Testbiotech e. V.
Institute for Independent
Impact Assessment
in Biotechnology

Risk Reloaded

Risk analysis of genetically engineered plants within the European Union

A report by Testbiotech e.V. Institute for Independent Impact Assessment in Biotechnology

www.testbiotech.org

October 2009
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Summary

This is a report on the risk assessment procedure for genetically engineered plants in the EU. It reveals substantial flaws and loopholes in the procedure and practice of the institutions concerned. Many of the flaws have their origin in the European Food Safety Authority's (EFSA) own main concept of risk assessment. This is essentially based upon guidelines that were developed by the OECD as early as 1993 on the assumption that the risks posed by genetically engineered plants are basically the same as those posed by conventional plants. This approach has admittedly been revised several times since 1993 but has in essence remained unchanged.

The report shows that the current guidelines are inadequate for sound risk assessment. New findings in genome research have in recent years transformed ideas of gene regulation and gene function. It has become evident that invasive intervention in genetic makeup and the transfer of isolated genes cannot be equated with natural mechanisms of heredity and gene regulation. The basic difference between conventional cultivation and genetic engineering of plants is becoming more and more distinct in the light of current genome research. Experience gained from cultivating conventional plants cannot – or only to a very limited extent - be applied to genetically engineered plants.

Even in conventional cultivation there are many changes in the genome but these do not break through the natural system of gene regulation. In contrast a new metabolism is forced upon genetically engineered plants. In fact the regularly observed changes in the activity of plant genes in this process are not an expression of natural gene regulation but an indication of disruption. These transgenic plants[1] are technically manipulated products and as such much be assessed unconditionally for constructional flaws, quality defects and risks.

The outdated basic concept of the OECD from 1993 and the subsequent concepts developed for risk assessment of genetically engineered plants (FAO/WHO, 2000; Codex Alimentarius, 2003; EFSA, 2006) mean that the safety, predictability and controllability of genetically engineered plants are not examined in detail within the framework of approval procedure.

Irradiated food, pesticides, chemicals and medicines are all unconditionally tested for possible risks. In order to thoroughly test genetically engineered plants, however, there first of all has to be some proof that there may be a risk. Genetically engineered (GE) plants are deemed to be safe as long as no proof to the contrary has been produced. This means that GE plants are tested much more superficially than irradiated food, pesticides, chemicals and medicines.

Overall the concept as defined by the EFSA (2006, 2007a, 2007b) does not meet the requirements of the EU for comprehensive testing. It replaces actual risk testing by a system of presupposed assumptions based upon conclusions that are hardly verifiable.

In this report the authors give an overview of the reasons for recent doubts about the safety of genetically engineered plants and present different examples which show the inconsistencies and failures in EFSA's risk assessment. One of the examples used to expose the lack of essential requirements for well-founded risk assessment is MON 810 maize which produces the Bt insecticide.
It is also extremely problematic that more and more cases are being documented showing that indepen-

1 In this report no distinction is made between transgenic and so called cisgenic plants, because both are the result of transferring isolated gene sequences

dent risk research is being hampered. In many cases it is not even possible to access necessary testing materials. Even the publication of findings is being obstructed. All in all the influence of industrial interests in research and the presentation of findings have reached alarming proportions.

Against the backdrop of various political discussions on the further development of testing standards in the EU, the authors make concrete suggestions on how testing systems can be improved to generate more data on the quality and safety of genetically engineered plants. They advocate more extensive testing on the compounds and genetic stability of GE plants before they are released into the field and companies can apply for market authorisation.

The plants should be subjected to a suitable level of exposure in specific “crash tests” to test their reaction to changing and extreme environmental conditions. Before field release and in order to collect more data on potential risk they should be tested (i.a. with different microorganisms) in a contained system to detect any interaction between the plants and a simulated environment. The authors suggest that these tests be introduced in the course of introducing improved step by step, case by case tests which have clearly defined test criteria for genetically engineered plants; with concomitant stronger collaboration between the authorities of member states and EU authorities and a higher consideration of ethical and socio-economic factors. The documentation of relevant information shall become a precondition for EU authorisation procedures.

