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Potential Health Effects of Foods Derived from Genetically Modified Plants: What Are the Issues?

by Arpad Pusztai and Susan Bardocz

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Third World Network

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Abstract

In the European Union, the acceptance and regulation of genetically modified (GM) crops/foods is based on the safety data which the biotech companies provide for the European Food Safety Authority (EFSA) and not on the results of EFSA's own investigations. The situation is worse in the USA where there is lax regulation and the commercialisation of GM crops/foods is based on the flawed concept of 'substantial equivalence'. This, without stringent quantitative criteria, can only serve, at best, as an indication of comparability, but at worst, it can be misleading. It is therefore imperative that each GM crop is subjected to, as a minimum, the following:

- comparison of the composition of the GM and isogenic lines with up-to-date analytical techniques, such as proteomic analysis (2D electrophoresis and mass spectrometric analysis of components)
- full biochemical, nutritional and toxicological comparison of the *in planta* expressed transgene product with that of the original gene used for the transformation
- microarray analysis of all novel RNA species in the genetically modified plant
- molecular examination of possible secondary DNA inserts into the plant genome
- full obligatory metabolomic NMR, etc. analysis of the transformed plant

- assessment of the variation of known toxins of GM plants grown under different agronomic conditions
- determination of the stability to degradation by acid or pepsin or other proteases/hydrolases of GM products, foreign DNA, including the gene construct, promoter, antibiotic resistance marker gene, etc. in the gut of animals *in vivo*
- with GM lectins, including the Bt-toxins, estimation by immunohistology of the presence/absence of epithelial binding in the gut
- investigation of the nutritional, immunological, hormonal properties, and allergenicity of GM products using the transgene product isolated from the GM crop and not with recombinant material from *E. coli*
- short- and long-term independent biological risk-assessment tests, first with laboratory animals, followed by human clinical studies of all GM crops/foods themselves and not just the transgene products. This paper describes a suggested protocol for the testing of GM crops and foods derived from them.

Chapter 1

Introduction

The basic tenet of the biotechnology industry engaged in the production of genetically modified (GM) crop plants and foods is that no 'credible' evidence exists that GM crops damage the environment or that GM foods harm human/animal health. Accordingly, they are as safe as their 'substantially equivalent conventional counterparts' and need no safety testing. The general acceptance of such a view could, of course, save a great deal of money for the biotechnology industry that otherwise would have to be spent on very expensive environmental and health risk assessments of their GM products.

However, practically all recent reviews that have critically assessed the results of GM crop/food safety research data published in peer-reviewed science journals have come to the conclusion that, at best, their safety has not yet been adequately established, or at worst, that the results of risk assessment studies, particularly (but not exclusively) those carried out independently of the biotechnology industry, have raised important safety concerns which have not been properly settled. Thus, one review concluded that the most pertinent questions on environmental safety of GM crops have not yet been asked (Wolfanberger & Phifer 2000). A more recent update (Snow et al. 2005) came up with a long list of important questions that regulatory authorities should ask before any GM crops

are released into the environment. Unfortunately, few of these questions have been addressed in the biotechnology companies' submissions to the regulatory authorities.

The situation is not much better with the results of studies in which the potential health effects of GM foods have been investigated. Thus, an early review (Domingo 2000) found only eight peer-reviewed papers published on the potential health aspects of GM food. Pryme & Lembcke (2003) reported a rather curious aspect of the results of health risk assessment studies using laboratory animals. It appeared that most independently funded research scientists who performed animal testing of GM crops reported some potential health problems, while the results of the studies sponsored by the industry indicated none. Further reviews confirmed the scarcity of GM risk assessment research, particularly research carried out independently of the biotechnology industry. Thus, there were just over a dozen academic research papers on the health aspects of GM crops published by 2003 (Pusztai et al. 2003) and this number had increased to approximately 20 by 2005 (Pusztai & Bardocz 2006).

A report by the Canadian Royal Society stated that without in-depth biological testing of GM crops, 'substantial equivalence' is a fatally flawed concept and regulation based on it exposes Canadians to potential health risks of toxic and allergic reactions. Neither did the British Medical Association accept that all GM crops/foods are safe, and therefore no testing is needed. In their report (The Medical Research Council 2000, recently updated) it was stated that 'any conclusion upon the safety of introducing GM material into the UK is premature as there is insufficient evidence to inform the decision making process at present'. It is, therefore, not surprising that the majority of British consumers think that GM foods are unsafe. As there is no demand for them most supermarkets in the UK have phased

them out. Most consumers in Europe demand, as a minimum, the labelling and rigorous, transparent and independent safety testing of all GM foods.

Most GM crops are grown in America, the bulk in the USA. It is therefore regrettable that effectively there is no regulation in the USA that would guarantee their safety. The food regulatory agency in the USA, the Food and Drug Administration (FDA), almost totally relies on voluntary notification by the biotechnology companies that they carried out their own safety assessment of the GM crops they want to release commercially and found them to be safe. The FDA has no laboratory of its own and never, in fact, underwrites the safety of GM crops/foods. It only accepts the assurances of the biotechnology companies that their product is safe. This, in most instances, relies on a safety assessment that is based on the poorly defined and not legally binding concept of substantial equivalence.

However, similarity in composition is no guarantee that GM food is as safe as conventional food. Thus, the content of proteins, lipids and carbohydrate components of a BSE cow (a cow suffering from a condition known as bovine spongiform encephalopathy) will be similar to that of a healthy cow but, obviously, these two cows cannot be regarded as substantially equivalent for consumer health. True, compositional analysis is an obligatory starting point in risk assessment but it cannot be its endpoint. Whether GM food is toxic or allergenic cannot be decided on the basis of chemical analyses but only by biological testing with animals.

