

Dead end developments – lessons learned from unsuccessful GMO

Broder Breckling

*(Chair for Landscape Ecology, University of Vechta, Germany –
bbreckling@iuw.uni-vechta.de)*

Introduction

In 1994, the “FlavrSavr” tomato was commercialised as the first genetically modified food for human consumption on the US market – and it turned out to be a failure. Was it a rare exception contrasting an overall successful trend in the development of genetically modified organisms – or does it represent a typical situation? To obtain a realistic impression about the technology, it is necessary not only to count the cases where a GMO so far met the expectations of economic gains. It is also required to see the cases that did not work. Since the reasons that rendered GMO unsuccessful are only partly documented in the scientific literature, a targeted search was required. A GMO is considered as a dead end development if it remained far below the initially expected application potential and either never became commercialised or was withdrawn from the market after economic damage occurred.

The tomato disappointment was documented by Martineau 2001, who participated in the development. Durable and aromatic fruits were the promise – resulting from blocking the expression of an enzyme involved in natural fruit maturation: The genetic information for polygalacturonase was inserted in reverse order, leading to a suppression of the formation of this enzyme. Only three years later, the transgenic trait was abandoned. Conventionally bred varieties proved to be superior. Since then, a large and partly unknown number of other GMO failed in practice. For an estimation how realistic future promises could be, it is quite useful to look back what happened to some of the previous attempts and promises.

The question is, whether there are underlying pattern which allow some indication of trends to expect by understanding the causes for cancelled developments. This could help avoiding unnecessary investment of both, public and private funds. We put forward the hypothesis, that there is not a typical threshold level that separates successful and disappointing traits. The reasons for failure cover the complete spectrum of possibilities, involving technical, genetic, ecological and agronomic as well as social and economic factors. Examples of failure on the different levels are given.

Prominent cases of unsuccessful GMO

After more than fifteen years of commercial use, the number of profitable GM traits is still limited compared to the numerous attempts in research and development. It mainly comprises herbicide resistance and insect toxic Bt plants. A small selection of the structurally more diverse abandoned cases is presented in reverse temporal order.

High Lysin maize LY038 (market introduction cancelled in 2009)

The purpose of the genetic modification was to increase the nutrition value of maize as animal feed by raising its content of the amino acid lysine. This was achieved by inserting a gene from *Corynebacterium glutamicum*. LY038 maize, developed by Renessen, a Monsanto / Cargill subsidiary, had gained admission for commercialisation in the USA. On other globally relevant markets, e.g. Canada, Japan, Australia and New Zealand the variety was also admitted for feed. The GM Crop database of the Centre for Environmental Risk Assessment (2008) lists notification documents. In a statement of 2005, Heinemann had raised scientific safety concerns. The developers applied for admission also in the European Union. The European Food Safety Authority (EFSA) requested additional data from the company to demonstrate the safety of the product. The applicant was asked to submit data on feeding experiments using processed (cooked) material. So far, only raw material had been tested. Cooked maize has a higher relevance to estimate safety for human consumption, e.g. in case of unintended impurities in processed food. The Bioscience Resource Project (2009) explained: cooking of food with high amounts of free lysine can lead to reactions of the amino acid with sugars, forming 'advanced glycoxidation end-products' (AGEs). They are known to be linked to the etiology of several human diseases, thus a relevant safety issue.

Instead of performing the animal feeding tests and providing the data, the applicant withdrew the application and insisted on a complete return of all documents from the authority. Thus, the safety concerns could not be investigated further (Bottemiller 2009). The withdrawal was said to be due to economic reasons. So, the request of data from a feeding experiment must have made a trait already admitted on major markets economically non-viable? Alternatively, it can be speculated whether a public controversy on health risks after admission might have been an issue.

Weevil resistant pea (development was stopped in 2005)

The purpose of the genetic modification was to protect pea cultivation in Australia against a weevil (*Bruchus pisorum*) which causes considerable damage. A bean-specific anti-nutrient was inserted to pea. The work goes back to approaches made during the 1980ies (Schroeder et al. 1995). The modification was tested to be efficient. Also feeding studies did not indicate problems with product safety. However, additional tests with the purified protein before commercialization caused the unexpected result that mice showed symptoms of inflammation of the lungs when exposed to the substance resulting from genetic modification unlike when exposed to the conventional substance (Young 2005). Further investigations revealed that even though the amino acid sequence of the protein was identical in pea and in beans, the end products differed.