Society, politics and approval boards should no longer close their eyes to the fact that agro-gene technology uses methods that are largely outdated and whose risk potential is higher than originally thought. It is not the fear of new products that make a critical appraisal of agro-gene technology necessary, but rather the fact that its scientific principles have been called more and more into question by new findings.

Introduction

The New York Times in 2007 featured an article about recent results in genome research which put in question long established views about genes and their regulation.[2] The international Encode project showed that the mechanisms in gene regulation are much more complex than had been thought so far (Encode, 2007). In the words of the New York Times:
"The scientists who invented recombinant DNA in 1973 built their innovation on this mechanistic, "one gene, one protein" principle. Because donor genes could be associated with specific functions, with discreet properties and clear boundaries, scientists then believed that a gene from any organism could fit neatly and predictably into a larger design - one that products and companies could be built around, and that could be protected by intellectual-property laws. This presumption, now disputed, is what one molecular biologist calls "the industrial gene". "The industrial gene is one that can be defined, owned, tracked, proven acceptably safe, proven to have uniform effect, sold and recalled," said Jack Heinemann ..."

The Encode project once again showed what had already been broadly discussed amongst experts in 2001. At this time the first analysis of the human genome was presented, showing that humans only have about 20,000 instead of about 100,000 genes, as had previously been thought. This remarkably low number of human genes is in striking contrast to their task to code for hundreds of thousands of proteins in the human body. Craig Venter, who played a decisive role in the human genome project, made an astonishing comment in Science (Venter et al. 2001):
"The modest number of human genes means that we must look elsewhere for the mechanisms that generate the complexities inherent in human development and the sophisticated signaling systems that maintain homoestasis."

These findings of genome research gave birth to something which is called by many experts the era of postgenomics. It is no longer the analysis of specific DNA sequences that catches the most scientific attraction, but the mechanisms of its complex regulation. This new focus of research is also widely accepted in plant genomics (see for example Clark et al., 2007).

The TestBioTech report presented here starts with the question of the extent to which this breakthrough in molecular biology also impacts genetic engineering in plants and their risk assessment. Several concepts for risk analysis are discussed against this background. Special attention is given to the practice of the European Union.

2 Caruso, Denise, „A Challenge to Gene Theory, a Tougher Look at Biotech", New York Times, 1. Juli 2007, www.nytimes.com

Concepts of risk assessment

1.

In the year 2000 it was reported that some experts had succeeded in genetically manipulating rice kernels to produce beta-carotene in their endosperm (Ye et al., 2000). The carotenoid can be used by the human body as a source for the production of essential Vitamin A. Because the kernels had a yellow colour (caused by an unintended effect), they were very soon called "Golden Rice" (for review see Then, 2009a). In spring 2009 it got noticed that trials with school children were conducted without the potential health effects of the transgenic rice being comprehensively tested beforehand.[3] Experts defending the project rejected any criticism by claiming that the risk could be rated as being minor.[4] The website of the Golden Rice Consortium even featured a statement saying the risks to school children would be comparable to those of eating a small carrot:
"The experiments were no more dangerous than feeding the children a small carrot since the levels of beta-carotene and related compounds in Golden Rice are similar."[5]

Experts at Tufts University, USA, and elsewhere have a different opinion. They published the first results of testing the genetically engineered rice in adult volunteers in the US, and explicitly mention that clinical trials cannot be avoided if the safety of the product is to be investigated (Tang et al., 2009).

