Genetically Modified Organisms in Food

Food Toxicology

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Learning Objectives

- Understand the background and history of the GMO in food debate.
- Explore the range of crops and foods that currently contain GMOs.
- Survey the current trends in GMO foods and their future implications.
- Understand the US advances and regulatory controls for GMO foods.
- Review early genetic engineering of GRAS ingredients in foods.
- Review recent incidents, US and international policies.

Advances in Biotechnology

- In the past several decades, new advances in biotechnology have yielded the tools and techniques to change the fundamental "molecules of life".
- This allows for "engineering" desired genetic traits in plants, animals and microbes.
- New concerns about "bioethics" are coupled with:
  - Public health risks vs. benefits
  - Environmental risks vs. benefits

Products of Biotechnology

Genetically Modified Organisms

- GMOs are organisms such as plants, animals and micro-organisms (bacteria, viruses, etc.), the genetic characteristics of which have been modified artificially in order to give them a new property.
  - Plant resistance to disease or insects
  - Improvement of a food's quality or nutritional value
  - Increased crop productivity
  - Plant tolerance of a herbicide
  - Functional food enhancement (vitamins, edible vaccines, etc)

The Molecules of Life

Bacteria	% of total weight	Types of molecules
Water	70	1
Proteins	15	3000
Nucleic Acids		
DNA	1	1
RNA	6	>3000
Polysaccharides	3	5
Lipids	2	20
Building block molecules	2	500
Inorganic ions	1	20

Bioethics of Biotechnology

- "Playing God"
  - Should we be doing this just because we can?
  - Are we opening a "Pandora's box" that we will never be able to close?
- Compassion and empathy for the "engineered" animals (or humans?)
- Balancing risks: Are the potential gains *(medicine, food supply, control of biology…)* worth the loss? *(loss of innocence, loss of biodiversity, potential for cataclysm…)*
- Absolutes vs. "Shades of Gray"
  - Slippery slopes
- Man's inhumanity to man:
  - "Every new technology necessitates a new war…"

The Legal Dilemma

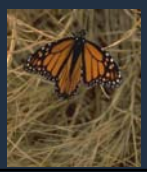
- Approved plants have been patented
- Patents are for products which are:
  - New
  - Novel
  - Non-obvious
  - Substantially different
    not "substantially equivalent"

Biotechnology: A Troubling Start

- Initial high profile products in agriculture targeted benefits for farmers (pest control) not consumers (food quality or availability).
- Advances in pharmaceutical products not "seen" at the general consumer level (e.g. insulin).
- "Trust us" dictum of research and regulatory authorities violated.
  - "Terminator" gene developed to limit 2nd generation harvest for seed; corporate control of food scenarios
  - "Star Link" Bt corn for feed found in human food products

Hazard Data Start Appearing

- A laboratory study by Cornell University entomologists indicated that Bt-corn pollen can kill 44% of Monarch butterflies.
- British scientist reports that GM potatoes stunt rats growth and damage their immune system.



Good Will, Public Relations Efforts

Monsanto offers free licenses to make 'golden rice'

The rice is enriched with vitamin A to help malnourished children.

Monsanto's methods ... 'golden rice' could be a life-saver

AP, Aug 7 2000

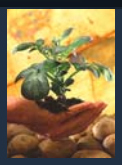
"By manipulating rice genomes, Monsanto scientists moved the production of beta-carotene from the rice husk...to the grain itself, the staple food of hundreds of millions of people."

Scripps-Howard, Aug 8 2000

Major GMO Concerns

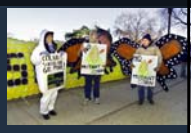
- Food safety
- Control of food supply
- Biodiversity loss via super-monoculture
- Biodiversity risk via interbreeding
- Non-target impacts (beneficial insects,…)
- Nightmare scenarios
  - Gene hopping, transgenic "monsters"
- Fear of the unknown
- It's not a 'natural' process

Major GMO Promises



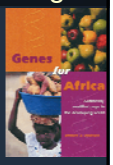
- More abundant and healthy food
- Less dependence on pesticides
- Decreased production risks for farmers: frost damage, pest and disease damage, higher yields
- More agricultural yield per land mass to feed a hungry, growing world population; therefore less loss of critical habitat
  - Rainforest and marginally arable land
- More precise than traditional breeding techniques
- Efficient production of life-saving medicines