Many proteins receive sugar molecules as attachments. The enzymes which catalyse the connections are to some extent species specific. Such an altered glycosylation pattern occurred and made the transgenic substance more immunogenic. After ten years of development in Australia, the trait was stopped due to these unexpected physiological effects.

Herbicide resistant wheat (market introduction failed in 2004)

Monsanto offers a number of plants which carry a transgenically mediated tolerance to the herbicide Round-up. In the USA, Argentina and Brazil, herbicide resistant soy beans have a very high market share and are commercially successful. To reduce the effort of weed control, also wheat varieties with this resistance were developed to the level of market introduction. In the public, there were environmental concerns e.g. that relying massively on a single herbicide may increase the spread of herbicide resistant weeds (Gurian-Sherman 2003). Crucial for the development, however, became objections from farmers and their organizations in Canada. The Canadian Wheat Board declared that for the moment no way was seen for an efficient segregation of GM and conventional wheat which might cause losses on export markets. It was pointed to consumer resistance in many countries. Monsanto declared to postpone the market introduction of the variety (Nickel 2009).

Triffid Flax (commercialization stopped in 2001 but “re-emerged” as an impurity in 2009)

At the University of Saskatchewan a genetically modified flax was developed with a resistance against ALS. The idea was to allow for higher levels of agrochemical residues from previous crops in the soil – to an extent that conventional flax does not tolerate. Admission was gained in the USA and in Canada. Growers, however, massively resisted – largely for crop purity reasons. Shortly after notification, the variety admission was withdrawn. It had been commercially available for a very short time only (Warick 2001). Almost ten years later, in 2009, GM impurities of Triffid flax in exports from Canada were discovered in Germany. For GMO without admission zero tolerance applies in most countries. Subsequent investigations in various other states around the globe found the same contamination in Canadian flax exports (GM Contamination Register 2010, Schmidt & Breckling, this volume). Many export charges had to be withdrawn leading to high economic losses. How Triffid became a widespread contamination so many years after withdrawal from the market remains an open question.

Interesting is also the name of the variety. It is identical with a 1960ies fiction movie about an imaginary carnivorous plant (Figure 1). The developer, who chose the name, Alan McHughen, served as the founding president of the International Society for Biosafety Research (ISBR). He is currently its treasurer (University of California, Riverside, 2009, spin profiles 2010). No information was found whether he or who else was held liable for the losses that occurred during the attempt to eliminate the widespread impurities from current cultivation.



Fig. 1: Advertisement poster of the triffid movie. Source: <http://en.wikipedia.org/wiki/File:Dayofthetriffids.jpg>

Starlink maize (withdrawn 2000)

This case is probably one of the most dramatic in the history of genetic modification (Bratspies 2003). It caused compensation payments which are estimated to sum up to several hundred millions of dollars (FOEE 2000). The Starlink maize variety, developed by Aventis Crop Science, contained a gene from *Bacillus thuringiensis* to make it toxic for the corn borer and other lepidopteran pests. The toxin was more stable than in other commercially available Bt maize variants. The degradation of the protein in digestive fluids was relatively slower. Admission was gained in the USA for feed only. Though farmers were informed and trained to segregate the maize from harvests for human consumption, Starlink traces were found in many food items with maize ingredients (Cox 2000). Cross-pollination between crops as well as mixing of harvests was likely to play a role in having brought up this impurity. Taco Bell taco shells were the first food in which the unapproved variety was discovered. Later, it was also found in maize exports and food aid in many countries.

Aventis had to pay the highest amount of compensation so far. In 2002, Aventis sold its Crop Science branch to Bayer.

The soil bacterium Klebsiella planticola (development stopped in 1999)

Klebsiella planticola can naturally grow in the rhizosphere of plants. A modified strain was engineered to speed up the fermentation of plant residues (Ingham 1999). In biosafety experiments, it was found, that unlike the wild type, the modified strain was able to damage crop plants like wheat when associating to crop plant roots (Holmes & Ingham 1999). After discovering this unexpected effect, development was stopped. Since then, the genetic modification of bacteria for commercial release to the open environment received little interest, if any.