The debate about this project, which has been going on for years, highlights the general controversy about risk assessment standards. Even more than ten years after the first commercial cultivation of genetically engineered plants (such as soy with herbicide tolerance or maize producing insecticides) there is no generally agreed perception about the risks inherited by those plants nor about the way to conduct proper risk assessment. There have been efforts to reach international consensus in papers drawn up by the FAO and WHO (FAO/WHO 2000) and various documents prepared by the OECD[6], as well as within the Codex Alimentarius (2003), which the European Food Safety Authority (EFSA) also uses as a basis. But as explained below these concepts cannot be seen as being a solution to the existing problems. These minimal standards are not in line with more recent scientific findings in molecular biology and not in accordance with the EU's legal requirements.
The main principle behind these international standards is the concept of 'substantial equivalence' developed by the OECD as long ago as 1993. This concept was harshly criticised by many stakeholders and experts but is still seen as the starting point for risk assessment (FAO/WHO 2000, Codex Alimentarius 2003). The notion works in practice as a hypothesis or a general assumption which is made before any real risk assessment takes place, thereby influencing the outcome of risk assessment in a significant way.

The controversy about feeding trials

1.1

An example of the controversies caused by this hypothetical practice is the question of whether feeding trials are necessary to test the safety of genetically engineered food, something already mentioned in connection with Golden Rice. The EFSA in 2007 conducted a specific report on this issue, referring to consensus documents from the FAO, WHO, OECD and Codex Alimentarius, as mentioned above. The EFSA report explains why the authority does not in general perceive feeding trials with genetically engineered plants (or derived food and feed) as being necessary. The EFSA (2007a) proposes a standard for risk assessment for genetically engineered plants (and derived food and feed) that is essentially different from those being used for radiated food, pesticides, chemicals or pharmaceuticals.

3 http://www.goldenrice.org/Content2-How/how3_biosafety.html
4 http://www.dailymail.co.uk/news/worldnews/article-1147635/British-scientists-condemn-using-children-GM-food-trials-unacceptable.html
5 http://www.goldenrice.org/PDFs/Daily_Mail_Letter_Feb_2009.pdf
6 OECD Consensus Documents for the work on the Safety of Novel Foods and Feeds, OECD. http://www.oecd.org/document/9/0,2340,en_2649_34391_1812041_1_1_1_37437,00.html

To prove the safety of radiated food, for example, feeding trials were conducted on mice, rats, dogs, monkeys and even humans (WHO, 1999). Feeding trials were performed over a duration of several years to investigate growth, carcinogenicity and reproductiveness:
"The safety of high-dose irradiated foods has been evaluated in many feeding studies conducted over *the past four decades that have involved a variety of laboratory diets and food components given to humans and a broad cross-section of animal species, including rats, mice, dogs, quails, hamsters, chickens, pigs and monkeys. These investigations, which have included subacute, chronic, reproductive, multigeneration and carcinogenicity studies, have been conducted under a variety of experimental protocols and have covered a range of doses."*

These kinds of feeding trials can be seen as being not necessary, and even immoral if the introduction of radiated food is seen as superfluous. But should they also be regarded as being completely useless from a scientific point of view?

By rejecting feeding trials using whole transgenic plants as suggested by the EFSA (2007a), one has to face a specific problem: risks emerging from products consisting of complex mixtures, including various different compounds, can hardly be assessed by just analysing some of their isolated components. In the case of genetically engineered maize, rice or soy, some of the plants at the same time tolerate herbicides (and are likely to have some residues from its application) and produce insecticides. These so-called stacked events (plants inheriting a combination of more than one transgenic trait) are cultivated in the US and some of them are also allowed for import into the EU. Cross activities between various compounds in the plants during their cultivation might produce results which can hardly be predicted from analyses of their single components.

