Genetically Modified Peas Caused
Dangerous Immune Response in Mice
Other GM Foods are Not Tested for This and May Be Harmful
Spilling the Beans, November – December 2005
By Jeffrey M. Smith

SUMMARY

Genetically modified (GM) peas under development created immune responses in mice, suggesting that they may also create serious allergic reactions in people. The peas had been inserted with a gene from kidney beans, which creates a protein that acts as a pesticide. When this protein is produced naturally in beans, it does not elicit a response from mice. When produced in the GM peas, however, it did cause a reaction. Using sensitive testing methods, scientists discovered subtle differences between the bean and the GM proteins – the added sugar chains were slightly different. They speculate that this difference caused the immune reactions. Based on the results of the study, the Australian developers abandoned their 10-year, $2 million project.

This study reveals serious and potentially deadly flaws in the regulations and assessments used to approve GM foods. GM crops on the market, like corn and soybeans, were never tested for immune responses using animals and never subjected to a similar analysis of their proteins. Thus, the transgenic proteins in GM foods may have subtle undetected differences that are causing health problems. It is sobering to note that if the GM peas were tested with only the methods used on soy and corn, it likely would have been approved as well.

The approvals of genetically modified (GM) food are largely based on four pillars. The first is the reliance on a long list of assumptions about food safety. Unfortunately, these assumptions are principally based on what was known about genetics 40 years ago, and many have been overturned.

The second pillar is that safety research on GM foods is primarily controlled by industry. Much of it is secret, and the few studies that have been made public are largely superficial – designed not to contradict the assumptions.

The third pillar is an ineffective regulatory system, often hijacked by people with close ties to industry. They accept unscientific assumptions and poor research, and ignore adverse findings.

The fourth pillar is spin – merciless, relentless, in-your-face spin – that magically flips facts to proclaim their opposite. Examples are forthcoming.

On November 17, those pillars took a considerable beating. GM peas under development were evaluated by tests normally applied to medicine – not to GM food. The peas created a dangerous immune response in mice which, if found in humans, might be life threatening. The 10-year pea project, costing over $2 million dollars (US), was abandoned. If those same peas had been evaluated with tests used for other GM crops, however, they could have sailed through the approval process anywhere in the world.

The peas were developed by Australian scientists at the Commonwealth Scientific and Industrial Research Organization (CSIRO) to assist the country’s $100 million pea harvest. They targeted the pea weevil, a pest that takes a hefty bite – up to 30% – out of yields. But if weevil larvae were to bite a GM pea plant, they would starve to death. That’s because the pea contains a protein called alpha-amylase inhibitor, an anti-nutrient that interferes with the bugs’ digestion. That protein is produced from a gene normally found in “common” (kidney) beans and when fully cooked is safe for humans. Scientists spliced the gene into peas, figuring it would be safe there as well.
Safety Assessment

Researchers checked the sequence of the kidney bean gene after it was inserted into the pea's DNA. It hadn't changed during the insertion process, but this is not always the case. Genes inserted into soybeans and corn, for example, were mutated, fragmented or truncated, and several appeared to rearrange over time. Remarkably, safety assessments don't always require that the transgene's sequence is determined. In the US, for example, gene sequencing is not part of the approval process.

If a gene’s sequence changes, it might create proteins with the wrong amino acids. But analyzing the sequence of amino acids is also not required. According to Bill Freese, a research analyst at Friends of the Earth, "At present, the standard practice is to sequence just 5 to 25 amino acids, – even if the protein has more than 600 in total. They assume that the rest are fine. Most of GM foods on the market have never had their novel proteins sequenced. The GM peas, however, were checked. The protein produced in the peas did have the same amino acid sequence as the original in the beans."

Scientists at the John Curtin School of Medical Research in Canberra tested the peas on mice, to see if they elicited an immune or allergic response. Groups of mice were fed a commercial diet and also given GM peas, non-GM peas or beans, twice a week for four weeks. After the feeding period, the mice were tested with a battery of immune response tests. Reactions were elicited only in mice that were fed GM peas. Specifically, injections of the GM protein into the footpad resulted in significant swelling; when introduced into the trachea, it caused mild lung damage and tissue inflammation (similar to asthma in humans). Lymph nodes also responded to the presence of GM protein. The researchers did not check for allergies, per se, but used tests that they say are predictive of allergenic sensitivity.

Simon Hogan, the lead researcher for the study, said, “The study is fairly conclusive.” He added, “These types of assays are commonly used in medical research.” They have not, however, been used in safety assessments for GM foods on the market. Even though experts with the Food and Agriculture Organization and the World Health Organization (FAO-WHO) recommend using animal studies to test for allergies, no government actually requires it, and it is almost never done.