Major Areas of GMO Debate



- Food safety testing
- Substantial equilivalence
- Co-existence with traditional crops
- Potential for environmental impact
- Economic impacts
- Scientific information and mis-information
- Labeling
- Traceability
- International and trans-boundary trade
- Patenting

GMO Risk and Risk Perception Challenges



- Acceptance and control of risk
  - Risks I willfully take (smoking, extreme sports, junk food, riding a motorcycle…)
  - Risks that I have less, limited or no control over (food safety, water quality, air quality…)
    - Often more difficult to rationalize
    - Especially troublesome when someone is viewed to be "profiting" from MY risk
  - Influence of poverty and life threats such as disease and war on relative risks
    - 1st world vs. 3rd world dilemma

Risk Perception: Carcinogens in Coffee

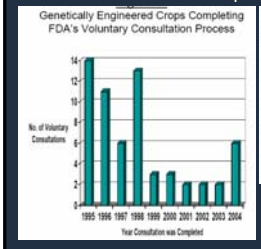
- Acetaldehyde
- Benzaldehyde
- Benzene
- Benzofuran
- Benzo[a]pyrene
- Caffeic acid
- Catechol
- 1,2,5,6 Di-benzanthracene
- Ethanol
- Ethylbenzene
- Formaldehyde
- Furan
- Furfural
- Hydrogen peroxide
- Hydroquinone
- Limonine
- Styrene
- Toluene
- Xylene

Current US Crops

- Today, most soy, cotton and canola is GMO, as is almost half of the field corn (used primarily for feed and grain)
  - Glyphosate herbicide resistance and Bt toxin
    - 10,000 acres of insect-resistant sweet corn (sold as a vegetable),
    - 1,800 of virus-resistant summer squash and
    - 1,100 of virus-resistant papaya.
- GMO wheat, tomatoes, potatoes abandoned commercially
- Possibilities in the next 5 to 10 years include herbicide-resistant sunflowers, soybean and canola for the production of healthier oil; and herbicide-resistant alfalfa and sugar beets.

Current US Trends

GMO Crops Withering? (2/2/2005)




Biotechnology appears to be withering as a food source

USA TODAY

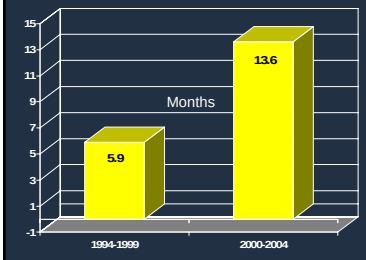
By Elizabeth Weise, USA TODAY

The promise of biotech crops — foods genetically engineered to resist pests and weeds or even to produce drugs for humans — may be going to seed.

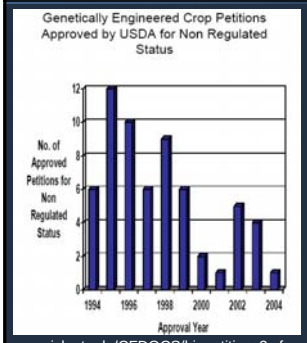
After years of significant growth, the number of biotech crops in the regulatory pipeline has plummeted, says a report out today from the Center for Science in the Public Interest, a group that supports a cautious approach to biotechnology.

www.cfsan.fda.gov/~lrd/biocon.html

US Regulatory Review Time has Doubled



Approved GMO Crops



www.isb.vt.edu/CFDOCS/biopetitions3.cfm

US Implications

- China and India aggressively pursuing Biotech and product development
- Will GMO development continue in less regulated nations?
- Implications for global environment and global food system
- Implications for US Biotechnology future
- Food security

US Advances and Controls

- Early view (1975-1985) was a healthy caution for recombinant DNA research.
  - Research protocols and reviews developed to protect against inadvertent release.
- The public debate influenced policy and enhanced regulatory concerns.
- Most concerns for end products of biotechnology already covered in US food safety and environmental laws.
  - New definitions and new regulatory approaches required.
- Can you patent a new life form?