These problems are moreover also relevant for transgenic plants that only inherit a single transgenic trait. Unintended effects can also occur in these plants with unpredictable impacts to human health and the environment. As Batista et al (2008) show, for example, the activity of many genes can be altered by inserting single gene sequences (see below). Because of these unintended effects experts such as Spök et al (2004) and Seralini et al (2009) explicitly urge feeding trials using the whole plants and not only single compounds, to get a better understanding of the associated risks. As Spök et al (2004) explain:
"Testing should be extended to include whole-plant/whole-food testing in both toxicity and allergenicity studies in order to more reliably detect unintended and detrimental effects of genetic modification."

These arguments are not followed by the EFSA. The European Food Safety Authority only suggests more detailed investigations in connection with products such as the Golden Rice (for which market authorisation has so far not been applied). According to the EFSA the metabolism of these plants can be regarded as being changed on several levels, so feeding trials with whole plants should be performed in order to avoid negative health effects. By arguing this way the EFSA (2007a) contradicts the position of the Golden Rice team. But it at the same time assumes that the transgenic plants where approval of commercialisation is currently being applied for should be seen as harbouring only minor risks. The EFSA does not consider feeding trials to be necessary even in the case of stacked events (EFSA 2007a).

The EFSA generally assumes that risks to human health can be deduced from the analysis of single compounds at least in the case of transgenic plants tolerant of herbicides or producing insecticides. The authority argues that the transfer of genes would change the plants only in relation to certain characteristics. Besides that, genetically manipulated plants can be seen as equivalent to plants derived from conventional breeding (EFSA 2007a):
"The current generation of GM plants cultivated for commercial purposes has been modified through the introduction of one or a few genes coding for herbicide tolerance, insect resistance or a combination of these traits. In these plants the genetic insert leads to the production of a gene product, which does not interfere with the overall metabolism of the plant cell, and does not alter the composition of the GM plant except for the introduced trait."

Where these plants are concerned it is assumed that unpredictable risks are not likely to arise, so that feeding trials with the whole plants are not necessary. If these transgenic plants do not show clear signs of unintended effects it is enough to screen for specific compounds, more detailed investigating of health risks not being necessary.

While risks to human health of products such as radiated food, pesticides and pharmaceuticals have to be investigated to prove their safety without anything being presumed, in the case of genetically engineered plants the risks first have to be proven before detailed investigations are made.

General prerequisites for risk assessment

1.2

According to the regulations of the European Union (Regulation 178/2002 and Directive 2001/18) and its underlying basis as elaborated in the White Book of the European Commission (Commission of European Communities, 2000), a high level of protection of the environment and consumers are the overarching goals of the EU's policy. In the case of uncertainties the precautionary principle shall prevail. In comparison the economical expectations associated with the commercialisation of genetically engineered plants have to be seen as being of minor importance.

Against this background it has to be acknowledged that risk assessment of genetically engineered plants shows a high level of complexity, since ecological impact, agronomic performance, human health aspects and questions regarding molecular biology and toxicology have to be taken into account. Some relevant issues are:

1. Molecular biology.- The place of insertion of new genes into the plants' genome is not the result of a targeted process, but is more or less based on chance. Methods like the 'particle gun', or more or less scattered shot technologies, are still being used. This can lead to distortions of the plants' genome at the place of insertion. Further, the biological activity of newly inserted gene sequences has to be enforced artificially (see for example Diehn et al, 1996). The plants' own gene regulation has to be knocked out (partially) to avoid silencing the additional gene constructs. The activity of various other genes can be altered by the genetic manipulation. This effect can be observed with gene sequences that are located at a far distance in the plants' genome as well as with gene sequences that are in the direct neighbourhood of the newly inserted genes. In Monsanto's genetically engineered soybeans, for example, Rang et al (2005) showed that the neighbouring gene sequences of the plant get fused with the artificial gene construct and show some unexpected activity. Similar results were described in genetically engineered maize by Rosati et al (2008). These unintended biological interferences can have various effects at the level of the genome, cell metabolism and or the whole organism. In some cases this interference has been overlooked for several years even after market authorisation.