Nutrient enriched soybean (1996 cancelled in a late stage of development)

One of the early ideas of genetic modification was an attempt to improve the nutrition value of soy beans for human consumption. It was intended to increase the content of the amino acid methionine, which is relatively rare in conventional soy. A protein with high methionine content from Brazil nut was transferred. Unknowingly, a major allergen was used. Persons with Brazil nut allergies showed strong symptoms when being exposed to the GM soy bean (Nordlee et al. 1996). The case sparked public debates whether it is useful to introduce compounds to other plants to improve the quality. Since then, an estimation of potential new allergens contained in GM plants became a standard.

Other cases

So far, cases were listed that received larger attention at the respective time. There are other cases which were not that widely discussed showing the relevance of additional factors that made a GMO unsuccessful.

Virus resistant sweet potato (Kenya)

For several years Florence Wambugu, a Kenyan molecular biologist and co-operant to Monsanto, toured the world to advertise GM to feed the poor in Africa (spinprofiles.org). About 6.000.000 \$ of research funds were used for development of a virus-resistant variety of sweet potato. At the end of the funding period the development was abandoned. The transformation did not make the variety more resistant than conventionally bred crops. In Uganda, a neighbouring country, a conventional variety was bred in less time with better resistance (deGrassi 2003; New Scientist 2004).

Bt sunflower.

Snow et al. (2003) published a paper reporting empirical evidence that wild and weedy sunflower populations might benefit from hybridising with transgenic Bt sunflowers. Under pest pressure, the weedy transgenic hybrids produced up to 50 % more seeds than the wild type. This caused the preoccupation that the transgene might escape cultivation and lead to weed problems in other crops or become invasive. Bt sunflowers were not introduced so far.

Pea for pig vaccination

To compensate for antibiotics which are phased out in industrial livestock farming, it was intended to develop a pea which expressed an antibody against a relevant infectious bacterium in piglets. The development was given up because of doubts in efficiency, because of limited interest of investors and because of public criticism. In 2008, the producer Novoplant (Gatersleben, Germany) went off the market after field releases and feeding tests ended (Biotop 2008; Bauer 2007).

Zeaxanthin potato

Using public funds under the framework of biosafety research, a potato with an increased content of Zeaxanthin was developed and tested at the University of Weihenstephan (Munich). The attempt to facilitate nutrient enhanced potato chips ended after the funding period was over in 2008. No investors were interested to commercialise the product. (<http://www.biosicherheit.de/de/kartoffel/inhaltsstoffe/467.doku.html>).

Conclusions: Reasons for canceling development or market withdrawal – implications for some still ongoing developments

The presented cases show, that the reasons for the failure of transgenic organisms are diverse. The cases cover practically all stages along the development pathway starting

with unreasonable ideas which did not get far beyond the first laboratory studies and ending after market introduction. Major reasons involved were in particular:

Difficulties during laboratory- or field-testing:

- the construct did not work as intended
- potential damage to other crops was anticipated
- the product was allergenic or had unexpected compositional properties
- unexpected non-target or environmental effects occurred
- low market potential was anticipated;

Issues relevant during or after market introduction:

- strong resistance of potential growers or lack of acceptance e.g. because of crop purity concerns (admixture avoidance)
- poor quality of the product
- no consumer acceptance, unforeseen lack of economic viability
- unexpected dispersal after commercialisation beyond of what the admission allowed
- liability problems.

Outlook on problematic cases still in development.

Considering past experiences, some currently still relevant cases can be identified where the prospects could be limited.

Starch modified AMFLORA potato (European Union)

In 2010, Amflora, a BASF development, was admitted for commercial cultivation in the EU. The variety is to be used for industrial purposes (Williams 2010). Only traces are allowed in food. The potato produces one type of starch. A second starch type normally contained in potato is blocked. This reduces purification efforts in industrial processing. Meanwhile conventional varieties with similar characteristics in starch composition exist. The question arises, why the society should take the efforts required for trait segregation after the intended quality was achieved also by conventional breeding. Therefore it may be assumed that the future of this modification could be limited.