US Food Drug and Cosmetic Act

Primary Legislative Authority

- FDCA 402(a)(1) - a food is adulterated if it contains any poisonous or deleterious substance which may render the food injurious to health
- Relates to unapproved substances added by man intentionally or non-intentionally
  - Can apply to products of conventional breeding; e.g. solanine toxin increases in new breeds of potatoes

Poisonous or Deleterious Substance

- Food Drug and Cosmetic Act 402(a)(1)
  - Pathogens such as E. coli O157:H7
  - Chemical example: lead, Hg, PCBs, dioxin, banned pesticides
  - Radionuclides
- Tolerance or action level based on metabolic profile, level of detection, risk assessment

Food Additives Amendment 1958

- Food Additives Amendment 1958 402(a)(2): A food is adulterated if it contains any 'added' poisonous or deleterious substance except one that is either:
  - Food Additive (Sec 409)
  - Generally Recognized As Safe 201(s) (GRAS)
  - Color Additive (Sec 706)
  - Registered Pesticide (Sec 408)
    - FQPA clarified as not an additive
  - Note that 'added' means intentional addition so would apply to GMO unless exempt it as additive or GRAS
    - Note: what if also a pesticide like Bt corn ?

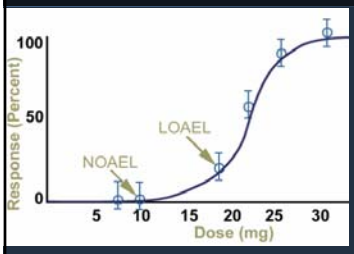
Generally Recognized as Safe: GRAS

- FDCA Sec 201 (s)
- Food additive or such substance that is generally recognized as safe (GRAS) among experts qualified by scientific training and experience to evaluate safety
  - Through adequately shown scientific procedures or in the case of a substance used in food prior to Jan.1 1958 through either scientific procedures or common use in food to be safe under the conditions of its intended use.

Additive Testing Under FDCA

- Additive testing requirements
  - Responsibility of company to collect data and submit findings to FDA
  - FDA Red Book
  - LD_{50} acute toxicity – often not required
  - Sub-acute toxicity - 90 days
  - Life-time chronic feeding trials
  - Safety (NRI) based on 1/100th the level of NOAEL
    - NRI = negligible risk intake
  - Also applied to new GRAS substances

No Observed Adverse Effect Level



Decision Process

- EDI (estimated daily intake) < NRI (negligible risk intake)
- Assessment
- Natural components
- Unintentional contaminants?
- Intentionally added constituents – ADI (acceptable daily intake)
- Added 100x factor to estimate NRI
- GRAS related?

Plant Breeding Example

- UM, UND and USDA potato research lab development of improved chipping variety of potato (Lenape)
- Submitted to US Food and Drug Administration (FDA) for approval under FDCA but found increased solanine level so withdrew from introduction
- Breeding successes in history based on nutrient level and natural toxicant levels
  - Spiher A.T. Hort Sci. 10:241-42 (1975) *The Growing of GRAS*

The Regulatory Issues

- What category of food ingredients do GMO-based varieties fit into ?
- What safety criteria are needed in testing, i.e. what are the protocols ?
- What does substantial equivalence mean?
- What role does the "precautionary principal" play?

FDA Policy

57 FR 22983-23005 May 29, 1992

Labuza

- The safety of foods derived from new plant varieties
- Genetic transferred material may be subject to food additive or GRAS process
  - DNA itself not a concern
- Toxicant trigger level:
  - Increase of >10%
- Nutrient trigger level
  - Decrease of >10%
- Is there a potential allergen?
- Current working policy
  - Over 50 products have been evaluated (US District Court upholds, Sept 2000)

Basis of FDA Policy

- Animal feeding studies problematic
  - Animal tests not sensitive; cannot supplement at high enough level
- Need multidisciplinary assessment process based on:
  - Genomic traits
  - Agronomic and quality analysis
  - Allergenicity potential
  - Analysis of toxicants and nutrients

Additive or GRAS

- Basis of policy 402 (a)(2) of FDCA
- GMO food crop will need approval as food additive if introduced protein is different than normal, otherwise GRAS

GMO: Food Safety Threats

- Crossing transgenic species
  - Brazil nut with soybeans for methionine
  - Fish antifreeze protein in potatoes
- Opens a different set of concerns than just "adjusting" the biochemical machinery in an organism

Allergenicity Flags

- Concern for transgenic introduction of allergenic protein that is
  - 10 to 70 KDa
  - Resistant to digestion
  - Stable to heat processing
  - Similar to amino acid homology in allergen binding sites

Office of Science and Technology Policy

1994

- Use risk-based scientific approach rather than crop development process used.
  - i.e. Don't focus on biotech process rather use the standard safety evaluation process.

