Why GE foods should be Labeled: Inadequate Regulations, Unanswered Safety Questions

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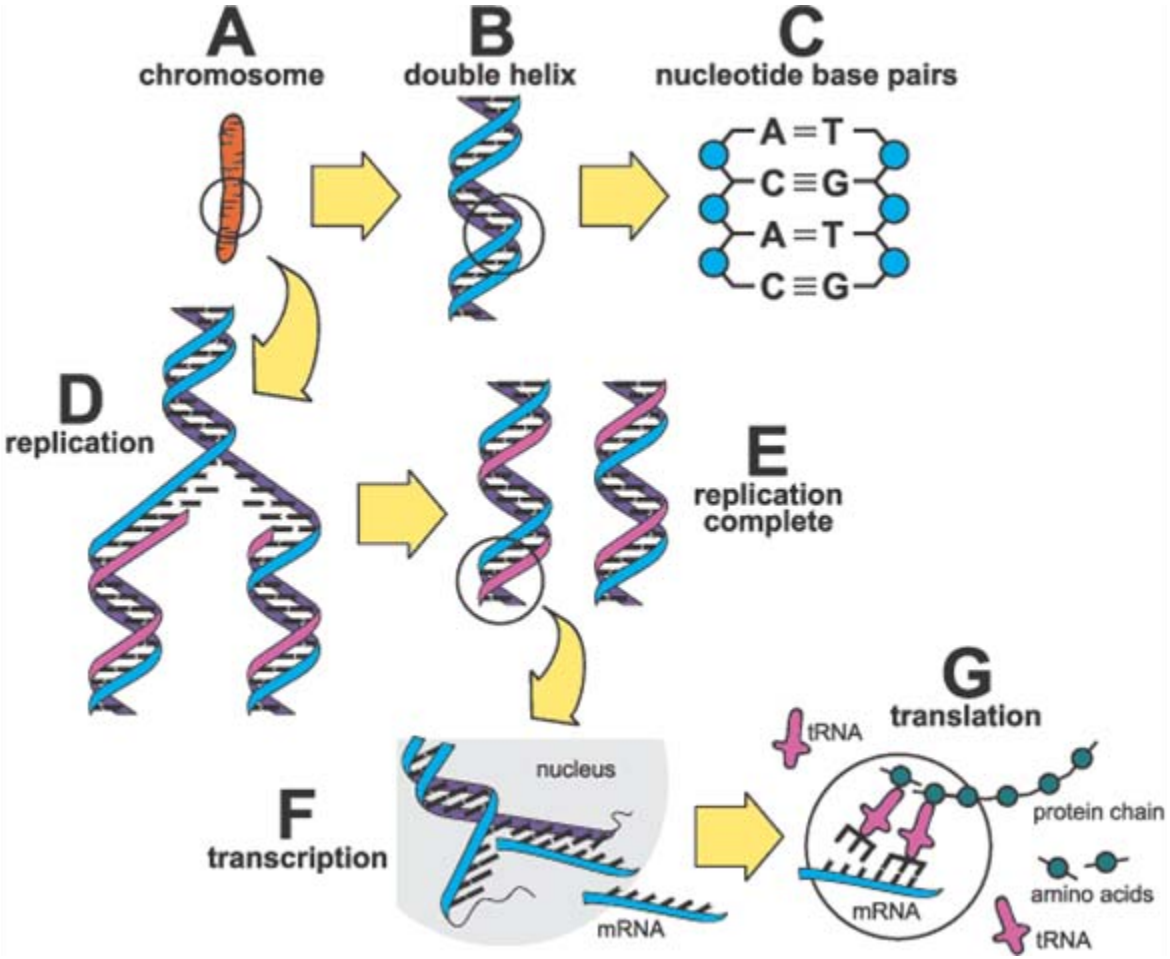
Outline

