin—to wit, see last week's "Swimsuit Issue" of Sports Illustrated—but we routinely

Anatomy of a Food Fight: The Olestra Debate

Fat-free feud: Let the consumer decide

Efforts to ban Olestra. A dieter, I can't say its side effects outweigh its benefits.

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Commentary
By Norman Ornstein

been government at its best, helping the market work by requiring businesses to provide important and relevant information to consumers, who can then make their own choices.

Companies were dragged, kicking and screaming, to the labeling table but have managed

consumers but also enhance the market for truth in labeling and for healthier foods in the marketplace.

But now the center and its hyperactive director, Michael Jacobson, have embarked on a relentless campaign to ban a new product, Olestra, which promises to provide low-fat versions of snack foods like potato chips that sacrifice none of the flavor or feel of the traditional high-fat varieties.

Jacobson failed in his effort to intimidate the Food and Drug Administration into blocking Olestra's limited approval. His next move was to

when I went to my new diet, but I cut back sharply and turned to the new low-fat variety. The Olestra-based chips have fewer calories and even lower fat content than the low-fat ones now on the market. I have been looking forward to having them available for an occasional indulgence.

Does it bother me that they might cause cramping or diarrhea? You bet it does. It also bothers me that beans can cause gas and that hot peppers and Tabasco sauce can give me heartburn. But as an educated consumer, I know the risks going in. I'll try the Ole-

vegetables and fruits.

No question, for many consumers having lower-fat foods has not meant lower-fat diets — they get lulled into eating too much. But that is their right and responsibility. For others, having such products truly does let us have our cake and eat it too, eating well and eating good at the same time.

Watchdog over business practices, protector of truthfulness in the marketplace, educator of consumers — these are useful, helpful and necessary roles in a modern market economy, roles that can and should be played by federal agencies like the FDA and the

Olestra not safe alternative to fat in food, watchdog says

By Karen Riley
THE WASHINGTON TIMES

A long-awaited fat substitute called olestra is unsafe for use in potato chips because it robs the body of important

not be asking FDA for approval. Period," said Gordon Brunner, P&G's senior vice president for research and development.

An FDA advisory panel next month is scheduled to decide whether to rec-

et part, focusing on reducing both fat and calories, was made in-



Editorials

Health-nut nannies are clearly indigestible

2 local TV stations say no to anti-olestra advertisements

KGAN-TV among those
set to air 30-second spot

By Adam Lowenstein

Gazette staff writer

The battle over olestra, America's controversial new fat substitute, has leaped to the airwaves.

time to oppose that simply because they have a private gripe," Waterbury said.

"The guys at CSPI don't want the marketplace to work for this, they want their own agenda. That's fine, but not on a paid basis. We cover it on a news basis. Those are two distinct things."

Waterbury said CSPI wanted \$12,000 worth of air time, which could mean as many as 100

Olestra maker pleased so far

Critic of substitute
calls report a joke

By The Associated Press
and Leader-Telegram staff

Consumer complaints about
olestra in snack foods that are being

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NO FAT
NO COMPROMISES



BRAND FAT REPLACEMENT

By MARIAN BURROS
RAPIDS, Iowa, May 17 —

William Raspberry

Can We Have Our Fries And Eat Them Too?

I'm firing my financial adviser. When he should have been telling me to sell the house and bet the whole bundle on Bill Gates, he was recommending municipals. I forgave him for that. I listened when he got skittish over the New Coke fiasco and recommended utilities and other low-risk investments ("At your age, you ought to be playing it pretty safe," he said). I forgave him for that too, though it is clear now that if I had cashed out my pension and put it all in Coca Cola I wouldn't still be typing for a living.

I made myself see his point when he argued that no one could have predicted that Coca Cola would rebound like John Goodman on a bungee cord, or that Microsoft was about to inherit the earth.

But what possible explanation could he have for not telling me—ordering me—to dump Walmart and Netscape and lay it all on Procter and Gamble?

quences of doing what we'll always choose the

And here's the corollary that actually doing what you go to get very rich.

It's the corollary that a Jug." Sipping that vi

"This new world will allow the government to discipline the crunchy, salty, greasy things ..."

THE NEW YORK TIMES 5/20/96

Question at Olestra's Debut: Is the 'Fake Fat' Truly Safe?

Indeed, it is this warning that stops Mrs. Mazzocca, her husband and her grown children from buying and consuming even more of the chips. "We've had no problem with them."