According to immunologist Ricki Helms, who has served on several expert panels examining the potential allergenicity of GM foods, “Animal models can contribute to the evaluation of allergenicity but cannot offer absolute certainty.” This lack of certainty is a common justification by industry scientists for why they don’t use animal allergy studies as part of their assessments. The two methods that they prefer, however, also lack certainty.

In the first method, the transgenic proteins are put into test tubes with digestive enzymes and acid to measure how quickly they are broken down. This test is based on the fact that allergenic proteins often – but not always – break down slowly in the stomach and intestines. The problem is that test tube studies do not accurately predict what happens inside humans. And even if they did, a protein that is broken down quickly may still cause allergies. Thus, potentially harmful allergenic proteins can pass this test. In the other method, researchers search databases to see if the amino acid sequences of the transgenic protein are similar to known allergens. This method also offers no guarantees – not all allergenic sequences have been identified and allergenic proteins can certainly pass this test as well. In spite of the shortcomings of these two methods, the FAO-WHO recommends them as part of the assessment and offers specific criteria for each. Regulators can ignore those recommendations. The GM soy, corn, and papaya on the market, for example, fail the FAO-WHO criteria. GM pea developer TJ Higgins told me that when his peas were evaluated for protein stability and amino acid similarity, they were “borderline”.

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In addition to creating an immune response in mice, GM peas also increased their immune system’s sensitivity to other substances. For example, mice fed the non-GM peas showed no response to egg albumin. The GM-fed mice did have an immune reaction to the albumin, as well as to three other substances tested. The ability of one food to increase the sensitivity to other foods is called an “adjuvant” response. It suggests that humans fed GM peas might develop allergic or immune responses to a wide range of other foods. According to Judy Carman, an epidemiologist and the director of The Institute of Health and Environmental Research in Australia, “If a GM food was introduced onto supermarket shelves and caused an immune reaction, it would be very difficult to find the culprit, particularly if it caused reactions to other, different foods, as this GM pea was found to do.” As you probably guessed, adjuvant testing is not part of any normal GM food approval process.

Independent researchers did test a GM product both for immune and adjuvant responses using mice.[2] They tested one type of Bt-toxin (Cry1Ac) found in GM cotton, which is similar to Bt toxins produced in several varieties of GM corn (Cry1Ab). Like the alpha-amylase inhibitor in peas, Bt toxins kill pests. Not only did the Cry1Ac produce a significant immune response, it elicited an adjuvant response as well. Another study showed that Bt toxins in spray form caused antibody responses and allergic symptoms in farm workers and others.[3] Taken together, these studies overturned several safety assumptions. In spite of claims to the contrary, Bt is not fully destroyed during digestion, it is bioactive in mammals (including humans), and current safety assessments are inadequate. By the time this research was done, Bt crops were already planted on millions of acres. Withdrawing them will apparently require more evidence of human harm.

Another assumption used often by the biotech industry is that cooking their GM crop will destroy its potential to create allergies. Cooking can change the protein’s structure, or ‘denature’ it. Proponents have claimed that when Bt is denatured, it is no longer effective as a pesticide and will therefore no longer be allergenic. The GM peas were boiled for 20 minutes. After cooking, the alpha-amylase inhibitor was denatured and was no longer effective in protecting against weevils. Industry assumptions notwithstanding, the cooked pea protein still caused an immune response in mice.

**Tracking Down the Cause**

What was it about the transgenic protein in the GM peas that caused it to affect the mice, when the “same” protein in its natural form in kidney beans did not? This question intrigued Hogan and his team. He said their “scientific, inquisitive nature” led them to look for subtle differences in the protein structure. Although the amino acid sequences of the GM and non-GM proteins were identical, that doesn’t tell the whole story. Amino acids are the building blocks, and according to Carman, “If you knock down a house and then study the pile of bricks, it won’t describe the house. Similarly, the amino acids don’t reveal the structure, shape and unique characteristics of the protein.”