Furthermore, the biotechnology companies try to claim as much 'confidential business information' concerning their risk assessments as possible, and therefore most of the time these are unavailable in full for public or independent scrutiny or even for some national regulatory bodies.

1.1 Present state of GM food science

One of the most important reasons for the present scarcity of GM safety data is the lack of funding for basic physiological and nutritional studies of the possible health effects of GM foods on consumers. The attitude of the industry is that GM foods are safe and therefore there is no need for independent risk assessment studies. Thus, it is not surprising that ten years after the commercialisation of the first GM crop, the FLAVR-SAVR tomato, there is still no generally agreed protocol for the risk assessment of GM products.

Although the EU has recently made an attempt to present a safety testing protocol for GM foods (Kuiper et al. 2004), the only previous independently funded research to set up a blueprint for GM risk assessment was the GM potato study carried out in Scotland between 1995 and 1998. Even though a blueprint for GM risk assessment based on this study was presented at an OECD meeting in Edinburgh in 2000 and subsequently published (Pusztai 2002), neither this nor the EU protocol has been generally accepted and put into practice. Accordingly, if there is any risk assessment carried out at all by the biotechnology companies this is usually an *ad hoc* study to suit their requirements. In the case of the more rare independent investigations into the possible biological effects of GM foods, the results obtained are non-binding on the regulatory authorities.

Our database on the likely biological effects of GM foods is woefully inadequate. This is not surprising, because from the published results of one human clinical trial and a few animal studies published to date it is impossible to establish reliable and reproducible factual conclusions that are fully supported by the experimental evidence. Neither is it much help that data obtained by the biotechnology companies are seldom published and therefore these results are unavailable for most scientists. In

the few cases when the industry's own risk assessment results have become public knowledge and they revealed statistically significant differences between the GM and non-GM crop/food, the GM biotech industry denied that these differences had any biological significance. When independent scientists find such differences they are vilified.

The complexity of GM foods makes their biological testing difficult even when funding for such studies can be obtained. Thus, any protocol that may be devised must take into account that, in addition to the generally recognised importance of testing for the direct effects of the expression of the transgene, its insertion into the plant genome via a gene construct may also cause significant, indirect and unintended physiological effects by disturbing the functionality of the plant's own genes (Ewen & Pusztai 1999a; Schubert 2002, Freese & Schubert 2003; Wilson et al. 2004) and special testing methods are needed to recognise these. The number of copies of the construct inserted and their location in the plant genome (positioning effect) are also of importance.

Although the presence and consequences of such unintended effects in GM foods have long been ignored by the GM biotechnology industry, their importance is now beginning to be recognised by the regulatory agencies. Indeed, testing for these is now recommended in the Codex Alimentarius guidelines (Haslberger 2003).

Unfortunately, most currently used methods to detect unintended changes in GM products are largely inadequate. Positioning effects in plants often occur with both conventional crossbreeding and genetic engineering and empirically selecting for the desired trait and discarding the potentially harmful ones, usually to eliminate their unwanted consequences (Haslberger 2003, Pusztai & Bardocz 2006). However, it may be difficult to have

appropriate selection criteria for establishing which trait is harmful or beneficial. As it is only possible to compare the known properties and constituents of GM and conventional plants but not to look for, and even less to analyse, unknown newly created components, the limitations on our selection criteria are severe. Reliance based solely on chemical analysis of macro/micronutrients and known toxins is at best inadequate and, at worst dangerous, even when new and more sophisticated analytical methods are used, such as mRNA fingerprinting, proteomics, secondary metabolite profiling, and other profiling techniques (Kuiper et al. 2003). However, and most importantly, there is an urgent need to develop a protocol for experimental investigations using comprehensive toxicological/nutritional methods which will equally be applicable to scientifically examine the veracity of the claimed benefits of genetic manipulation and screen for its unintended and potentially harmful consequences for human/animal health. As the first contact point of exposure to any foods/feeds, including that which has been genetically modified, is the gastrointestinal tract (GIT), the first task in any proper risk assessment protocol should be to establish the consequences for the gut of short- or long-term exposure to diets that contain such foods/feeds (Ewen & Pusztai 1999a; Pusztai 2002). It is also important to point out here that any risk assessment protocol must take into account that it is not only the biological effects of the transgene product(s) that need to be unravelled, but also the direct and indirect effects of the DNA vector constructs.

Chapter 2

Alimentary Tract as the First Target of GM Food Risk Assessment

To show by chemical methods the presence of new toxins/allergens in GM food products is, at best, difficult. In contrast, the presence of even minute amounts of unexpected but harmful potent bioagents in GM foods could be more easily established from their possibly disproportionally large effect on health. Thus, exposure of individuals to biologically active transgenic proteins can have major effects on their gastrointestinal tract. As most proteins are immunogenic their consumption may trigger immune/allergic effects both in the mucosal immune system of the gut and the body. It is also likely that, in addition to the effects on the gastrointestinal tract, the size, structure, and function of other internal organs will be affected, particularly in young and rapidly growing humans or animals. According to some recent unconfirmed reports, the dietary exposure to GM foods may also have harmful effects on reproduction (see Annex). In addition, the risks will also have to be investigated as to whether measurable amounts of the transgenic DNA constructs in GM crops/foods survive in a functionally active state/size in the gastrointestinal tract of the human/animal ingesting them, and whether they can incorporate into the genome of the cells of their gut and body organs and what will be the consequences, if any, for the individual. The GM risk assessment protocol presented in the following chapter outlines

a gradual, step-by-step course of investigation by reliable and up-to-date methodology that addresses all these possible effects. These steps must be regarded as a minimum before any foods/feeds based on GM crops are allowed into the human/animal food chain.