It took Procter & Gamble a quarter of a century and between \$1 million and \$300 million to win approval for olestra, a synthetic pound of sugar and vegetable passes through the body

Fat-Free Fantasy

IT'S BEEN A long time since a decision on food additives has gotten as much attention as the struggle over whether the Food and Drug Administration should approve Olestra, the fat-free fat substitute, as an additive to "savory snacks" such as potato chips. On Wednesday the agency finally granted its approval, but with

Procter & Gamble, the firm that wants to add back the leached

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WASHINGTON POST

Fat Chance

Will the Wizards of the FDA Lighten Up on Olestra?

By Jodie T. Allen

I HAVE this friend who's invented a terrific product. It's something you can eat—though you probably wouldn't want to eat it all by itself, but when you fry it in a pan with something like potatoes, or mix it up with other things and bake it, or even freeze it, it tastes terrific. Sort of mellow and round and smooth and creamy. Kinda rolls right off your tongue.

My friend thinks there would be a huge market for this stuff, but he's got one worry: the Food and Drug Administration. He's afraid that the meal police will look askance at some of the side effects that people can experience if they eat too much of his miracle menu. Turns out that gorging yourself on his product can cause your waist to swell, your thigh to be



Colman McCarthy

Living in a Fake-Fat World

Sorry: As enhanced as civilization may be by the FDA's approval of olestra—Procter & Gamble's fake fat additive—it isn't enough. Shelves remain stacked with high-fat Snickers, Ben & Jerry's, butter cookies, pizzas, poundcakes and other yummys that keep obesity rates rising, arteries clogged and bypass surgeons wealthy.

Why causes rhea, fe problem small by

The Fat File on Olestra

Apparently working from little more than a Procter & Gamble press kit and a few news clips, Jodie Allen ["Fat Chance," Outlook, Jan. 14] ridiculed the Food and Drug Administration (FDA), the Center for Science in the Public Interest (CSP) and unnamed "nutri-biddies"

Beyond “Toxicity” Studies

- For some food ingredients / additives, including olestra, the traditional portfolio of “toxicity” studies is of limited value in defining the entire safety picture because it does not produce a *comprehensive* view of additive safety under conditions of use.
- When that is the case, then other information must be sought and evaluated:



Beyond “Toxicity” Studies

- For olestra there was *not* an “ADI,” as such...

But...

- There was the likelihood of be significant “nutritional effects”
- As well as significant “physiological effects”



Beyond “Toxicity” Studies

In fact....

- Clinical data may become as important as “toxicological” data
- Chemical Identity / SAR may be of value
- “ADME” studies may be more important
- Human “Tolerance” studies can play a role
- Clinical studies of various types may be needed
- Post-market monitoring (both passive and active surveillance) may be justified as well



Summary of Olestra Data Review

- So, let's review olestra's overall data picture:
 - Chemical identity and probable consumption
 - A portfolio of “traditional” toxicity studies in a range of species
 - Nutritional Impact Studies (swine and humans)
 - GI effects, physiological responses from clinical studies
 - FDA's Decision Process



Summary of Olestra Data Review

- Identity and Use
 - Manufacturing Process
 - Constituents
 - Specifications
 - Stability
 - Estimated Daily Intake; “probable consumption”



Summary of Olestra Data Review

Toxicity Testing Data

- Toxicity Data
 - ADME (rat, guinea pig, mini-pig)
 - Teratology studies
 - Sub-Chronic Feeding Studies (rats, 90 d)
 - Chronic / Carcinogenicity Feeding Studies in rats and mice; dog feeding studies

No adverse effects seen upon which to determine an ADI in the traditional sense.



Summary of Olestra Data Review

Drug Interference Data

- Effect of Olestra on Absorption of Drugs (?)
 - Selected Lipophilic Drugs
 - Range of lipophilicity from aspirin to ethinyl estradiol
 - Effect of olestra on drug bioavailability
 - Effect on systemic levels of steroidal hormones in women taking oral contraceptives



Summary of Olestra Data Review

Nutritional Studies

- Nutritional Studies (in both animals / humans)
 - Hypothesis; olestra interferes with the absorption of fat-soluble nutrients when those nutrients partition into olestra in the GI tract.
 - Both fat-soluble and water soluble nutrients studied
 - Folate, Vitamin B₁₂, calcium, zinc, and iron
 - Vitamins A, D, E, K
 - Studies (DR, VR) conducted in both humans and pigs



