Why Genetically Engineered (GE) Foods should be Labeled: Inadequate Regulations, Unanswered Safety Questions

Michael Hansen, Ph.D.
Senior Scientist, Consumers Union
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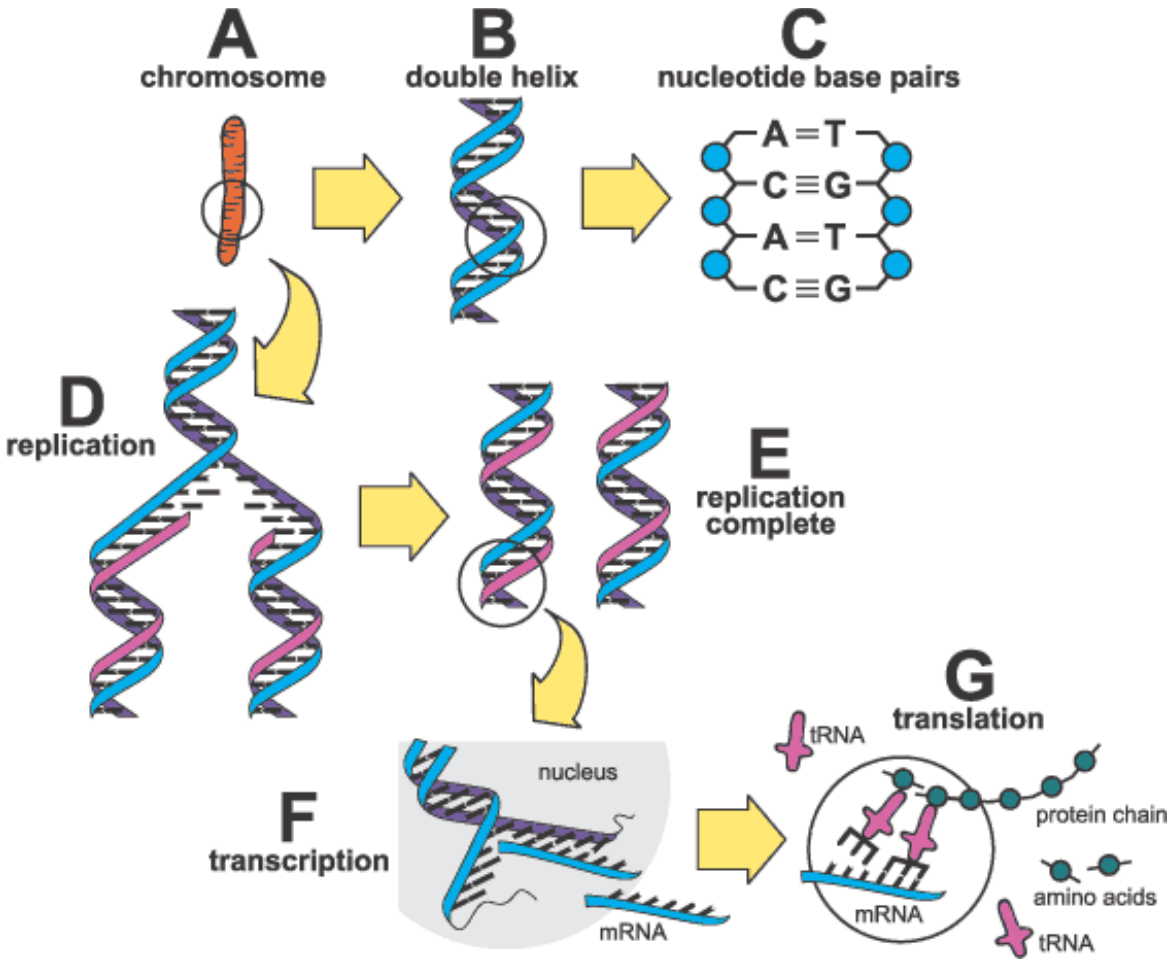
Outline