Chapter 3

Suggested Protocol for GM Crop/Food Health Risk Assessment

Before any new GM crop could be made potentially safe transgenes must be identified and selected in preliminary model studies. The main criterion of the selection should be that the selected transgene and its protein product must have no toxic effects on humans or animals when given orally. However, the process of selection must be taken a step further by verifying that the selected transgene does function in the GM plant as intended. The transgene product must therefore be isolated from the GM plant and show unequivocally that its chemical and biological properties are the same as those of the gene product expressed in the original source from which the transgene was taken. It is absolutely essential that all safety studies be carried out on this isolated transgene product and not on *E. coli* recombinant surrogates.

In the GM safety studies performed by the biotechnology industry great emphasis is laid on the assertion that, according to their *in vitro* tests, all transgene products rapidly break down in simulated intestinal proteolytic digestion tests. Obviously, should a transgenic protein quickly break down to amino acids and small peptides in the alimentary tract its toxic effects or allergenicity could not be more than minimal and thus the safety of the GM crop should apparently be assured. However, in contrast to the protocols used in the biotechnology industry's safety assessment, true proteolytic digestibility must

be established in the gut *in vivo* and not in a test tube *in vitro*. Clearly, one of the most important differences between the digestion of a protein in the alimentary canal and in a test tube using only pancreatic proteases is that *in vivo*, the binding of the transgene product to the intestinal wall and/or to the food matrix reduces the availability of the transgene protein (particularly in the case of the widely used transgenic lectins, such as the various *Bacillus thuringiensis*, Bt-toxins) to the action of the proteases. Thus, an *in vitro* assay may give a false assurance of safety. In addition, as the structure, conformation and stability of a transgenic protein expressed in and isolated from *E. coli* is very different from that expressed in GM plants, no scientifically valid conclusions may be drawn from the results of experiments in which the assessment of the digestibility of a plant transgenic protein is attempted with an *E. coli* recombinant. Plants and eukaryotic bacteria are aeons apart on an evolutionary scale and therefore no bacterial recombinants should be used in tests aimed at establishing the true properties of transgenic proteins expressed in GM plants even though they are coded for by the same DNA.

3.1 Chemical composition

One of the first steps in any proper risk assessment protocol should be the characterisation of the GM plant using well-authenticated and up-to-date methods of chemical analysis to estimate the contents of its major and minor components and to compare their amounts to those of the corresponding parent line. Although the results of such analysis and comparison can also be used to establish whether the GM and non-GM plants are 'substantially equivalent', first and foremost, this is an obligatory step that will allow us to carry out further biological risk assessment tests. However, for such a comparison to be scientifically valid large numbers of the GM and the isogenic lines grown side-by-side and harvested at the same time are needed to be tested for the measurement of their major and

minor constituents in parallel by classical and new analytical methods (proteomics, finger-printing, DNA/metabolic profiling, microarray analysis of all novel RNA species, full molecular biological examination with particular attention to the possibility of secondary DNA insertions into the plant genome, obligatory metabolomic NMR analysis of the transformed plant, stability of expression of foreign DNA, including the gene construct, promoter, antibiotic resistance marker gene, etc.).

3.2 Nutritional/toxicological testing with animals

As outlined, GM crops/foods will need to be examined in obligatory short- and long-term nutritional/toxicological tests with laboratory animals under controlled conditions. The intention is to find out whether there are any toxic effects in the animals fed on diets containing GM foods that would make the progression to human clinical trials unsafe. The animal tests are therefore designed to establish the effects of the GM crop/food on growth, metabolism, organ development, immune and endocrine functions (Pusztai & Bardocz 2006), with particular emphasis on how diets based on GM food will affect the structure, function and bacterial flora of the animal gut. As the normality of these functions determines the development of young animals into healthy adults, the absence of significant differences between the health statuses of animals fed on GM and non-GM diets may possibly indicate that the GM crop is not unsafe, at least in animal nutrition.

3.3 Diet

It is of paramount importance that the conditions of nutritional testing are rigorously standardised. Thus, all diets must be *iso*-proteinic and *iso*-energetic (i.e. contain the same amounts of protein and energy) and are fully supplemented with vitamins and essential minerals. The composition of the control diet containing the parent line should be as close to the GM diet as possible. Diet formulation is therefore – particularly when there

are significant compositional differences between the GM and its corresponding non-GM parent-line crops (e.g. see data for GM potatoes in Table 1) – not an easy task and supplementation with pure ingredients may be necessary to make good the compositional differences. In a second control diet, the parent line should be supplemented with the gene product isolated from the GM crop whose concentration should be the same as in the GM crop. All crops/foods should be fed both raw and after heat-treatment.

Table 1. **Compositional values for 'Desiree' potato tubers and two GM lines expressing the snowdrop (*Galanthus nivalis*) bulb lectin, GNA (Pusztai 2002)**

Constituent	Parent line	GM lines	
		Line 71	Line 74
Protein (% w/w)	7.2[a]	7.2[a]	5.6[b]
Lectin (µg/g)	6.7 (0.4)[b]	7.9 (<0.1)[a]	5.8 (0.8)[c]
Trypsin inhibitor (mg/g)	3.4 (<0.1)[a]	3.1 (0.1)[b]	2.7 (0.1)[c]
Chymotrypsin inhibitor (mg/g)	2.7 (0.1)[a]	2.6 (0.1)[a]	2.2 (0.1)[b]

The plants were grown side-by-side in field tunnels. The values are means (sd) of analyses of at least four determinations of each constituent independently carried out by two workers. Values with different superscripts are significantly different ($p<0.05$).