Herbicide resistant creeping bentgrass (USA)

Herbicide tolerant golf courses are considered desirable by a developer in the USA. The tolerance is against the same herbicide as used for crop plants. Creeping bentgrass also occurs as a weed and is a target of herbicide application in crop management. The grass is wind pollinated and seeds are light and have a high dispersal potential (Reichman et al. 2006). The risk is very high that HR bentgrass would invade crop land. This appears as an efficient way to make other commercial GM herbicide resistance traits in crop plants obsolete. Nevertheless, considerable amount of investment of real money went into this idea.

Brinjal (India)

The egg plant and its wild relatives are native to India and play an important role in the traditional diet. It was considered to be a good idea to create a Bt variety though a comparable situation exists as with Bt sunflowers. The genetic modification would be difficult to control and to limit its dispersal because of potential gene escape and traditional small-scale and subsistence agriculture (Assam Small Farmers' Agri Business Consortium 2006). As a response to the heated public controversy in India, the government halted admission.

The considered cases support the conclusion, that commercially successful GMO require very high levels of safety testing together with an explicit acceptance of the society. Less controversial applications are those under containment conditions as for many micro-organisms used to synthesise pharmaceutical ingredients. Since an “all inclusive” view in development anticipation seems not to be a common place at the moment, we can expect a continuing number of failures. To avoid them, not only technical feasibility but the entire range of issues along the development pathway would have to be considered in advance – from molecular issues, physiological and ecological implications to socio-economic and cultural issues. When used in agriculture, GMO interact with very complex systems. While a large number of feasible ideas end already at the lab stage, it was shown that even after market introduction commercial disasters can occur. If expanding the time-scale of consideration also the currently economically viable GMO (in particular the currently marketed herbicide resistant crop plants and Bt plants) might to lose economic viability on the long run because of the emergence of resistant pests.

Is it reasonable to expect that anticipation will improve so far that dead end development of GM crop plants becomes exceptional? It seems that the frequency of unexpected problems is not decreasing. Genetic modification seems to share this with developments in other fields of technology where former achievements become obsolete. The difference with GMO is that, unlike in other technologic products, after deliberate release GMO can reproduce, multiply, disperse and evolve.

References

All quoted internet sources were accessible in May 2010.

- Assam Small Farmers' Agri Business Consortium (2006) Briefing paper on Br Brinjal.
http://assmagribusiness.nic.in/bt_brinjal_briefing_paper.pdf.
- Bauer A. (2007) Genbank Gatersleben: Gentechnik oder genetische Ressourcen? Umweltinstitut München. http://www.umweltinstitut.org/download/gatersleben_hintergrund.pdf.
- Bioscience Resource Project (2009) Transgenic High-lysine corn LY38 withdrawn after EU raises safety questions. <http://www.bioscienceresource.org/news/article.php?id=43>.
- Biotop (2008) Novoplant-insolvenz: Aus für die Pharma-Erbesen.
<http://biotop.de/news/article+M51ef5393c34.html>.
- Bottemiller H. (Nov 2009) GM Corn pulled due to food safety concerns.
http://greenbio.checkbiotech.org/news/gm_corn_pulled_due_food_safety_concerns.