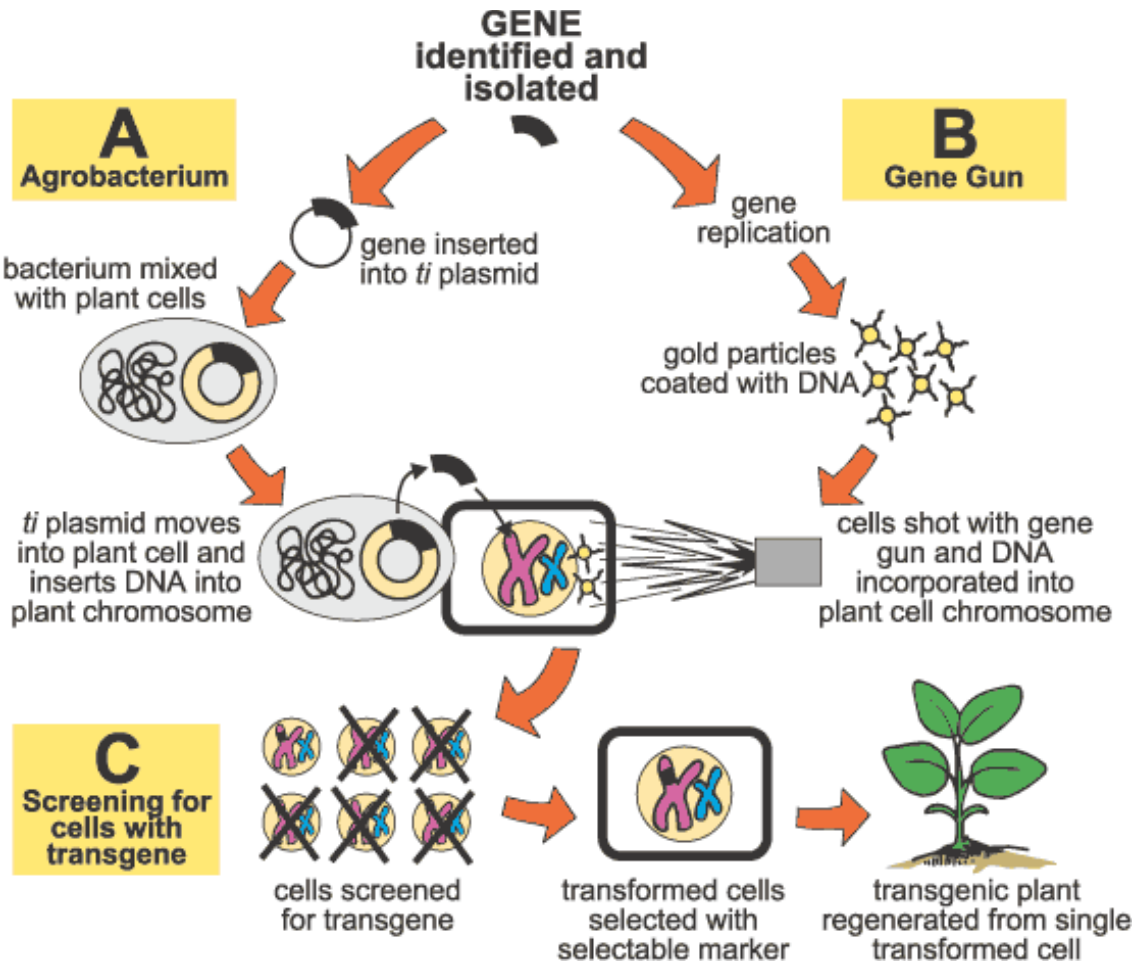
- Basics of Biotechnology
- FDA + global policy on GE, including labeling
- New science raises safety questions
- Professional conflicts of interest bias outcomes in favor of finding no health or safety issues
- Summary

- Biotechnology Basics

The basic structure and functions of genes and chromosomes



Plant transformation with *Agrobacterium* (Ti plasmid) and gene gun



FDA Policy on Genetically Engineered Plants 1992 Statement of Policy

- Introduced at press conference at an industry gathering on May 27, 1992 by then Vice-President Dan Quayle as a deregulatory initiative

- Based on notion “that the new techniques [e.g. genetic engineering] are extensions at the molecular level of traditional methods and will be used to achieve the same goals as traditional plant breeding” and “no basis for concluding that bioengineered foods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding.”(57 FR 22991, May 29, 1992)

FDA Policy on Genetically Engineered Plants 1992 Statement of Policy

- No requirement for human safety testing, only "voluntary safety consultations"; to date, some 99 voluntary safety consultations have been held

- "Ultimately, it is the food producer who is responsible for assuring safety" (57 FR 22991, May 29, 1992)

- "Monsanto should not have to vouchsafe the safety of biotech food … Our interest is in selling as much of it as possible. Assuring its safety is the FDA's job" Phil Angel, Director of Corporate Communications, Monsanto. *New York Times Magazine*, October 25, 1998.