Studies to Assess Nutritional Effects of Olestra Consumption

Human Studies

- 8-Wk clinical DR
- 8-Wk clinical VR
- 6-Wk V D/K status
- 16-Wk V E status
- 14-d V A/fat absorption

Pig Studies

- 26-Wk DR & VR
- 39-Wk VR
- 12-Wk DR
- 12-Wk VR
- 4-Wk “dietary context”



Summary of Olestra Data Review

Human Clinical Studies

- Primary reliance on two 8-week clinical studies on *dose-response* and *vitamin restoration*:
 - Complete control of nutrient intake
 - Double-blind placebo-controlled
 - Olestra added to food vs. triglyceride; 0, 8, 20, 32 g/d
 - Diets 15% cal from protein; 55% from carbs; and still 30% from triglycerides
 - GI symptoms recorded if experienced



Summary of Olestra Data Review

8-Wk Clinical Dose-Response Study

- Serum levels of A,D,E,K, folate, B₁₂, and Zinc measured
- Decreases in serum levels of fat sol. Vitamins seen (serum retinol only for A)



Summary of Olestra Data Review

8-Wk Clin. Vitamin Restoration Study

- Determined levels of vitamins A,D,E, and K to add back to food to compensate for any losses due to olestra



Summary of Olestra Data Review Studies in Swine

- Five nutritional studies of varying lengths (12, 12, 26, 39, and 4 Wks).
- Helped determine DR; and Vitamin restoration levels appropriate to avoid any lowering of serum levels (or liver stores of Vitamin A)



Nutrient Status Measurements in 12-Week Pig DR Study

Nutrient

Measurements

Vitamin A.....	Liver & Serum conc.
Vitamin E.....	Liver, Serum, Adipose tissue conc.
Vitamin D.....	Serum Conc of different forms
Vitamin K.....	Prothrombin time
Folate.....	Plasma concentration
Vitamin B ₁₂	Liver concentration
Calcium.....	Bone, serum Ca, bone ash conc.
Phosphorous....	Bone and serum concentration
Iron.....	Liver iron and serum concs.
Zinc.....	Liver, bone, serum concentrations



Carotenoids

- Serum levels *are* affected
- Much discussion from all sides (the petitioner, many comments, special FDA consultants, food advisory committee, NCI, and NEI experts)
- FDA concluded that effects of olestra on absorption of lipophilic carotenoids, “reasonably certain to be insignificant from a public health standpoint.”



GI Effects

Issues that were of potential concern to FDA:

1. Potential for loose stools or diarrhea to result in electrolyte and fluid loss
2. Interference with normal daily life
3. Special concerns for subpopulations (children, GI compromised, the elderly)
4. Microfloral changes in the gut



GI Effects

- After review by FDA of submitted studies, and the FDA Food Advisory Committee, including gastroenterologists, etc., FDA concluded:
 - Reasonable certainty of no harm w.r.t. potential for olestra to cause GI effects
 - Could cause loose stools, but not adverse because do not threaten health.



Some Conclusions from the Olestra Data Review

- Conclusions from Nutritional Studies:
 - Olestra affects the status of fat sol. vitamins
 - Potential losses can be compensated for
 - Compensation levels determined quantitatively
- Conclusions on GI Effects:
 - There are effects, but they do not adversely affect health



FDA's Safety Review: Summary

- Standard regimen of toxicological studies
- Supplemented by a range of special studies (nutritional impact studies, e.g., in swine and other species, including human clinical studies) to elicit information about the *nutritional* characteristics and impact of the material on those who ingest it.
- Consultations 1/1 with and a roster of noted experts on animal and human nutrition, physiology, medicine, etc., B. Schneeman, then of U. Cal. Davis, as primary consultant.