2. Toxicology and health impacts. - The range of intended compounds that are produced in the transgenic plants covers substances meant to protect human health up to toxic proteins meant to defeat pest insects. In addition one has to take into account unintended components caused by occasional interference of the plants' metabolism.

3. Environmental impact. -The relevant risks are not of a steadily fixed nature, they involve dynamic processes involving factors like the growth of the plants and various environmental influences. Insecticides in genetically engineered cotton and maize, for example, are influenced by several environmental conditions (Then&Lorch, 2008a). Exposed to external stress factors, genetically engineered plants can also exhibit unexpected effects not noticed before (Matthews et al, 2005).

4. Unintended gene transfer. - Gene sequences enabling resistance against antibiotics can be transferred to hazardous microorganisms, at least in theory. Debates and even minority votes within the EFSA's

GMO panel show that this risk is still seen as controversial after many years.[7] The potential health effects of inserted gene sequences (gene constructs) if used in food and feed (as for example argued in Cotter&Mueller, 2009, Myhre et al., 2006) are another point of discussion. Special cause for concern is the fact that the spread of the artificial gene constructs via pollen and other escape routes cannot be prevented.

All in all one has to deal with a complex matter of ecological, biological and health related issues which is dependent on a broad range of additional external factors which are not fully understood in all details even after many years of research. Traavik (2008) describes the situation:
"The dynamic and interconnected regulation of the genome is now slowly being revealed. The genome does not function in a constant, stable and linear fashion, but is instructed by and fine-tunes its activities according to networks of signals received from the external ecosystem and the internal environment of the organism. The genomic signal pathways may be modified by ecosystem variation as well as by physiological changes in the organism. Thus, the chromatin structure, the genome, the epigenome, the transcriptome, the proteome, the metabolome, and the interactome are interlinked and intertwined in various ways with information transfer in multiple directions."

The recent political debates in the EU show how difficult it really is to develop a system for risk assessment that has a sufficient scientific basis. The EU Commission[8] as well as the members states[9] have repeatedly been highly critical of the work of the EFSA's GMO panel in the last few years.

1.3 Assumptions and hypotheses underlying EU risk assessment

According to the 'Guidance Document of the Scientific Panel in genetically modified organisms for the risk assessment of genetically modified plants and derived food and feed', which the EFSA has drawn up as a basis for its risk assessment (EFSA 2006), the underlying principle of its risk assessment is a so-called "comparative approach", which tries to draw a comparison between the genetically engineered organisms and their counterparts produced in conventional breeding. In this approach the EFSA uses the concept of "familiarity" for the risk assessment of the cultivation of transgenic plants and "substantial equivalence" for the risk assessment of food and feed (EFSA, 2006).

The underlying hypothesis of this principle implies that genetically engineered plants are not completely new organisms but similar to plants as used for centuries in conventional agriculture and only changed in distinct characteristics. Thus the plant derived from conventional breeding and the transgenic plant are defined as being substantially equivalent as long as no major differences can be found by comparing plant compounds and agronomic characteristics:
"The concept of familiarity is based on the fact that most GM plants are developed from organisms such as crop plants, the biology of which is well researched. In a risk assessment it is appropriate to draw on this previous knowledge and experience and to use the non-GM crop as the comparator to the GM crop [...]"
and:
"The concept of substantial equivalence is based on the idea that an existing organism used as food/feed with a history of safe use, can serve as a comparator when assessing the safety of the genetically modified food/feed [...]." (EFSA, 2006)

Risk assessment can thus be reduced to selected distinct aspects. But this principle of a "comparative approach" can easily provoke wrong interpretations. If - due to insufficient scientific methods - no sub-

7 http://www.efsa.europa.eu/EFSA/Statm_of_Efsa/gmo_biohaz_st_ej1108_ConsolidatedARG_en.pdf?ssbinary=true
8 http://europa.eu/rapid/pressReleasesAction.do?reference=IP/06/498&format=HTML&aged=1&language=EN&guiLanguage=en
9 http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/envir/104553.pdf

stantial differences can be found between the transgenic plant and its comparator, the product is likely to be categorised as being safe. So if for example adequate methods for detailed investigation of the proteome are not available and thus certain differences are overlooked, the product will be categorised falsely as being substantially equivalent. It is important here to know that methods especially relevant in the analysis of the proteom and the metabolom have not yet been developed sufficiently to be used as standard procedures in risk assessment (EFSA 2007 a), despite these methods having been seen as decisive tools for several years.