Early Genetic Engineering of GRAS Ingredients in Foods

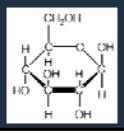
- Chymosin recombinant technology
  - Inserted gene for calf rennet into E. coli
  - >80% of world cheese making

Early Genetic Engineering of GRAS Ingredients in Foods

- Chymosin
  - Deemed to be GRAS 21CFR 184.1685(a)(2)
    - 57 FR 10932-6 23/3/90 E coli
    - 57 FR 6476-9:1992 yeast
    - 58 FR 27197-203: 1993 mold
  - Same protein structure
  - Most impurities removed
  - Organism destroyed in processing
  - Anti-biotic resistant marker destroyed

Early Genetic Engineering of GRAS Ingredients in Foods

- Insoluble glucose isomerase; used to make fructose from glucose
- GRAS 21 CFR 184.1372 (Aug 23, 1996) recombinant enzymes from bacteria and molds
- Bound on reactor bead surface so does not go into food - processing aid



The First Controversy: Monsanto

- Milk - Recombinant BST or rBGH
  - Milk production hormone; growth hormone
- Neither GRAS nor Food Additive
- It is an approved New Animal Drug

Flavor-Savr Tomato

- Calgene asks for food additive status for enzyme
  - FDA Docket # 90A-0416, 91A-0330
- FDA findings enzyme introduced well documented @ <0.16 ppm and
- Enzyme digested
  - 59 FR 26700-711 May 23, 1994
- Marker gene easily digested
- Nutrient level the same
- No change in toxic substances
  - Tomatine alkaloid
- No need for special labeling

Other Early FDA Approvals

- 1994 squash - disease resistant
- 1995 potato - insect resistant
- 1996 soybean - herbicide resistance
- 1997 corn - corn borer resistance

WHO-FAO

- 1993 - marker genes not a safety issue (< 1/250,000 of DNA consumed)
- Report 93.6 2000 - reconfirms prior statement "safety aspects of genetically modified food of plant origin"

Nature Biotechnology

Volume 18 Number 11 p 1119; 2000

- Safety and labeling standards for foods, food ingredients, and feeds should be applied regardless of the techniques used in their production and manufacture.
- Genetic engineering may be safer/more precise than conventional breeding
- Foods should continue to be assessed on the basis of substantial equivalence, with labeling required only for (GM) foods that differ significantly in composition or nutritional value from their conventional counterparts.

Substantial Equivalence Principles

- Term is not in any FDA document
  - Reduction by <10% in key nutrients
  - Increase by <10% in natural, non-added background toxicants
  - New proteins well-characterized and appear in other foods
  - Source of gene well characterized
  - Need for feeding trials questionable
  - Concern for allergenicity
    - From typical allergenic food or
    - properties flag as allergen

1987 National Academy of Sciences

- Introduction of recombinant DNA engineered organisms into the environment: Key issues
  - No evidence of unique hazards
  - Risks similar to introduction of unmodified organisms or those modified by other methods

The Farm to Market Transport Industry

- Farm truck
- Silo
- Train car
- Barge
- Boat
- Train car
- Truck

Large potential for contamination

GMO Analytical Challenges

- Problems in evaluating %GMO
- On farm, at commercial silo, at processor?
- Mixing in transport (bulk supplies…)
- Cost of test (small margin industry…)
- Time (perishable…)
- Sample size and reliability (statistical significance…)

Allergen Analysis Failures

- Problems
- Extraction
- Denaturation and false +/-
- Need for specific ELISA
  - Not available for most allergens

Identity Preservation Outrage

- The Adventis Bt Corn Incident (Starlink)
  - Contains Cry9C, an insecticidal protein (Bt toxin)

Starlink Corn

- Starlink corn with Cry9C based Bt toxin protein
- 63FR28258
  - Bacillus Thuringiensis Subspecies tolworthi Cry9C Protein and the Genetic Material Necessary for its Production in Corn; Exemption from the Requirement of a Tolerance May 22, 1998

EPA Allergenicity Evaluation

- Homology - EPA says no known homology of the 8 aminoacid sequence - but not all known
- Cry9c is resistant to digestion
- Cry9c is stable to thermal processing
- MW (68 kD) is in upper range for allergens
- Thus EPA warned in approval that may be linked to allergens
- Other EPA arguments to allow approval
- Abundance of protein low but patent argues high toxicity
- Low environmental exposure but what about corn dust?