FDA's Safety Review: Summary

- Separate consults w/ NCI (Dr. Greenwald) re: carotenoids, and NEI (Dr. Kupfer) re: no macular degeneration potential
- Assembling of FDA's Food Advisory Committee (4 days in November 1995)
- Special Labeling required (to preclude product misbranding in the marketplace; interim requirement)
- Use of passive and active post market surveillance
- Final regulation published FR January 30, 1996
- Second FAC June 1998
- Labeling requirement rescinded, FR August 2003



Labeling of Foods Containing Olestra

- Olestra-containing foods were originally required to carry the following label statement:

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



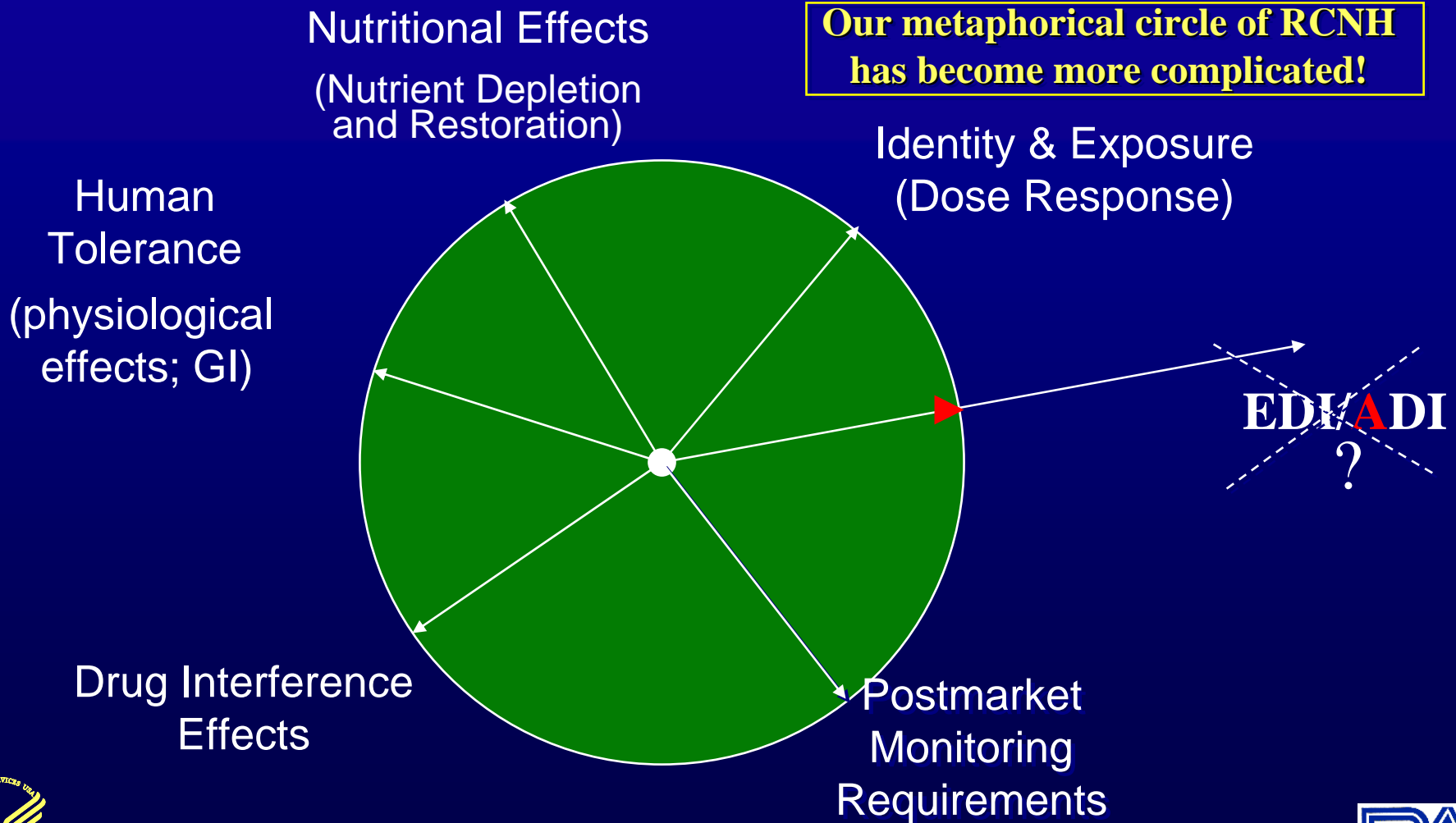
Overall FDA Conclusions

- Olestra is not toxic, carcinogenic, genotoxic, or teratogenic.
- It is essentially not absorbed or metabolized.
- It has an effect on the absorption of vitamins A, D, E, and K.
- It is possible to supplement foods containing olestra with all four vitamins so as to compensate for amounts not absorbed from the diet due to the action of olestra.
- No harmful effects on water soluble vitamins / minerals, including vitamin D mediated calcium uptake.
- Carotenoids need not be compensated for.
- GI effects seen do not represent significant adverse health consequences.
- FDA did initially require a label statement, active and passive postmarket monitoring, and a follow-up Food Advisory Committee within 30 months of approval.
- Other, later studies (home use study; n=3000) show little problem



A More Complex “Circle” of Reasonable Certainty of No Harm

Our metaphorical circle of RCNH has become more complicated!