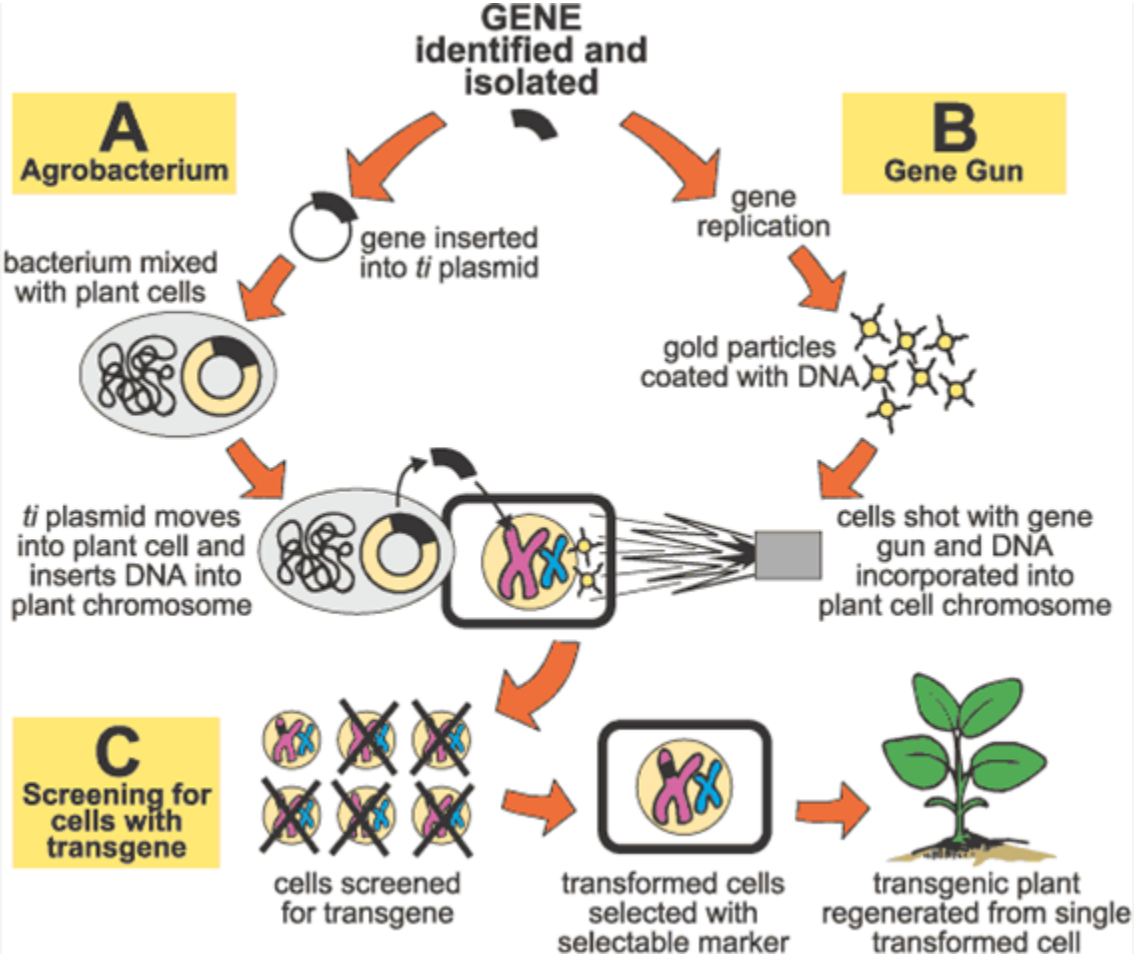
- Basics of Biotechnology
- FDA GE policy + global policy
- New science raises safety questions
- Summary

- Biotechnology Basics

The basic structure and functions of genes and chromosomes



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



Major GE crops on the market

- Main traits—herbicide resistance (HR), insect resistance (~99.5% acreage), virus tolerant
- Main crops engineered:
- Soybean (HR)—93%
- Sugarbeets (HT)—95%
- Corn (Bt and HR)—88%
- Canola (HR)—93%
- Cotton (Bt and HR)—94%
- Papaya (virus tolerant)—80% (Hawaii)
- zuchinni (virus tolerant)—13% (2005)

- **FDA Policy on Genetically Engineered Plants**

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” (57 FR 22991, May 29, 1992)

- No requirement for human safety testing, only “voluntary safety consultations”; to date, some 94 voluntary safety consultations have been held

Key phrases in US Food and Drug Administration safety consultation letters

- MON 810 (Bt corn), dated Sept. 26, 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."
  www.fda.gov/fFood/Biotechnology/Submissions/ucm161107.htm

- A variation of this sentence is found in all 94 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**
- **1996 Uruguay Round of General Agreement on Tariffs and Trade sets up 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)**

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

- 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."

Velirimov et al. 2008. Biological effects of transgenic maize NK603xMON810 fed in long term reproduction studies in mice.

- Carefully designed Austrian study: GE corn and a near isogenic line grown in adjacent fields in Canada in the same year (2005, 2007).
- Large sample sizes were used to detect more subtle adverse effects.
- Major result: statistically significant adverse reproductive effects shown in the reproductive assessment by continuous breeding (RACB) study. RACB is a feeding study whereby a pair of mice are fed GM maize for 140 days, during which time the female is bred so that she delivers 4 litters. RACB puts mice under stress making it easier to detect adverse effects.

Velirimov et al. 2008. Biological effects of transgenic maize NK603xMON810 fed in long term reproduction studies in mice.

- 24 pairs of mice. In the non-GE group all 24 females delivered 4 litters. In the GE group the number of deliveries declined with time. In the 4th litter only 20 deliveries occurred ($p=0.055$). The average number of pups born was always lower in the GM group.