The underlying hypothesis and assumptions of substantial equivalence and familiarity are not a matter of discussion in the EFSA's daily work – they are simply seen as a precondition. The authority will as a result classify a product simply as being safe if it does not reveal specific risks after some initial superficial investigation. Furthermore the concept as applied by the EFSA leaves substantial room for assumptions and interpretation. Whether or not even significant differences between the transgenic plant and its comparator are interpreted as being substantially equivalent or not (see below) can depend on the point of view of particular experts.

A completely different concept of risk assessment would apply if the underlying hypothesis took into account the fact that transgenic plants are derived from a technical process that cannot be compared to methods used in conventional breeding. The resulting products therefore have to be classified as technical constructs that have no real counterpart in plants derived from conventional breeding. In risk assessment genetically engineered plants have to be investigated without any restriction to any relevant technical and biological details. One could for example imagine something like a crash test as being applied to other technical products to reveal hidden risks and technical deficiencies. Even the EFSA admits that a completely different approach to risk assessment would be necessary if the hypothesis of similarity and comparability were not the starting point of its assessment:
"Where no appropriate comparator can be identified, a comparative safety assessment cannot be made and a comprehensive safety and nutritional assessment of the GM crop derived food/feed per se should be carried out. For instance, this would be the case where a trait or traits are introduced with the intention of modifying the composition of the plant significantly." (EFSA 2006)

Such a comprehensive approach to a risk assessment without the precondition of similarity and comparability has not been applied by the EFSA in any case so far. In the light of more recent findings in molecular biology the necessity for comprehensive testing is becoming evident, since it enables better understanding of the potential impacts of the technology used to create transgenic plants.

The need to treat genetically engineered plants as organisms that do not have a history of safe use because they are created by methods that cannot be compared to any other method of breeding was raised from the very beginning of this technology. But this was always harshly rejected by the proponents of genetic engineering and very soon also rejected by US legislation. As is argued below, it is time to correct this development.

Substantially equivalent or different?

1.4

The basic difference between conventional breeding and genetic engineering is becoming more and more evident because it can be shown that the mechanism for the regulation of the genome is far more complex than was estimated some years ago. This reveals the insufficiency of concepts and principles such as comparability, equivalence or familiarity.

1.4.1

Networks of regulation instead of isolating genes

Since the human genome project was completed, general understanding about gene function and genome regulation has changed substantially. Before it was quite common to define a gene as a distinct DNA sequence with a fixed function. But since then the pattern of explaining a gene's mechanism has been getting more and more complicated. Mattick (2003) for example describes genes as "fuzzy transcription clusters with multiple products".

The idea of genome regulation has changed drastically not only for humans and mammals (ENCODE 2007), but also for plants (see, for example, Clark et al., 2007). All in all the organisation of the genome is much more defined by networks and (quantitative) synergies of gene clusters than by the function of single genes. Wentzell et al. (2008) for example describe how networking of genes can influence the plants' characteristics and also interfere with the environment, with this based on mechanisms that are far beyond being understood in all their details:
"Most phenotypic variation present in natural populations is under polygenic control, largely determined by genetic variation at quantitative trait loci (QTLs). These genetic loci frequently interact with the environment, development, and each other, yet the importance of these interactions on the underlying genetic architecture of quantitative traits is not well characterized."