Beyond the “Tox” Framework:

(other areas where ADI concept alone may not be feasible)

- Macro Ingredient Substitutes
 - lipids
 - carbohydrates
 - proteins
- Enzymes used in food processing
- Fiber sources
- Complex mixtures
- Irradiated food
- Herbals and other “bioactive” ingredients in conventional foods and supplements



**“Generally Recognized as Safe”
(GRAS)
Food Ingredients**

FFDCA Definition of “food additive”

“Component” part
of the definition

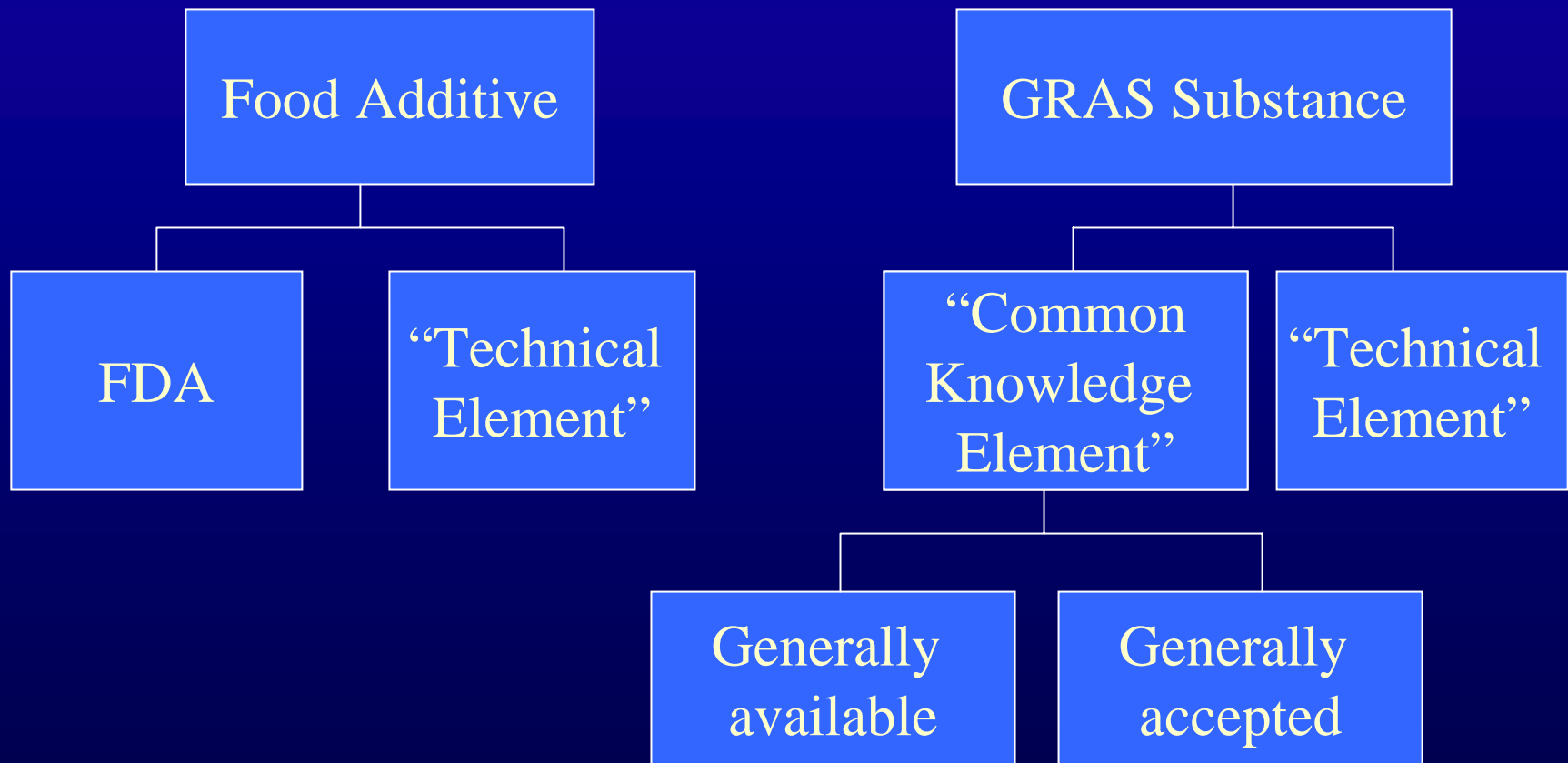
201(s): “...any substance, the intended use of which results or may be expected to result, directly or indirectly, in its becoming a **component** or otherwise affecting the characteristics of any food...