3.4 Experimental protocol

Groups of young rapidly growing animals (5–6 in each group) closely matched in weight (less than ± 2% w/w), housed separately, should be strictly pair-fed these diets in short- and long-term experiments. Both males and females should be tested. The progress of the animals should be closely monitored, urine and faecal samples collected throughout the experiment and the nutritional performance of the animals and the nutritional value of the diets assessed by Net Protein Utilisation (NPU),

and with measurements of nitrogen and dry weight balances and feed utilisation ratios. The animals should be weighed daily and any possible abnormalities observed. Blood samples should be taken before, during and at the end of the feeding experiments for immune studies (immune responsiveness assays (Table 2), Elispot, etc.), hormone assays (insulin, CCK, etc.) and determination of blood constituents. At the end of the experiments the animals should be killed, dissected, and their guts rinsed and the contents saved for further studies (enzyme contents, GM products, DNA, etc.), gut sections taken for histology, the wet and dry weights (after freeze-drying of the tissues) of organs recorded (Table 3), and the organs subjected to compositional analyses. All these data could be used to comprehensively characterise the health and metabolic status of the animals and the behaviour of the GM-fed animals could be directly compared with that of the controls. The results could then be evaluated by appropriate methods of statistics.

If any of the effects of the diet containing the GM crop on the rats is significantly different from that of the non-GM parental line control diet, the inclusion of the GM crop in food is unsafe and therefore not recommended. If the effects of feeding rats with the parent line control diet are significantly changed when this is spiked with the isolated transgene product, the *transgene is unsafe*. Most importantly, if the effects of the diets containing the GM plant and the parent line control spiked with the gene product differ, the harm is likely to be due to the use of the particular construct vector or caused by an unintended and unforeseen effect of the *transgene insertion or position* in the plant genome. Accordingly, this method of gene transfer and the resulting GM crop is unacceptable. Thus, further research is needed to find other, more precise and safer methods of genetic modification.

Table 2. **Results of lymphocycte proliferation assays in rats fed for 10 days on diets containing raw GM, control/non-GM potatoes, or control/non-GM potatoes supplemented with the gene product, GNA, *Galanthus nivalis* agglutinin (Pusztai 2002)**

	µg Con A/well				
Diet	**0.3**	**1.0**	**3.0**	**6.0**	**9.0**
Parent	10.3 (13.4)	16.0 (18.5)	4.4 (4.9)	1.9 (1.0)	1.6 (1.6)
Parent + GNA	2.5 (4.3)	2.6 (3.5)	2.0 (3.6)	1.1 (0.5)	0.9 (0.6)
GM	1.5 (0.9)	1.7 (1.1)	1.0 (0.4)	1.6 (1.1)	1.6 (1.5)
Significance (p<)					
Parent vs Parent+GNA	ns	p<0.05	ns	p<0.05	ns
Parent vs GM	p<0.05	p<0.05	p<0.05	ns	ns

Rats were fed on different diets for 10 days. At the end of the experiment blood samples were taken and subjected to standard lymphocyte stimulation assay with Concanavalin A (Con A) as the mitogenic signal. The results are expressed as stimulation indexes vs control. Values are means (sd) and significance was assessed by Student t test.

Table 3. **Relative dry organ weights of rats significantly affected by feeding with diets containing raw or boiled GM potatoes and/or parent potatoes spiked with the gene product (GNA, *Galanthus nivalis* agglutinin) (Pusztai 2002)**

	Raw potatoes			Boiled potatoes
Diet	**Pancreas**	**Jejunum**	**Prostate**	**Liver**
Parent	0.68 (0.08)	0.62 (0.06)	0.24 (0.08)	3.78 (0.14)
GM	0.81 (0.05)	0.72 (0.07)	0.16 (0.02)	3.28 (0.21)
Parent + GNA	0.70 (0.08)	0.67 (0.04)	0.18 (0.02)	3.40 (0.28)
Significance (p<)				
Parent vs GM	0.01	0.03	0.05	0.001
Parent+GNA vs GM	0.03	ns	ns	ns

Rats were fed with the diets for 10 days. The values of relative dry organ weights (g organ weight/100 g dry body weight) are means (sd), n=6, by multivariate statistical analysis.

Chapter 4

Differences in Nutritional Performance Useful for Diagnosis of Harm

Organ weight changes are useful indicators of metabolic events after feeding laboratory animals with diets containing GM foodstuffs, particularly if followed up by histological examinations as part of the safety assessment of GM crops. Assessment of potential deviations in the normal development of key organs is of great diagnostic value, as shown in one of our GM-potato rat feeding studies. Sections of the various compartments of the gut taken for histology (Ewen & Pusztai 1999b) (Figure 1) indicated a strong trophic effect of the GM potatoes on the rats' small intestine and, to a lesser extent, on their stomach. This hyperplastic gut growth was of particular significance because the jejunum was not enlarged when the parent line diet was supplemented with the gene product, GNA (*Galanthus nivalis* lectin), confirming previous observations which showed that the gene product had negligible growth factor effect on the jejunum, even when included in the diet at a several hundredfold concentration in comparison with that expressed in the GM potato lines (Pusztai et al. 1990). This was, in fact, one of the main reasons for selecting the gene of the natural insecticidal GNA for the genetic transformation of potatoes (Gatehouse et al. 1996) to make them pest-resistant but nutritionally safe.