David Schubert of The Salk Institute for Biological Studies points out that in higher organisms such as plants and animals, “each cell type expresses a unique repertoire of enzymes capable of modifying protein structure.” Depending on where they are, a protein may have added molecular chains, “such as phosphate, sulfate, sugars, or lipids,”[4] which alter their function. In a 2002 article in Nature Biotechnology, Schubert argues, “With our current state of knowledge, however, there is no way of predicting either the modifications or their biological effects.”[5]

We can, however, detect such modifications. For instance, when sugar chains are added to proteins, this process, known as glycosylation, can influence allergic responses. Hogan’s team used the sensitive MALDI-TOF mass spectrometry technique, and confirmed that the GM and non-GM proteins had slightly different glycosylation patterns. They believe that these subtle differences may be the cause of the immune responses.
Here again is more bad news. The MALDI-TOF method is not required and has rarely been used for the safety assessments of GM food already on the market. According to Doug Gurian-Sherman, a senior scientist at the Center for Food Safety and formerly at the US Environmental Protection Agency, the differences in glycosylation between the GM pea protein and the non-GM counterpart in kidney beans "would not be detected by the tests that are currently required by US regulatory agencies." If companies do assess differences in protein, it is typically by "gel" tests, which won't reveal the subtle differences in glycosylation that may have caused the immune response. In fact, TJ Higgins looked at gel tests in the 1990s and did not see any difference between the GM and non-GM proteins.

**Approvals Rely on Dangerous Assumptions**

Industry's assumption that proteins will act in a predictable manner in a new organism has been pivotal and it certainly helped them get GM foods approved. Take, for example, their acute toxicity tests where they feed rodents just the isolated protein. They don't necessarily extract the protein from the GM crop. Instead, they almost always produce the protein using genetically engineered bacteria, since it is cheaper and easier. They then test the animals' reactions to this surrogate protein, assuming that if animals don't react to the bacterial form, then they – and humans – won't react to the plant form.

These tests, therefore, avoid measuring the health impact of any changes in the protein in the GM crops we actually consume. The pea study revealed that significant, potentially deadly changes occurred when the gene from kidney beans is inserted into peas' closely related species. But the genes put into GM foods already on the market cross entire kingdoms. Bacterial genes are spliced into GM soybeans, corn, cotton and canola, and viral genes are inserted into papaya, zucchini and crook neck squash. How these crops will alter bacterial proteins is anyone's guess – unfortunately.

Glycosylation is related to another possible problem. Proteins are sometimes folded in precise formations by specialized "chaperone" folders inside the cell. If a novel protein appears in a species where it has never before existed, the chaperone folders might not do their jobs right. A mis-folded protein can be quite dangerous. In the case of the peas, the difference in glycosylation means that the protein is almost certainly a different shape, but there may be other shape-related issues that contributed to the immune reaction in mice.

In addition to changes in the target protein, side-effects from the gene insertion process can create toxins, allergens, or adjuvants. Earlier unpublished tests on the GM peas, for example, showed a doubling of trypsin inhibitor, a known allergen, and a fourfold increase in an anti-nutrient called a lectin. These or some other unknown change in the peas' composition might have played a part in increasing the immune responsiveness of the mice. In short, we don't really know why genetically engineered peas are more dangerous. We do know that the body interprets something in the pea as foreign, different, and offensive, and it reacts accordingly. On the other hand, all GM foods, by definition, have something foreign and different. It makes sense that the immune systems in humans or animals that have never eaten these novel substances before may react to them.

A handful of studies that have looked for immune responses have found them. In 1995, a Brazil nut gene inserted into soy DNA created an allergic reaction in human blood, and the project was stopped.[6] In 1998, a GM potato caused immune system damage in rats, among other problems.[7] Studies implicating the Bt-toxin have already been cited above. On top of those, a Bt potato caused abnormal and excessive cell growth in the small intestine of mice.[8] A feeding study with Bt corn called MON 863 caused a significant increase in male rats of three types of blood cells: basophils, lymphocytes (22%) and total white cell counts (20%).[9] This strongly suggests that consuming GM
corn caused changes in the immune system. According to GM safety research expert Arpad Pusztai, “A consistent feature of all the studies done, published or unpublished, including MON 863, indicates major problems with changes in the immune status of animals fed on various GM crops/foods, the latest example of this coming from the GM pea research in Australia.”[10]

We don’t have the advantage of sophisticated human clinical trials, so our evidence for immune reactions in humans is limited and preliminary. For example,

- Soy allergies jumped 50% in the UK just after GM soy was introduced;[11]
- An expert panel in the US determined that there was a moderate likelihood that StarLink Bt corn contained a human allergen; [12]
- Filipinos living next to Bt cornfields developed severe symptoms three years in a row – only while the corn was pollinating; [13] and
- A recent health report claims that Indian farm workers exposed to Bt cotton developed moderate or severe allergic reactions. [14]

Certainly allergies and asthma are on the rise in many nations, but at this point, we can only guess whether GM food plays a part. The pea study provides a clue how it might be related.