Starlink Corn Problem

- Starlink corn produced by Adventis Corp (Research Triangle NC) with Cry9c Bt toxin protein Labuza
- Approval given by EPA in 1998 but restricted to animal feed as noted by potential for allergenic response in humans based on four criteria
- September 2000 Consumer group (FOE) analyzes taco shells and finds Cry9c Bt protein.
  - Sept 11, 2000 calls on EPA to remove
  - Taco Bell begins recall of tacos from supermarkets, as does Safeway for corn products made by Kraft

EPA announcement 10/10/00

- Adventis CropScience (NC) is financially responsible for the failure and must pay for it.
- Not the farmers fault.

Starlink Corn Problem

- Kellogg's shuts down corn flakes cereal plant (10/18/2000) as precaution against potential for allergenic response
- 10/19/00 Adventis says problem is farmers co-mingled corn into human food destined corn.
- Of 260 grain elevators, about 106 sent out to food processors which is 12% Starlink corn or 9 million bushels

Millers and Grocer Impact (Reuters)

10/10/00

- Kroger and Albertsons remove cereal and tacos.
- Mission Foods recalls all Tacos (largest US maker)
- Azteca Milling will take back all yellow 2 corn flour
- ConAgra stops operations at Kansas corn flour mill
  - Will not disclose customers
- Nov 3, FDA announces over 300 products with potential risk

Commentary on the Incident

- Ricki Hall Ark. Children's Hospital "Right now sensitivity to the protein is an unknown"
- FDA/USDA/EPA says little if any risk
- Les Crawford, Georgetown Univ. "It's not the human health risk that is concerning. It's that it got there in the first place."
- Cargill Chair W. Staley says although found in some silos that problem is under control. Will institute new tests. He notes that problem was irresponsible procedures by a few in the chain. "There is a process of protocols to be followed, unfortunately people didn't handle things correctly."

Science Testimony to EPA

- Statement to EPA regarding Starlink incident
  - Would need repeated long-term exposure to Starlink to develop allergy to it
  - Cry9C accounts for 0.013% of corn grain while most allergens at 1 to 40% in food
  - "this clearly would not produce protein levels of any health concern"

International – Cartegena Protocol (2000)

- Major issues
  - Adequacy of biosafety procedures
  - Conservation and biological diversity
  - Human health
  - Trans-boundary movement

2000 UN Secretariat of the Convention on Biological Diversity

International: Codex Alimentarius

- Codex Alimentarius: WHO/FAO Food Standards
  - Principles for the Risk Analysis of Foods Derived from Modern Biotechnology CAC/GL 44(2003)
  - Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants CAC/GL 45(2003)
  - Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms CAC/GL 46(2003)

The European Experience

A Harsh Decade for Agriculture

- UK Ministry of Agriculture said "trust us"
  - Consumer outrage as result of BSE incident ~ 80 dead
- 1999 Belgium Dioxin contamination
- EU concern over lack of data so invoke precaution "don't know enough, don't approve"

Major EU/International Issues

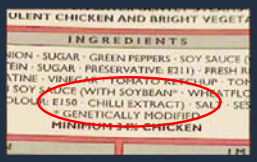
- Food safety (for GM crops and organically grown food), patents, labeling, regulations, and controls
- Co-existence of GM and conventional crops?
  - Freedom of choice.

European Union

- Directive 90/219/EC
- Directive 2001/18/EC
- Regulation (EC) 1829/2003
- Regulation (EC) No 1946/2003
- Regulation (EC) 1830/2003

Major EU Regulatory Themes

- Labeling
- Traceability
- >0.9% GMO in the food/feed product regulated
- Substantial equivalence
- Transboundary movement



EU and GMO

- Fears GMO crops will compromise local ecosystems and interfere with efforts to develop organic products and local varieties.
- Many member states have a temporary moratorium on the cultivation of GM crops, concentrating instead on "integrated and sustainable agricultural practices."

Current EU Status

- No GM products have been approved for importation into the EU since 1998.
- New stricter EU regulations on labeling and traceability of GM products took effect as of October 2003.