As similar hypertrophic and other similar changes in gut ultrastructure in the ileum of mice fed GM potatoes expressing

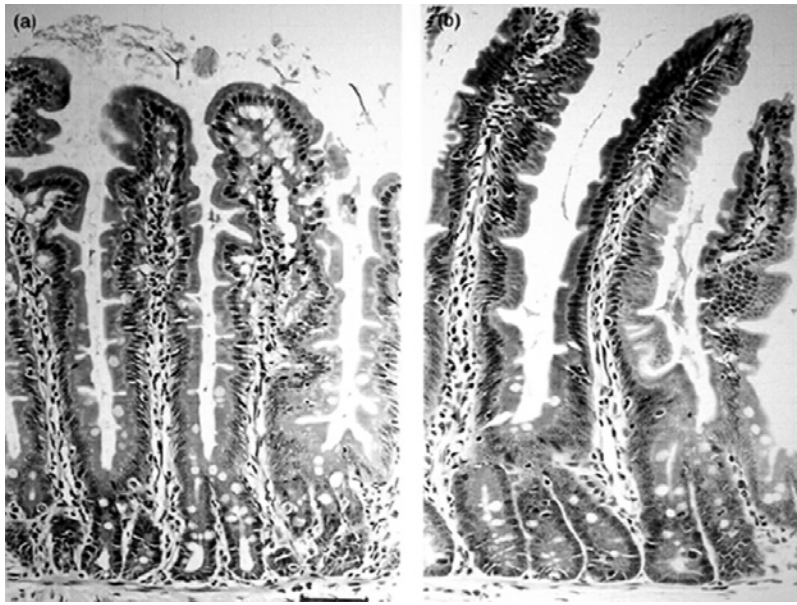

Figure 1. Histology of jejunal sections of rats fed GM potatoes (Pusztai 2002). Jejunal crypt length and cells exhibit marked enlargement after feeding rats a diet of raw GM potato for 10 days, (b) in comparison with that of rats given a parental line potato diet (a). The villus length is similar in both but intraepithelial lymphocyte cell counts appear to be increased on GM potato diet. (14 mm bar = 100 μm).

Bacillus thuringiensis var. *kurstaki* Cry 1 toxin gene or the toxin itself were shown in a different study (for reference see Pusztai et al. 2003), GM potatoes of different origins may have common trophic effects on the gut. Changes in the ultrastructure of other organs, such as the liver, pancreas, etc., on feeding with GM crop containing diets, as shown by the work of the Malatesta group (for references see Pusztai & Bardocz 2006), may also be taken as a first indication of possible harmful effects that should make follow-up studies mandatory.

Changes in blood cells and blood protein levels in GM-fed animals may also suggest serious health problems, including

disturbances in erithropoiesis, blood protein synthesis and the immune system. Thus, measurement of immune responsiveness could be a useful follow-up study when blood cell counts show significant differences in lymphocyte numbers that may point to one of the potentially serious hazards of the ingestion of GM foodstuffs (e.g. see our GM potato studies, Table 2). This is a particularly useful method because it is in general clinical use and could therefore be easily carried out with humans. Although no hormone assays were performed on rats fed GM or non-GM diets in our GM potato study, the consistently strong pancreatic growth stimulated by GM potato diets in the feeding studies suggests that this possibly was the result of the release of CCK (cholecystokinin) or some other humoral growth factor from the duodenum by an unknown growth/proliferative signal only found in the GM potatoes. Again, GNA (*Galanthus nivalis* lectin) could not be responsible for this because it does not stimulate the enlargement of the pancreas when fed to rats in its original source (Pusztai et al. 1990).

The measurement of circulating insulin levels after ingestion of GM diets would also be a good indicator for possible disturbances in the general metabolic state of the animals, particularly as insulin assays can be easily done on humans. Changes in blood basophile counts may also suggest possible problems of allergenicity that need to be followed up by more dynamic studies. Although the recommended decision-tree approach is a useful start to look at the allergenic potential of the GM crop, the criteria used in this, such as the lack of structural similarities of the GM protein to known allergens, the lack of glycosylation, small molecular size, or the *in vitro* digestibility of the GM protein, etc., are not sufficiently decisive to exclude the possibility that the GM protein is an allergen. The development of delayed hyper-sensitivity reaction found recently in GM peas expressing the kidney bean α-amylase inhibitor gene has demonstrated that proteins that are not

known to be allergens in the original plant source can develop allergenic reactivity when their genes are transferred to other plant species by genetic engineering, even in the case of closely related species (Prescott et al. 2005). Finding immune-reactive antibodies to GM proteins in blood circulation, particularly of IgE-type, in humans or animals should, of course, be strong evidence for the occurrence of immune/allergenic reactions. Although there is at present no satisfactory animal model for allergenicity testing of GM proteins, immunisation studies in brown Norway rats (*Rattus norvegicus*) show some promise.