- Bratspies R. (2003) Myths of voluntary Compliance: Lessons from the StarLink Corn Fiasco. Michigan State University DCL College of Law, Public Law and Legal Theory Working Paper Series Research Paper No. 01-07. http://papers.ssrn.com/sol3/Delivery.cfm/SSRN_ID421700_code030808500.pdf?abstractid=421700&mirid=3.
- Center for Environmental Risk assessment (2008) GM Crop database REN-00038-3 (LY038). Food Standards Australia New Zealand (2006) Final Assessment Report Application A549 Food derived from high lysine corn LY038. <http://cera-gmc.org/docs/decdocs/07-219-001.pdf>.
- Health Canada (2007) Novel Food Information High Lysine Corn Ly038. <http://cera-gmc.org/docs/decdocs/07-075-001.pdf>.
- Cox J. (2000) StarLink fiasco wreaks havoc in the heartland Developer wants EPA to approve seed for food supply. USA Today 27.10.2000. <http://www.netlink.de/gen/Zeitung/2000/001027.html>.
- deGrassi A. (2003) Genetically modified crops and sustainable poverty alleviation in Sub-Saharan Africa. An assessment of current evidence. Third World Network – Africa. <http://allafrica.com/sustainable/resources/view/00010161.pdf>.
- FOEE (2000) The Starlink Scandal FOEE Biotech Mailout 6(7). <http://www.foeeurope.org/GMOs/publications/vol6no7.pdf>.
- GM Contamination Register (2010) FP967 ('Triffid') flax has been grown illegally in Canada and exported around the globe. http://www.gmcontaminationregister.org/index.php?content=nw_detail1.
- Gurian Sherman D. Roundup Ready Wheat – an overview based on advancements in the risk assessment of genetically engineered crops. <http://www.cspinet.org/biotech/reports.html>. http://www.cspinet.org/biotech/RRwheat_paper.pdf.
- Heinemann J. (2005) Submission on Application A549 Food derived from High Lysine Corn Ly038: to permit the use in food of high lysine corn. Submitted to Food Standards Australia/ New Zealand (FSANZ) New Zealand Institute of Gene Ecology, University of Canterbury, 69 pp. http://www.testbiotech.org/sites/default/files/LY038-highlysinecorn-INBIsubmission_Heinemann.pdf.
- Holmes M., Ingham E.R. (1999) Ecological effects of genetically engineered *Klebsiella planticola* released into agricultural soil with varying clay content. *Appl. Soil Ecol.* 3: 394–399.
- Ingham E. (1999) Good Intentions and Engineering Organisms that Kill Wheat. By Elaine Ingham, Oregon State University. <http://www.greens.org/s-r/18/18-14.html>.
- Martineau B. (2001) Food fight: The short, unhappy life of the Flavr Savr tomato. *The Sciences* 41 (2): 24–29.
- New Scientist (2004) Monsanto failure. A showcase project to develop a genetically modified crop for Africa has failed. <http://www.newscientist.com/article/mg18124330.700-monsanto-failure.html>.
- Nickel R. (2009) Canadian wheat board cautious about GM wheat. <http://www.reuters.com/article/idUSTRE54E59X20090515>.
- Nordlee J.A., Taylor S.L., Townsend J.A., Thomas L.A., Bush R.K. (1996) Identification of a Brazil-Nut allergen in transgenic soybeans. *The New England Journal of Medicine* 334: 688–692. <http://content.nejm.org/cgi/content/full/334/11/688>.
- Reichman J.R., Watrud L.S., Lee E.H., Burdick C.A., Bollman M.A., Storm M.J., King G.A., Mallory-Smith C. (2006) Establishment of transgenic herbicide-resistant creeping bentgrass (*Agrostis stolonifera* L.) in nonagronomic habitats. *Molecular Ecology* 15: 4243–4255.
- Schmidt G., Breckling B. (this volume).

- Schroeder H.E., Gollasch S., Moore A., Tabe L.M., Craig S., Hardie D.C., Chrispeels M.J., Spencer D., Higgins T.J.V. (1995) Bean α -Amylase Inhibitor Confers Resistance to the Pea Weevil (*Bruchus pisorum*) in Transgenic Peas (*Pisum sativum*). *Plant Physiol.* 107: 1233–1239. <http://www.plantphysiol.org/cgi/reprint/107/4/1233.pdf>.
- Snow A.A., Pilson D., Riesenbergl L.H., Paulsen M.J., Pleskac N., Reagon M.R., Wolf D.E., Selbo S.M. (2003) A Bt transgene reduces herbivory and enhances fecundity in wild sunflowers. *Ecological Applications* 13(2):279–286, Ecological Society of America.
- Spin Profiles (2010) Alan McHughen. http://www.spinprofiles.org/index.php/Alan_McHughen. Spinprofiles.org. Florence Wambugu. http://www.spinprofiles.org/index.php/Florence_Wambugu.
- University of California, Riverside (2009) Alan Mc Hughen. <http://www.plantbiology.ucr.edu/faculty/mchughen.html>.
- Warick J. (2001) GM Flax seed yanked off Canadian market – rounded up, crushed. <http://www.rense.com/general11/gm.htm>.
- Williams N. (2010) One new potato. *Current Biology*, Volume 20, Issue 7, R301, 13 April 2010. doi:10.1016/j.cub.2010.03.040. <http://download.cell.com/current-biology/pdf/PIIS0960982210003659.pdf?intermediate=true>
- Young E. (2005) GM pea cause allergic damage in mice. *New Scientist*. <http://www.newscientist.com/article/dn8347-gm-pea-causes-allergic-damage-in-mice.html>.