Key phrases in US Food and Drug Administration safety consultation letters

- MON 810 (Bt corn), dated Sept. 26, 1996
- "Monsanto submitted a summary assessment of corn containing transformation event MON 810 on June 6, 1996"
- "Based on the safety and nutritional assessment you have conducted, it is our understanding that Monsanto has concluded that corn products derived from this new variety are not materially different in composition, safety, and other relevant parameters from corn currently on the market, and that the genetically modified corn does not raise issues that would require premarket review or approval by FDA."
  http://www.fda.gov/Food/FoodScienceResearch/Biotechnology/Submissions/ucm161107.htm

- A variation of these two sentences are found in all 97 safety consultation letters

- FDA does not require premarket safety assessment and does not state its own opinion about the safety of the GE crop

Martineau, B. 2001. First Fruit: the Creation of the Flavr Savr tomato and the Birth of Biotech Foods

- **“Rather than personal opinion, the scientific community should give the public facts, hard facts; the results of studies that indicate these foods are safe to eat . . . simply proclaiming ‘that these foods are safe and there is no scientific evidence to the contrary’ is not the same as saying ‘extensive tests have been conducted and here are the results.’ In fact, without further elaboration, ‘no scientific evidence to the contrary’ could be construed as ‘no scientific evidence, period.’ ”(Martineau, 2001: 232-233)**

FDA. 2001. Premarket Notice Concerning Bioengineered Foods. Federal Register January 18, 2001. Vol. 51(12): pp. 4706 – 4738

http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Biotechnology/ucm096149.htm

- "[B]ecause some rDNA-induced unintended changes are specific to a transformational event (e.g. those resulting from insertional mutagenesis), *FDA believes that it needs to be provided with information about foods from all separate transformational events*, even when the agency has been provided with information about foods from rDNA-modified plants with the same intended trait and has had no questions about such foods. *In contrast, the agency does not believe that it needs to receive information about foods from plants derived through narrow crosses* [e.g. traditional breeding]" italics added (FR 66(12), pg. 4711)

- FDA admits that there is a difference between GE and traditional breeding, yet they still follow the 1992 policy

Codex Alimentarius

- **Food safety standard setting organization of the United Nations. Joint World Health Organization (WHO) and Food and Agriculture Organization (FAO)**
- **Set up in 1960s to help developing countries with range of voluntary, standards, guidelines and recommendations associated with food safety**
- **1995 Marrakech Agreement, General Agreement on Tariffs and Trade (GATT) replaced by World Trade Organization (WTO)**
- **Codex standards, guidelines and recommendations considered “trade legal”**

Codex Alimentarius

- **Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (2000 – 2003; 2005-2008)**
- **Hosted by Japan**
- **Developed 4 key documents:**
- **CAC/GL 44 Principles for Risk Analysis of Foods Derived from Modern Biotechnology (2003)**
- **CAC/GL 45 Guideline for the Conduct of Food Safety Assessment of Foods Derived from Modern Biotechnology (2003, 2008)**
- **CAC/GL 46 Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms (2003)**
- **CAC/GL 68 Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals (2008)**

Codex Alimentarius: Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (CAC/GL 44—2003)

- “18. Risk managers should take into account the uncertainties in the risk assessment and implement appropriate measures to manage these uncertainties.
- 19. Risk management measures may include, as appropriate, food labeling, conditions for market approval and post-market monitoring.” (para 18, 19 CAC/GL 44—2003)

Codex Alimentarius

- Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants

  - *"Unintended effects due to genetic modification may be subdivided into two groups: those that are "predictable" and those that are "unexpected" . . . A variety of data and information are necessary to assess unintended effects because no individual test can detect all possible unintended effects or identify, with certainty, those relevant to human health. These data and information which considered in total, provide assurance that the food is unlikely* to have an adverse effect on human health" italics added (paras 16 and 17, CAG/GL 45-2003)

Guideline for the Conduct of Food Safety Assessment of Foods Derived from Modern Biotechnology (CAC/GL 45, 2003)

- **Unintended effects**
- "Unintended effects in recombinant-DNA plants may also arise through the insertion of DNA sequences and/or may arise through subsequent conventional breeding of the recombinant DNA plant" (para 14). [e.g. stacked traits]