Chapter 5

Problems and Perspectives

Compositional studies and animal tests are but the first steps in GM risk assessment. Next, long-term, preferably lifetime-long metabolic, immune and reproduction studies with both male and female laboratory and other animal species should also be conducted under controlled conditions. However, setting up proper protocols for these is a task that has not been accomplished yet. If none of the short- or long-term risk assessment tests on animals show harm, only then could the safety of the GM food be further tested in double-blind placebo-controlled clinical studies with human volunteers. However, it should be pointed out that most clinical studies rely on volunteers in a reasonably good state of health even though any possibly harmful effects of GM foods are expected to be more serious with the old, young and the diseased. Thus, even the results of human clinical investigations may not be representative for the whole population, particularly when it is considered that, according to some estimates, up to 40% of the population may suffer from some sort of disease of the gastrointestinal tract. It also has to be taken into consideration that because it is an irreversible technology once a GM crop is generally grown on the land and foods based on these are released into the human food chain and included in animal rations, its removal or recall will become nearly impossible.

5.1 Effects of transgenic plant DNA

In addition to the changes in protein/metabolite profiles and the possible formation of new toxins and allergens in the plant resulting from the unanticipated effects of transgene insertion and the destabilisation of the recipient genome and the interference with the expression of the plant's own genes, the effects of transgenic plant DNA should also be considered. Thus, it is essential in any risk assessment protocol to determine in humans/animals ingesting GM foods whether appreciable amounts of the DNA vector construct used for developing the GM plant survive in the gut in functional form, whether they are taken up and integrated into the genome of the individual, and what, if any, effects the foreign transgenic DNA will have on them.

Chapter 6

GM DNA Safety Studies in the Gastrointestinal Tract

The first task is to trace the GM DNA used for the development of the GM crop, such as the Bt toxin-expressing maize lines, through the intestinal tract, measure the proportion of the construct DNA surviving in functional form, establish by appropriate methods whether it is absorbed by the gut epithelial cells or by gut bacteria and integrated into the genome of these cells and whether they will express the transgene. Next, it has to be shown whether the GM DNA is absorbed into the systemic circulation and taken up by cells of body organs. In addition, it has to be investigated whether the GM DNA can pass into the placenta in pregnant females, foetus and brain, and, if so, what the biological consequences are.

In these investigations, special emphasis should be laid on whether parts of the DNA constructs, particularly the promoter, such as the cauliflower mosaic virus 35s (CaMV 35s) are taken up by the gut and have biological effects. Obviously, as discussed in previous sections, it is of particular relevance whether the Bt toxin expressed in the GM plant has any harmful effect on the gut, body organs and the immune system. When an antibiotic resistance gene is used in the DNA construct as a selection marker gene, one of the most important questions that the risk assessment protocol will have to answer is whether this antibiotic resistance gene can transform gut bacteria *in vivo*. This has become highly pertinent since it was shown that functional

DNA constructs used in the development of GM soybean survived in sufficient quantities in human volunteers and were found to be taken up by the bacteria in the gut (Netherwood et al. 2004 and also see Pusztai & Bardocz 2006).

Chapter 7

Final General Considerations and Conclusions

In the absence of safety studies, the lack of evidence that GM food is unsafe cannot be interpreted as proof that it is safe, particularly as all well-designed GM safety studies published to date and carried out independently of the biotechnology industry have demonstrated potentially worrisome biological effects of GM food as referred to in this paper and recently documented by Smith (2007). Unfortunately, the regulators have largely ignored these.

In the light of these problems one can ask whether the future of the present generation of GM crops/foods rests on solid scientific foundations. If not, as it appears, the question is whether it is needed at all, particularly as according to the FAO apparently there is sufficient food for feeding the world population, providing that it is evenly and properly distributed. It is possible that GM foods may be needed in future but should such a need arise we ought to first find more reliable and safer genetic transformation techniques for the development of GM crops. However, even then, their safety must be rigorously tested with biological methods, as without proper, transparent, inclusive, and independent testing the sceptical public is unlikely to be convinced of their safety and accept any present-day or future GM foods.

Annex

Recent Studies on Human Health Impacts of GM Crops

Studies on rodent reproduction

Of all the issues of GM safety the most important for the future is whether the consumption of GM crops could have any effect on human and animal reproduction. Many scientists and certain sections of society have been demanding that such studies with GM crops must be performed right from the beginning of the introduction and commercialisation of GM food crops. Despite the considerable resistance of the biotechnology industry to performing or even financing such studies, two recent independent reproduction studies have now been carried out. Their results have given us reasons to be worried.

1. GM soy — A senior Russian scientist, Irina Ermakova, published a rat reproductive study in which she examined the effect of glyphosate-resistant (RR) GM soybean seeds fed to pregnant female rats on the number and weight of pups delivered (Ermakova 2006). The study was originally published in Russian, and was heavily criticised for using coated seeds ready for planting instead of beans suitable for feed. The control non-GM soybean was not the isogenic parent line, either. However, because of the possible serious implications of the results of this study for humans and animals it should have been repeated and possibly verified by other scientists with the correct GM soybean diets. Indeed, she has repeatedly pleaded for this but no one dared to try to reproduce her experiments.

In her study rats were fed with laboratory rat chow and this diet was complemented with GM or conventional soybean for two weeks before mating, during the pregnancy and during suckling and the body mass and the number of pups were observed (Table A1). The data indicated that on the GM soybean-supplemented rat chow significantly fewer pups were born, and with smaller body mass, than on the control non-GM soybeans.