Spin

No report on GM research is complete without the fourth pillar – spin. How do you suppose the industry will respond to these pea findings that expose an inept regulatory process that under normal test procedures would almost certainly have allowed these peas onto the market? Consider the response of GM pea developer TJ Higgins, “I think that this shows that the regulatory system works.”[15]

But before we condemn Higgins as a spin master, we must consider that he might have been the victim of spin himself. I have spoken with many biotech scientists, people of high integrity and a strong belief in what they are doing, who have absolutely no idea about the wretched state of regulations or safety assessments. They focus on their own area of expertise and have bought the industry spin about safety.

I called Higgins in Australia and quizzed him on the state of affairs of regulations and assessments of other GM foods. He said, “I didn’t feel that we were breaking particularly new ground. . . . We were following basically the recommendations for a proper risk assessment and I feel it is typical of the kinds of assessments that have been done for other GM crops around the world.” Lead researcher Simon Hogan told me the same thing. I pointed out to both scientists several unique features of their study and challenged them to name a single GM food on the market that has had the same level of tests. They couldn’t come up with any, but they were sure that these tests were done. They’re in for a shock.

Years ago, a pro-GM scientist with high integrity also had confidence in GM regulators and industry scientists. Higgins had asked him to coauthor a rat feeding study with his GM peas, because the scientist was the world’s most qualified person to do the work. This scientist was also awarded a UK government research grant to create a rigorous safety assessment protocol, which was to be required in the UK and eventually the EU. One day, he was asked to review several confidential industry studies that were used to get GM foods approved. He told me that reading those studies was perhaps the greatest shock of his life. The studies were so superficial, so poorly done, he realized that industry was doing as little as possible to get their foods on the market as quickly as possible. They were not doing safety studies. A few weeks later, this scientist confirmed that a GM
potato he was working on caused considerable damage in rats, including damage to their immune systems. Unlike Higgins, this man knew full well that his dangerous potatoes could have sailed through industry “safety” studies and onto plates around the world. He went public with his concerns.

The scientist’s name is Arpad Pusztai, and he paid dearly for his integrity. At the hands of a pro-GM government and industry-backed scientists, he was fired, silenced with threats of a lawsuit and mercilessly attacked. It was biotech spin at its “finest”.

Pusztai has since published his potato research and is now considered a top expert in GM safety testing. He just published a review of all the peer-reviewed assessments and has studied nearly every industry submission. He assured me that the GM pea immune study does, in fact, break new ground. Likewise, Professor G.E. Seralini, who has officially reviewed all of the submissions to Europe as well as all the commentaries on the submissions, wrote me: “To my knowledge, no GM plant on the market has undergone such detailed experiments to assess allergenicity.” Doug Gurian-Sherman and Bill Freese, who are experts on submissions to US authorities, also acknowledge that industry immune studies are considerably weaker than the pea study. And Judy Carman, who has studied the GM applications to Australia and New Zealand, concurs. In fact, Marc Rothenberg, who is a co-author of the pea study and was also on the expert panel that analyzed the allergenicity of StarLink corn, said of the pea research, "It was very unique. It was much more extensive and rigorous than what was previously done."

It appears that the director of the pea assessment (Higgins) and the lead researcher in the study (Hogan) were uninformed about the state of affairs in GM crop assessments. They appeared to be unaware that their study was actually a breakthrough. If Higgins had known that his peas would likely have been approved if they were tested only with the less expensive, less rigorous research typically used for GM crops, he might not be so quick to defend GM regulations worldwide.

I sent Higgins a peer-reviewed paper called “Safety Testing and Regulation of Genetically Engineered Foods.”[16] It not only shreds the assessment process in the US, it also presents a case study of how one GM corn variety gained approval based on wrong assumptions, poor research, ineffective regulations and spin – the four pillars. I wrote Higgins, “I am confident that after reading this article, you will agree with the authors that the tests used for approving this Bt corn, as well as other varieties, were not sufficient to protect the public.” I asked that he then make corrective statements about GM regulations. More importantly, Higgins is The Deputy Chief of CSIRO Plant Industry. If he acknowledges that even one GM crop has not been thoroughly tested, I asked him to propose that his organization immediately conduct rigorous safety assessments on that crop to protect the health of consumers. I understand that CSIRO has business relationships with Bayer Crop Science and Monsanto. The close ties between research organizations and the biotech industry has, in many instances, stifled criticism of GM crops and even stopped important research from being conducted. I am hopeful that Higgins, who pioneered new safety assessments on GM food crops and canceled his own 10-year pea project based on the findings, will direct his institution to similarly break new ground. I will be sure to report his response in future columns.

In the meantime, my Institute for Responsible Technology is passing the hat to collect money to fund independent research on the GM foods already on the market. We are not willing to wait.

Jeffrey M. Smith is the author of Seeds of Deception, and is working with a team of international scientists to compile all known risks of GM foods.