- "Unintended effects can result from the random insertion of DNA sequences into the plant genome which may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes. … Molecular biological and biochemical techniques can also be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects". (paras 15, 16) [importance of –omics technologies, e.g. genomics, transcriptomics, proteomics, metabolomics, as well dsRNA profiling which need to be validated and incorporated into regulatory risk assessments]

Codex Alimentarius

- Codex Committee on Food Labeling has worked on a guidance on labeling GE foods since 1995

- “Codex Alimentarius Commission has stated that governments are free to decide on whether and how to label foods derived from modern biotechnology, including foods containing genetically modified organisms. The labeling should be done in conformity with the text approved by the Codex Commission, to avoid a potential trade barrier. The decision, which will help inform consumers’ choices regarding genetically-modified foodstuffs, was taken at the 34th Session of the Commission, held in Geneva from 4-9 July 2011. More than 600 delegates from 145 of the 184 member countries, UN, inter-governmental and non-governmental organizations attended”

- UNINTENDED EFFECTS

Transformation—pleitropy, epistatis, unexpected effects

From Kuiper et al. 2001. Assessment of the food safety issues related to genetically modified foods. *The Plant Journal*, 27(6): 503-528

Table 6. Unintended effects in genetic engineering breeding*

Host plant	Trait	Unintended effect	Reference
Canola	overexpression of phytoene-synthase	multiple metabolic changes (tocopherol, chlorophyll, fatty acids, phytoene)	Shewmaker *et al.* (1999)
Potato	expression of yeast invertase	reduced glycoalkaloid content (–37–48%)	Engel *et al.* (1998)
Potato	expression of soybean glycinin	increased glycoalkaloid content (+16–88%)	Hashimoto *et al.* (1999a); Hashimoto *et al.* (1999b)
Potato	expression of bacterial levansucrase	adverse tuber tissue perturbations; impaired carbohydrate transport in the phloem	Turk and Smeekens (1999); Dueck *et al.* (1998)
Rice	expression of soybean glycinin	increased vitamin B6-content (+50%)	Momma *et al.* (1999)
Rice	expression of provitamin A biosynthetic pathway	formation of unexpected carotenoid derivatives (beta-carotene, lutein, zeaxanthin)	Ye *et al.* (2000)
Soybean	expression of glyphosphate (EPSPS) resistance	higher lignin content (20%) at normal soil temperatures (20°C); splitting stems and yield reduction (up to 40%) at high soil temperatures (45°C)	Gertz *et al.* (1999)
Wheat	expression of glucose oxidase	phytotoxicity	Murray *et al.* (1999)
Wheat	expression of phosphatidyl serine synthase	necrotic lesions	Delhaize *et al.* (1999)

*Data from publicly available reports.

Zolla, L. et al. 2008. Proteomics as a Complementary Tool for Identifying Unintended Side Effects Occurring in Transgenic Maize Seeds As a Result of Genetic Modifications. *Journal of Proteome Research*, 7: 1850-1861.

- Proteomics is the study of expressed proteins. This is good way to detect unintended effects associated with GE, particularly the disruptive effects due to the random insertion of transgene

- Superior study design: GE maize (MON810) and near isoline grown side-by-side in growth chamber, to control for environmental effects

Zolla, L. et al. 2008. Proteomics as a Complementary Tool for Identifying Unintended Side Effects Occurring in Transgenic Maize Seeds As a Result of Genetic Modifications. *Journal of Proteome Research*, 7: 1850-1861.

- Results: "43 proteins resulted up- or down-regulated in transgenic seeds with respect to their controls (T06 vs WT06), which could be specifically related to the insertion of a single gene into a maize genome by particle bombardment." (pg. 1850). Of these 43 proteins, 14 were down-regulated, 13 up-regulated, 9 shut off and 7 newly expressed.

- "Interestingly, a newly expressed spot (SSP 6711) corresponding to 50 kDa gamma zein, a well-known allergenic protein, has been detected. Moreover, as a major concern, a number of seed storage proteins (such as globulins and vicilin-like embryo storage proteins) exhibited truncated forms having molecular masses significantly lower than the native ones." (pg. 1855)

- Animal Feeding Studies

Finamore, A et al. 2008. Intestinal and Peripheral Immune Response to MON810 Maize Ingestion in Weaning and Old Mice. *Journal of Agricultural and Food Chemistry*

- Well designed study: MON810 and near isoline grown simultaneously in neighboring fields in Landriano, Italy, to control for environmental effects

- "This study evaluated the gut and peripheral immune response to genetically modified (GM) maize in mice in vulnerable conditions. Weaning and old mice were fed a diet containing MON810 or its parental control maize . . . for 30 and 90 days. . . As compared to control maize, MON810 maize induced alterations in the percentage of T and B cells and of CD4+, CD8+, T, and RT subpopulations of weaning and old mice fed for 30 or 90 days, respectively, at the gut and peripheral sites. An increase of serum IL-6, IL-13, IL-12p70, and MIP-1 [cytokines involved in allergenic and inflammatory response] after MON810 feeding was also found. These results suggest the importance of the gut and peripheral immune response to GM crop ingestion as well as the age of the consumer in the GMO safety evaluation."