The “GRAS Exemption”

if such substance is not **generally recognized**, among experts qualified by scientific training and experience...**to be safe** under the conditions of its intended use”



GRAS Criteria: Comparing a GRAS Substance to a Food Additive



GRAS Notification Procedure

based on the April 1997 FR Proposal

- Voluntary
- Notifier informs FDA of notifier's view that a use of a substance is GRAS
- FDA responds by letter



3 Types of Response to a GRAS Notice

- FDA has “no questions”
- Notice “does not provide a basis” for a GRAS determination
- At notifier’s request, FDA ceased to evaluate the notice
- Letters available on the Internet at <http://www.cfsan.fda.gov/~rdb/opa-gras.html>



Other Examples of “Bioactive” Food Ingredients?

- Other macroingredient substitutes (for lipids, carbohydrates, proteins)
- Phytosterol Esters and Vegetable Oil Sterol Esters in spreads (e.g., Benecol™ and Take Control™)
- Range of materials in GRAS Notices (enzymes, fiber sources, herbs in conventional food)
- Infant Formula Ingredients (e.g., novel sources of DHA and ARA (LCPUFAs) as IF ingredients)



Other Examples of “Bioactive” Food Ingredients in GRAS Notices

Examples where FDA Had “No Questions”:

- Vegetable oil sterol esters (Take Control™)
- Phytosteranol esters (Benecol™)
- Lactoferrin (GRN 77)
- Fructooligosaccharides (GRN 44)
- Small planktivorous pelagic body fish oil (GRN 102)
- Fish oil concentrate (GRN 105)
- Tuna oil (GRN 109)
- Diacylglycerol oil (GRNs 56 and 115)
- Inulin (GRN 118)



Other Examples of “Bioactive” Food Ingredients in GRAS Notices

Examples where FDA “Questions” the
notifier’s GRAS notice:

- 6 Chinese Herbs (GRN 13)
- Garcinia cola (GRN 25)
- Crospovidone-cranberry extract (GRN 30)
- Hempseed oil (GRN 35)
- Milk thistle extract (GRN 66)
- Grape Seed Extract and Grape Skin Extract
(GRN 93)



Nutritional Risk Assessment?

- For Nutrients added to food, or possibly
- For other Bioactive ingredients in food
- When we may expect nutrition related effects aside from any potential toxicological responses



Nutritional Risk Assessment

Requires:

- Expanded understanding of the exposure scenario of the population and/or subgroups to substances of nutritional interest or bioactive capacity in foods.
- The context of such exposure scenarios in comparison to all other substances important to the diet.
- An understanding of the relevant dose/response relationships, both beneficial and detrimental for substances in the diet. (For nutrients or other bioactive ingredients, this may include knowledge of both the benefits of exposure to adequate levels, as well as risks associated with ingesting too much, and the relevant biochemical mechanisms of both.)



Nutritional Risk Assessment

- An understanding of the inherent and methodological errors and uncertainties associated with those dose-response relationships.
- Understanding of the interactions among nutrients or other bioactive ingredients, and other components of the diet that influence nutrient bioavailability or additive safety
- Impact of novel foods and food components on overall dietary patterns
- Physiological responses to the presence of the substance in the diet, such as gastrointestinal intolerance, etc.