- More pups born in the non-GE than in the GE group (1035 versus 844). Furthermore females of the GE group always had smaller litters ($n<8$) as compared to females of the ISO group."

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.

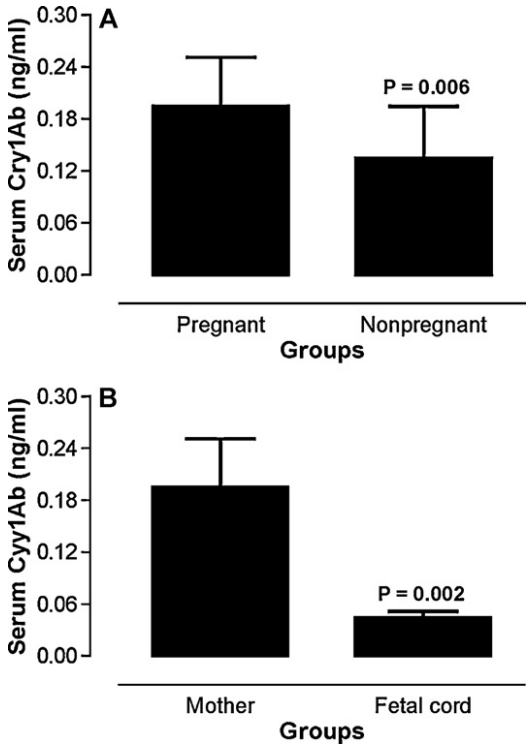


Fig. 2. Circulating concentrations of Cry1Ab toxin in pregnant and nonpregnant women (A), and maternal and fetal cord (B). Blood sampling was performed from thirty pregnant women and thirty-nine nonpregnant women. Levels of Cry1Ab toxin were assessed using an ELISA method. *P* values were determined 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/23/1/10

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

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.

Séralini et al. 2012. Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize.
Food and Chemical Toxicology, 50: 4221-4231.
http://www.sciencedirect.com/science/article/pii/S0278691512005637

- First long-term (2 years) feeding study of GE foods; involved rats fed Roundup-resistant corn (NK 603) at three levels, cultivated with and without Roundup
- Results: Females: died 2-3 times more quickly, and developed mammary tumors more often than controls. Males have liver and kidney problems at higher rate than controls, and more large tumors.

Séralini et al. 2012. Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize.
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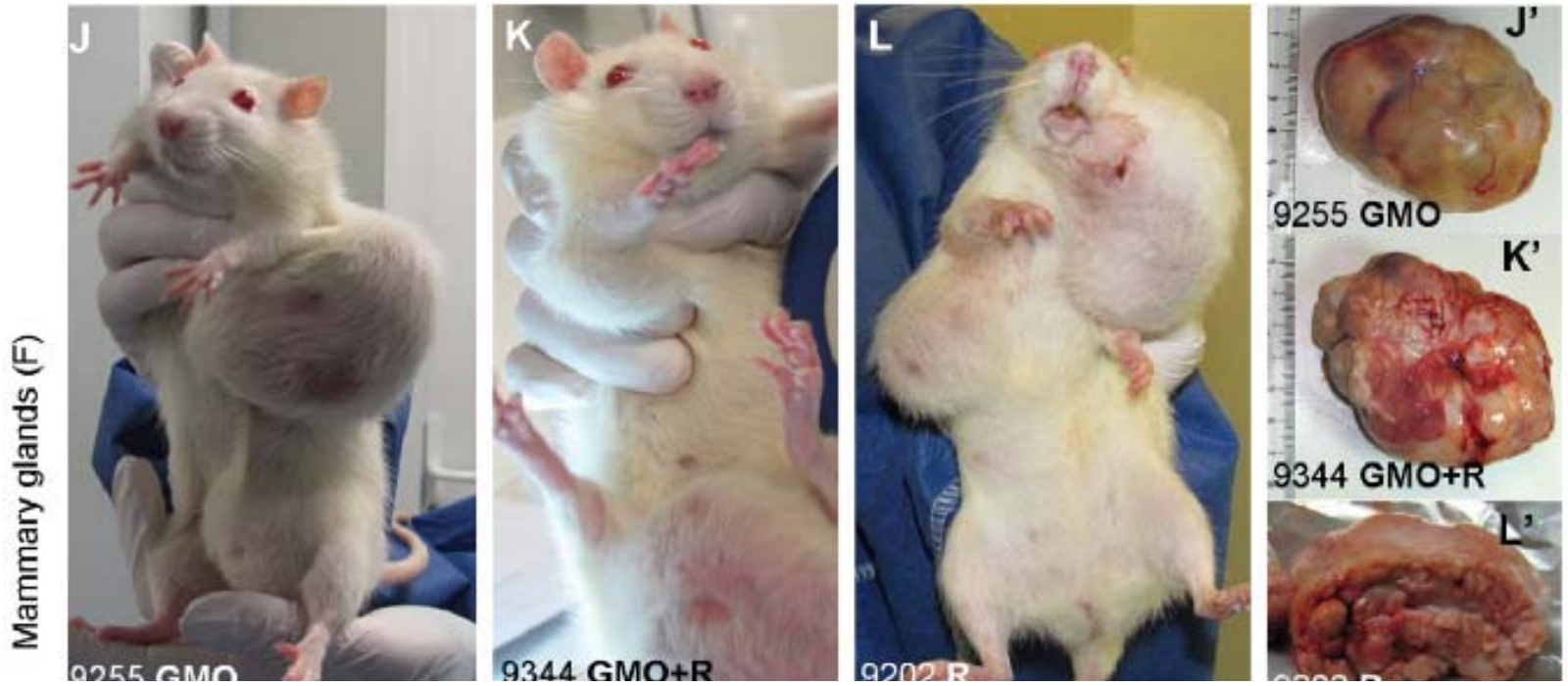