Table A1. **The reproduction performance of rats fed laboratory chow (control), traditional soybeans, or glyphosate-resistant soybeans (GM)**

Diet	Females pregnant/ delivers	No. of pups born/ survived	Died	Body mass (g)
Control	6/4	44/41	3	10-20g: 6% 20-30g: 44% 30-40g: 38%
Traditional soy	3/3	33/30	3	10-20g: 7% 20-30g: 73% 30-40g: 20%
GM soy	6/4	45/20	25	10-20g: 36% 20-30g: 41% 30-40g: 23%

Brasil et al. (2009) found that rats fed on GM soy showed altered morphology of the uterus and the ovaries: had greater volume density of endometrial glanular epithelium, reduced follicle number and increased corpus luteum numbers (a tendency to

abort or less of a chance to get pregnant). Although the GM diet was not supplemented with cysteine as the other diets, and it is difficult to assess if the results were due to consumption of the transgenic soy itself or were due to the presence of glyphosate (and/or AMPA), always present in GM seeds, the findings are disturbing and warrant further studies.

A recent study found that GM soy-fed animals have developed hair inside the oral cavity more often than control (Baranov et al. 2010).

2. *GM maize* — A study entitled "*Biological effects of transgenic maize NK603xMON810 fed in long term reproduction studies in mice*" authored by Dr A Velimirov, Dr C Binter, Univ. Prof. Dr J Zentek, with scientific contributions by N Cyran, Dr C Gülly, Dr S Handl, G Hofstätter, F. Meyer, Dr M Skalicky and Prof. Dr R Steinborn was published by the Austrian Ministries of Agriculture and Health in October 2008.

The aim of this long-term feeding study was to examine the effects on longevity and reproduction of mice fed on diets containing a stacked GM crop, the NK603xMON810 (a glyphosate-tolerant and insect-resistant) corn. Three different experiments were performed:

- a multi-generation study (MGS),
- a reproductive study by continuous breeding (RACB) and
- a life-term feeding study (LTS).

All experiments were performed with the laboratory mice-strain OF1. The test diets contained either 33% NK603 x MON810 maize (GM), or the non-GM corn of a near-isogenic line (ISO). Both these corn lines were grown under identical conditions and harvested in Canada in 2005, with a 75 m isolation distance.

However, because of some cross-contamination of the control line with the GM corn, in the MGS experiment a third group fed with a diet based on non-GM corn cultivated in Austria (REF) was also included. All diets were supplemented with all necessary nutrients (vitamins, minerals, etc.), contained 25% protein and had equal energy contents.

In the LTS experiment the average life span of mice fed on diets containing the three different maize varieties was followed. No statistically significant differences in the survival of the three groups of mice were found (Table A2).

Table A2. **Differences in the life span of OF1 mice fed on different maize diets**

Group	(month)
REF	15.7
ISO	16.3
GM	17.0

The common cause of death was cancer (leucosis).

The MGS experiment had a multi-generation design in which four generations of mice were produced. The outcome of four pregnancies of 24 pairs of males and females was examined and the number and body mass of the pups were followed. From the F0 generation on all animals were fed the 33% GM, ISO or REF diets until the F4 litters were produced.

In the MGS experiment in the parental body mass there were no statistically significant differences. The production parameters showed that the average litter size and body mass as well as the number of weaned pups were best in the ISO group. More

pups were born on the ISO diet (1,035) than on the GM (844), and litter sizes were also smaller on GM, but not significantly. In all the four generations about twice as many pups died before weaning in the GM group (14.6%) compared to the ISO group (7.4%).

From the F2, F3 and F4 generations 5-5 male and female pups were randomly selected out, and their organ weights examined. Generally, there were no significant differences between organ weights, except for the kidneys. However, on some of the organs electron microscopic ultrastructural investigations were performed to detect any possible changes at the organ and cell level. Gene expression patterns were also compared by micro array expression profiles at the intestine and feed interface and by real time PCR (polymerase chain reaction).

The results of histological investigations by electron microscopy of cell nuclei revealed differences in fibrillar centres, dense fibrillar components and in the pore density of hepatocytes, and cells from the spleen and pancreas. This indicates metabolic differences caused by the GM diet in the cell nucleus of some internal organs. Micro array investigations of the small bowel tissue also showed significant differences between the GM- and non-GM-fed groups. Analyses of the metabolic pathways indicated differences in the activity of the interleukin-signalling pathway, cholesterol biosynthesis and in protein synthesis, metabolism and post-synthetic processing of proteins.

The RACB experiment followed the output of 24 breeding pairs over four mating and pregnancies.

All the females fed the ISO line maize got pregnant all the time, while infertility of more females was observed in the GM maize-fed group, and this became significant by the fourth generation

(Table A3). The number of pups was always fewer on GM, and the litter size was also smaller, but not statistically significantly for the first two deliveries, but it become significant for the 3rd and 4th litters (Table A3).

Table A3. **The performace of females over 4 consecutive mating and pregnancies (F1-F4) on the GM maize (GM) or on its isogenic parent line (ISO)**

Diet:	ISO	GM	ISO	GM	ISO	GM	ISO	GM
	F1		F2		F3		F4	
Pregnant	24	23	24	23	24	22	24	20
Delivers	24	23	24	23	24	17	24	19
Pups	216	189	260	245	286	213	273	197
Dead	16	2	19	19	32	2	38	24
Alive	200	187	241	226	254	207	235	173

The RACB study showed time- and mating-related negative reproductive effects of the GM maize.

To summarise, in these experiments the GM maize had no influence on the life span of mice, but influenced their reproductive performance. Fewer pups with smaller body mass were produced by mothers fed the GM-containing diet, and more animals died before weaning. In the RACB study the differences become statistically significant with the 3rd and 4th litters. Although it is impossible to extrapolate from animal experiments to the human condition the results of these experiments demand that similar reproduction experiments must be incorporated in safety analysis protocols with all GM crops before they are commercialised. These results are all the more important because they have been obtained with GM crops already approved in the EU and several other countries.