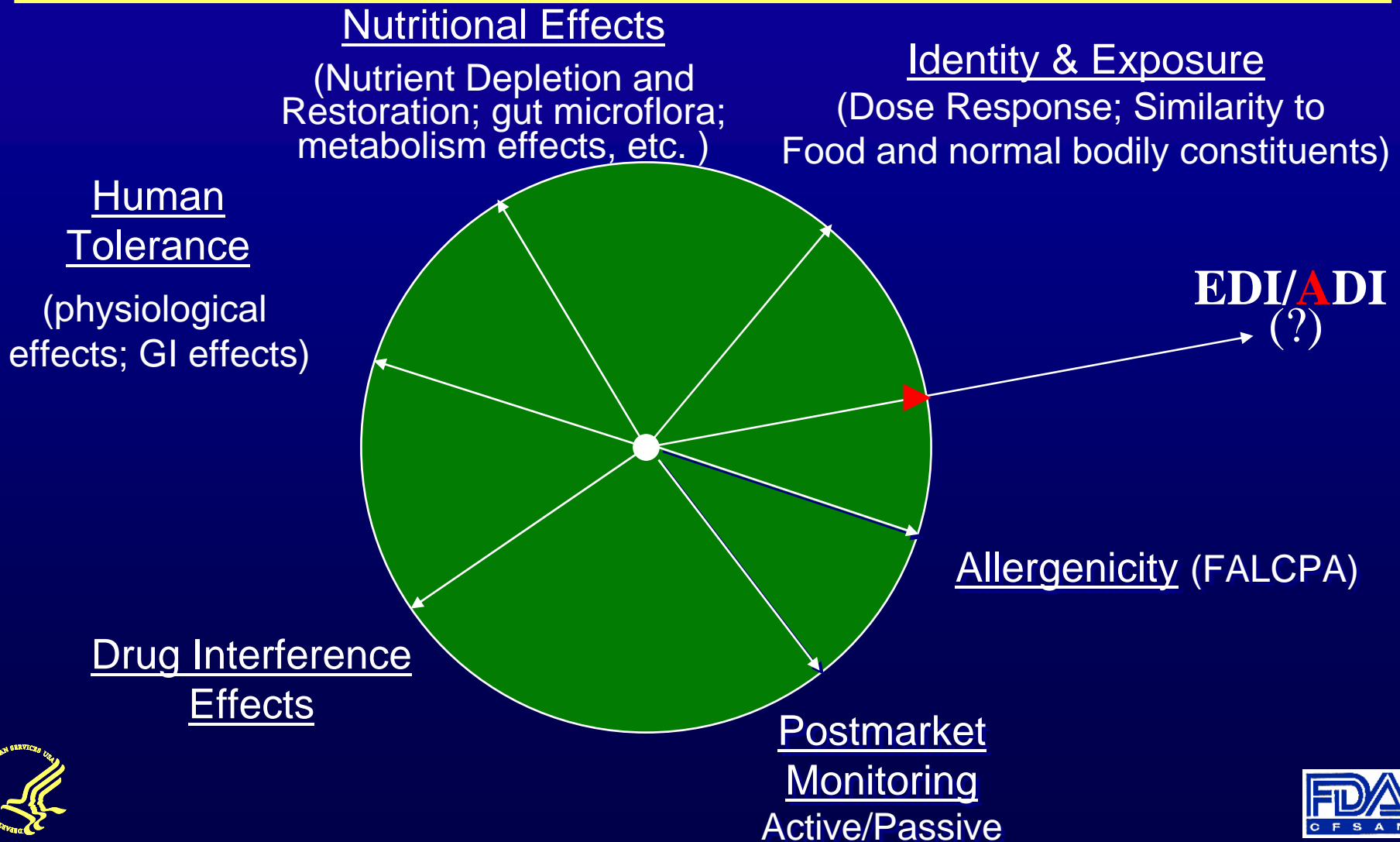


Nutritional Risk Assessment

- Data from animal models (both dose response and mechanistic information) as well as human clinical data
- Need for application of various types of quantitative and statistical modeling techniques, including Monte Carlo models for premarket and active and passive postmarket monitoring and analyses
- Other sources of relevant information on safety from the new fields of genomics, metabolomics, proteomics, and now, “nutrigenomics,” etc.



A Still More Complex “Circle” of Reasonable Certainty of No Harm



Relative Food-Related Concerns (A Popular View)

- Added Food Chemicals
- Environmental Contaminants in Food
- Food Hazards of Natural Origin
- Microbial Contamination of Food
- Nutritional Hazards



Relative Food-Related Concerns

(A Possibly More Accurate View)

- Nutritional Hazards
- Microbial Contamination of Food
- Food Hazards of Natural Origin
- Environmental Contaminants in Food
- Added Food Chemicals



Nutritional Safety Assessment ties the top and bottom together!

- ▶ ■ **Nutritional Hazards**
- Microbial Contamination of Food
- Food Hazards of Natural Origin
- Environmental Contaminants in Food
- ▶ ■ **Added Food Chemicals**



The End!

Thank You!