Aris, A. and S. Leblanc. 2011. Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. *Reproductive Toxicology*, doi:10.1016/j.reprotox.2011.02.004.

- Study involved 30 pregnant, 39 nonpregnant women in Quebec, Canada.
- Blood taken from women and from fetal cord blood and tested for 3 pesticides associated with GM: glyphosate, glufosinate, Cry1Ab
- Results: detected metabolite of glufosinate (3-MPPA) and Cry1Ab in maternal (93%), fetal (80%) and nonpregnant women's blood (69%)

Aris, A. and S. Leblanc. 2011. Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. *Reproductive Toxicology*, doi:10.1016/j.reprotox.2011.02.004.

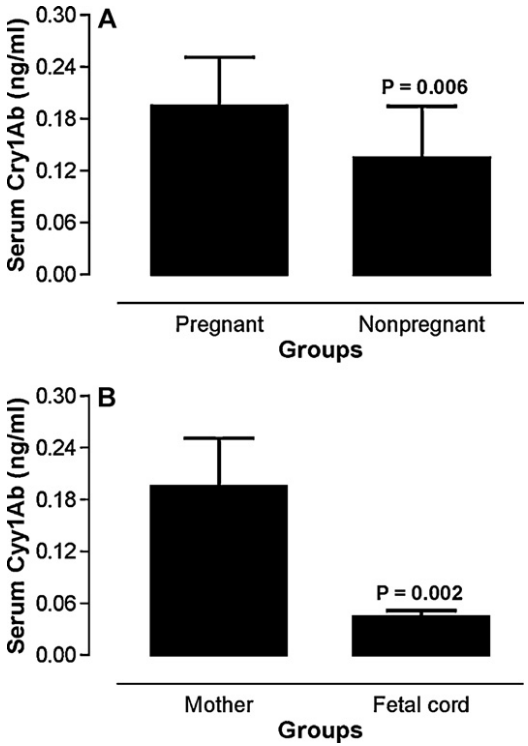


Fig. 2. Circulating concentrations of Cry1Ab toxin in pregnant and nonpregnant women (A), and maternal and fetal cord (B). Blood sampling was performed from thirty pregnant women and thirty-nine nonpregnant women. Levels of Cry1Ab toxin were assessed using an ELISA method. *P* values were determined by Mann–Whitney test in the comparison of pregnant women to nonpregnant women (A). *P* values were determined by Wilcoxon matched pairs test in the comparison of maternal to fetal samples (B). A *P* value of 0.05 was considered as significant.

Aris, A. and S. Leblanc. 2011. Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. *Reproductive Toxicology*, doi:10.1016/j.reprotox.2011.02.004.

- Conclusion: "To our knowledge, this is the first study to highlight the presence of pesticides-associated genetically modified foods in maternal, fetal and nonpregnant women's blood. 3-MPPA and Cry1Ab toxin are clearly detectable and appear to cross the placenta to the fetus. Given the potential toxicity of these environmental pollutants and the fragility of the fetus, more studies are needed, particularly those using the placental transfer approach."

Séralini et al. 2011. Genetically modified crops safety assessments: present limits and possible improvements. Environmental Sciences Europe 2011, 23:10 http://www.enveurope.com/content/pdf/2190-4715-23-10.pdf

Table 1 Review of the longest chronic or subchronic toxicity studies in mammals fed with commercialized GM soybean and maize representing more than 80% of edible GMOs (2010)