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Table 1
Protocol used and comparison to existing assessment, and to non-mandatory regulatory tests.

Treatments and analyses	In this work	Hammond et al., 2004	Regulatory tests
Treatments + controls	GMO NK603, GMO NK603 + Roundup, Roundup, and closest isogenic maize	GMO NK603 + Roundup, closest isogenic maize, and six other maize lines non substantially equivalent	GMOs or chemicals (in standard diet or water)
Doses by treatment	3	2	At least 3
Duration in months	24 (chronic)	3 (subchronic: 13 weeks)	3
Animals measured/group/sex	10/10 SD rats (200 rats measured)	10/20 SD rats (200 rats measured/total 400)	At least 10 rodents
Animals by cage (same sex)	1–2	1	1 or more
Monitoring/week	2	1	1 or more
Feed and water consumptions	Measured	For feed only	At least feed
Organs and tissues studied			For high dose and controls
Histology/animal	34	17/36	At least 30
Organs weighted	10	7	At least 8
Electronic microscopy	Yes	No	No
Behavioral studies (times)	2	1 (no protocol given)	1
Ophtalmology (times)	2	0	2
Number of blood samples/ animal	11, each month (0–3) then every 3 months	2, weeks 4 and 13	1, at the end
Blood parameters	31 (11 times for most)	31 (2 times)	At least 25 (at least 2 times)
Plasma sex steroids	Testosterone, estradiol	No	No, except if endocrine effects suspected
Liver tissue parameters	6	0	0
Number of urine samples	11	2	Optional, last week
Urine parameters studied	16	18	7 if performed
Microbiology in feces or urine	Yes	Yes	No
Roundup residues in tissues	Studied	Not studied	Not mandatory
Transgene in tissues	Studied	Not studied	Not studied

The protocol used in this work was compared to the regulatory assessment of NK603 maize by the company (Hammond et al., 2004), and to non mandatory regulatory *in vivo* tests for GMOs, or mandatory for chemicals (OECD 408). Most relevant results are shown in this paper.

Reaction of ANSES (French Agency for food, environmental and occupational health and safety) to Seralini et al. study

http://www.anses.fr/Documents/PRES2012CPA20EN.pdf

- “The expert assessment carried out by the Agency concludes that the results of this research do not cast doubt on the previous assessments of genetically-modified NK603 maize and Roundup.”

- “ANSES draws attention, however, to the originality of this study, namely its focus on a subject rarely investigated to date: the long-term effects of GMOs in association with plant protection products.”

Reaction of ANSES (French Agency for food, environmental and occupational health and safety) to Seralini et al. study
http://www.anses.fr/Documents/PRES2012CPA20EN.pdf

- “ANSES recommends initiating studies and research on the long-term effects of GMOs in combination with plant protection products”

- “ANSES calls for public funding on the national and European level to enable large-scale studies and research for consolidating knowledge of insufficiently documented health risks”

Commission and EFSA agree need for two-year GMO feeding studies EU Food Policy, 17 December 2012

http://www.eufoodpolicy.com/cgi-bin/view_article.pl?id=5590

- “The European Commission is trying to fund two-year GMO feeding studies on rodents, Ladislav Miko, deputy director general of DG SANCO (food) said last week.”

- “EFSA's executive director, Catherine Geslain-Laneelle, pointed out that the study would be on MON810, not NK603 - the GM maize used by Prof Seralini.”

- “But at the EFSA board meeting on Thursday last week there was agreement that long-term studies were needed and it was now just a question of how to fund them.”

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
  - labeling not required
- Unanswered health questions persist for GE plants
- 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.
- Support H. 112