This preliminary study has been criticised with regard to its statistical analysis. However, its findings remain a serious cause of concern that needs to be investigated further.

The question of human/animal safety of glyphosate

Glyphosate is not a genetically modified product but because its use in agriculture is inseparable from the cultivation of herbicide-tolerant GM crops in a particular technology package, its effects on health need to be examined also with that of the glyphosate-resistant GM crops.

Although the declared aim of the introduction of glyphosate-resistant GM crops was that with these crops the amount of herbicide sprayed on the land should decrease, due to the ever-increasing area of cultivation of glyphosate-resistant Roundup Ready (RR) GM crops, the use of glyphosate has in fact increased (Benbrook 2004, 2009). The glyphosate-containing sprays destroy all weeds but the growth of the glyphosate-resistant GM crop is protected regardless of how much glyphosate is sprayed on to the land. To make sure that all weeds are destroyed the use of glyphosate and consequently the glyphosate load of the land has been substantially increasing after the first few years of a slight reduction (Benbrook 2004, 2009).

This has happened despite the ever-increasing number of publications showing that glyphosate has many serious and detrimental effects on the environment and biodiversity (Relyea 2005) with the development of herbicide-resistant weeds (Duke 2005; Owen and Zelaya 2005; Warwick et al. 2007; Loux et al. 2007; Zelaya et al. 2007).

There is also an urgent need to consider the potentially seriously damaging effects of this total herbicide on human/animal health, particularly as it is used in large amounts. Indeed, there are a

number of recently published papers that all indicate possible damaging effects of glyphosate on health and reproduction which need to be taken seriously.

By building on previous work the findings of French scientists (Marc et al. 2005) have confirmed and extended their previous results by showing that the main ingredient of commercial Roundup formulations, glyphosate, in a milimolar concentration range, particularly when used together with the obligatory polyoxyethylene amine surfactant, inhibited the transcription of one of the enzymes involved in hatching of sea urchin embryos and therefore significantly delayed their hatching. When it is considered that farm workers inhale commercial herbicide sprays in which the active ingredient concentration exceeds by about 25 times of that used in the transcription inhibition studies by the French scientists, health concerns due to the use of glyphosate must be acute.

In another study it was shown that in the oral treatment of Wistar rats with increasing concentrations of the herbicide Glyphosate-Biocarb, a formulation used in many countries such as Brazil, the number of Kupffer cells in hepatic sinusoids increased, followed by large deposition of reticulin fibres and the leakage of hepatic aspartate-aminotransferase and alanine-aminotransferase into the circulation, indicating hepatic damage in these animals (Benedetti et al. 2004).

The work of another group of French researchers showed that glyphosate, particularly as used together with polyoxyethylene amine surfactant in Roundup Ready formulations, was toxic to human placental JEG3 cells at concentrations lower than that used in agricultural practices. Even at subtoxic concentrations RR was an endocrine disruptor on aromatase activity and its mRNA level as glyphosate interacted with the active site of the purified enzyme (Richard et al. 2005; Benachour et al. 2007). It

is possible that the pregnancy problems in agricultural workers using Roundup may be traced back to the exposure to this herbicide (Savitz et al. 2000).

All these findings indicate that there is an urgent need to carry out systematic and direct studies, independent of the biotech industry, on the short- and long-term effects on animal (and human) health of exposure to glyphosate and its more effective commercial formulations alone and/or preferably in combination with the appropriate GM crop. With the presently cultivated huge areas of Roundup Ready crops and the anticipated even-larger future extensions of this glyphosate-dependent GM crop technology the potential danger for animal/human health needs to be dealt with in advance and not if or when it occurs. If we consider that RR soybeans may in themselves damage reproduction, a combination of the similar, possibly synergistic effects of the GM crop and glyphosate could be a potential disaster waiting to happen.

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No. 14 Potential Health Effects of Foods Derived from Genetically Modified Plants: What Are the Issues? *by Arpad Pusztai and Susan Bardocz* (48 pages)

This paper examines the potential health effects of foods derived from genetically modified (GM) plants. While such an important topic, the database on the likely biological effects of GM foods is woefully inadequate.

In the absence of safety studies, the lack of evidence that GM food is unsafe cannot be interpreted as proof that it is safe, particularly as all well-designed GM safety studies published to date and carried out independently of the biotechnology industry have demonstrated potentially worrisome biological effects of GM foods.

However, the complexity of GM foods makes their biological testing difficult. The authors propose a suggested protocol for GM crop/food health risk assessment, which uses comprehensive toxicological/nutritional methods that will equally be applicable to scientifically examine the veracity of the claimed benefits of genetic manipulation, and screen for its unintended and potentially harmful consequences for human/animal health.

Dr Arpad Pusztai *is a Fellow of the Royal Society of Edinburgh (FRSE) and holds a BSc in Chemistry and a PhD in Physiology and Biochemistry. Pusztai was formerly Head of Protein Chemistry at the Rowett Research Institute, Aberdeen, Scotland. His main research interest is biologically active food components – lectins, plant anti-nutrients, and the effect of GMOs on animal and human health. His research also focuses on cancer prevention by dietary means. He has published over 300 primary scientific papers and nine scientific books. He is holder of the Stilmark Medal; Honorary Professor of the University of Tartu, Estonia; Leverhulm Fellow; Auber Bequest Fellow; and Recipient of the Federation of German Scientists' Whistleblower Award 2005.*

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Both received the Pro Biocultura Prize in 2008 in Hungary, and the Stuttgart Peace Prize in 2009.

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