References	Plant	Pesticide contained	Name of event	Species	Duration	Main observations
[17,38,39,19,15]	Soybean	Roundup herbicide	mCP4 EPSPS	Mouse	240 days	Ultrastructural histochemistry disturbed
[14]	Soybean	Roundup herbicide	mCP4 EPSPS	Rat	91 days	Weight problems
[40]	Soybean	Roundup herbicide	Optimum GAT DP-356Ø43-5	Rat	93 days	Statistical differences[a]
[41]	Soybean	Roundup herbicide	Not precise	Rat	104 weeks	Statistical differences[a]
[42]	Maize	Roundup herbicide	Optimum GAT DP-Ø9814Ø-6	Rat	91 days	Statistical differences[a]
[43,5]	Maize	Roundup herbicide	NK603	Rat	90 days	Controversial results
[44,5]	Maize	mCry1Ab insecticide	MON810	Rat	90 days	Controversial results
[25,24,5]	Maize	mCry3Bb1 insecticide	MON863	Rat	90 days	Controversial results
[16]	Maize	mBt insecticide	not indicated	Rat	Multi-generational (F3)	Histopathological, biochemical, organ weights alterations
[45]	Maize	mCry1F insecticide - glufosinate ammonium-based herbicide	DAS-Ø15Ø7-1	Rat	91 days	Statistical differences[a]
[46,47]	Maize	mCry34Ab1, mCry35Ab1 insecticides - glufosinate ammonium-based herbicide	DAS-59122-7	Rat	90 days	Statistical differences[a]
[48]	Maize	mCry1F, mCry34Ab1, mCry35Ab1 insecticides - glufosinate ammonium-based herbicide	DAS-Ø15Ø7-1 × DAS-59122-7	Rat	92 days	Statistical differences[a]

[a]Statistical differences are not biologically meaningful for the authors; however, this can be debated. Oilseed rape and cotton have been excluded because they are not directly edible and not primarily grown for feed. This table includes authorized events for food and feed at least in the European Union and America.

Séralini et al. 2011. Genetically modified crops safety assessments: present limits and possible improvements. Environmental Sciences Europe 2011, 23:10

http://www.enveurope.com/content/pdf/2190-4715-23-10.pdf

Table 2 Meta-analysis of statistical differences with appropriate controls in feeding trials

All parameters measured *in vivo* in GMO toxicity studies	Measured by organ (%)/Total (694-698)		Disturbed in each organ (%)/Total disrupted parameters (approximately 9%)	
	Females	Males	Females	Males
Liver	22.9	22.9	**30.8**	26.1
Kidney	23.7	23.7	26.4	**43.5**
Bone marrow	29.5	29.5	29.7	22.8
Total for 3 tissues	76.1	76.1	86.9	92.4

Commercialized soybean and maize GMOs were fed to rats and their blood analyses were obtained. The different parameters are classified according to the tissue [2] to which they are related (e.g., liver, kidney, bone marrow). Of the total parameters measured 76.1% are related to these three organs. The percentages of significantly different parameters to the controls are called "disrupted parameters." There are in total 9% of disrupted parameters and, for instance, 43.5% of these are concentrated in kidneys in males. The bold values are significantly over the parameters measured per organ.

Conclusions: The 90-day-long tests are insufficient to evaluate chronic toxicity, and the signs highlighted in the kidneys and livers could be the onset of chronic diseases. However, no minimal length for the tests is yet obligatory for any of the GMOs cultivated on a large scale, and this is socially unacceptable in terms of consumer health protection.

American Medical Association policy on bioengineered foods, passed at June, 2012 AMA meeting. http://www.ama-assn.org/resources/doc/yps/ref-comm-e-grid.pdf

- (4) **Our AMA supports mandatory pre-market systematic safety assessments of bioengineered foods** and encourages:
- (a) development and validation of additional techniques for the detection and/or assessment of unintended effects;
- (b) continued use of methods to detect substantive changes in nutrient or toxicant levels in bioengineered foods as part of a substantial equivalence evaluation;
- (c) development and use of alternative transformation technologies to avoid utilization of antibiotic resistance markers that code for clinically relevant antibiotics, where feasible; and
- (d) that priority should be given to basic research in food allergenicity to support the development of improved methods for identifying potential allergens. The FDA is urged to remain alert to new data on the health consequences of bioengineered foods and update its regulatory policies accordingly.

Summary

- US policy on GE plants inadequate
  - safety assessments not required, even though FDA admits GE differs from conventional breeding
  - labeling not required
- Global agreement that GE is different than conventional breeding and that safety assessments should be required
- Unanswered health questions persist for GE plants and more independent tests are needed
- Labeling is needed to potentially detected any health impacts of GMOs, e.g. to serve as a risk management measure to deal with scientific uncertainty.