The Syngenta company is using similar expressions in its patent application WO2008087208:
"Most phenotypic traits of interest are controlled by more than one genetic locus, each of which typically influences the given trait to a greater or lesser degree (...) Generally, the term "quantitative trait" has been used to describe a phenotype that exhibits continuous variability in expression and is the net result of multiple genetic loci presumably interacting with each other and/or with the environment."

These complicated and complex models of gene functions are not well suited for transferring isolated genes beyond the barriers of species. Predicting the biological role of a DNA sequence that gets isolated and transferred to another organism looks like a matter of major uncertainty, since the biological function of a gene is always defined by its background (or environment). As Pickardt (2002) writes: "A genetically transferred gene sequence must then be understood as genetic information the context of which has been altered in an uncontrolled way." Thus this new insight into gene function and genome regulation also has a substantial impact on the development of hypotheses on the risk assessment of the transfer of isolated genes (see also Greenpeace, 2005).

1.4.2

Optimising existing potentials or reprogramming by technical intervention?

To get a closer idea of the differences between transgenic methods and conventional breeding it might be helpful to take a closer look onto the technical procedures used to create a plant with an artificial gene insert. Diehn et al. (1996) describe the creation of plants producing insecticides. By introducing gene sequences for so called Bt toxins (insecticides normally produced by the bacteria Bacillus thuringiensis) plants such as maize and cotton were armed to resist pest insects. Before the bacterial gene was successfully expressed in the plants, it was necessary to overcome several technical and biological hurdles:
In a first attempt the DNA was transferred to plants in the full length and structure it occurs in bacteria. But the plants showed only a very low content of the toxin.
In a next step the gene sequence was shortened, and some non essential parts were cut off. The gene sequences showed a higher biological activity but the level of toxin in the plants was not high enough to kill the pest insects.

In a further trial the promotor (derived from cauliflower mosaic virus) was doubled to enhance the biological activity of the Bt gene. As a result the Bt genes showed a tenfold higher activity.
But even this technically derived enhancement was not sufficient for the level of the Bt toxin necessary to kill the pest insects to be reached. It took some further changes in the structure of the Bt genes to finally reach the desired result.

This example shows that several hurdles have to be overcome in natural existing gene regulation to enable the biological activity of transferred gene sequences. Diehn et al. (1996) are of the opinion that their observations reveal basic mechanisms used by plants to protect themselves against the transfer of foreign DNA and its products:
"The mechanisms that limit the expression of unmodified Bt toxin genes are vital plant mechanisms that naturally affect endogenous RNA and protein levels."

It is also known from effects called gene silencing that plants try to defend themselves against the insertion of additional genes. Even if foreign genes get activated successfully they can still be switched off by epigenetic effects in the plants (see Finnegan, 1994; review by Moch, 2006).

One can thus say in summary that the new genetic information and its expression in the cells have to be forced into the plants by technical means. The normal mechanisms of gene regulation have to be surrounded or even (partially) knocked out. Invasive methods like this are not used in conventional crossings or mutation technologies. The mechanisms of normal gene regulation are not changed by any other breeding method. If, for example, new genetic information obtained inconventional breeding (for example caused by mutations) will only be used if it fits with the existing genetic background of the plants (e.g. see Fernandez-Martinez et al. 1997, for general background see Nijhout, 2003).

For the risk assessment of genetically engineered plants it is crucial not to deny the basic distinction between methods for breeding and technical construction of genetically engineered plants. While conventional breeding uses existing biodiversity and its potentials developed by evolution over a long period of time, genetic manipulation tries to enforce a technical program without obeying the rules of normal gene regulation.

Collaterals

1.4.3

The changes associated with genetically engineering plants are not restricted to specific regions in the genome. Experimental investigations with fruit flies show that change in biological activity of one gene can induce changes in the activity of several hundred other genes (Anholt et al., 2003). It is also known from the transfer of genes to plants that this process impacts the genome and cell regulation on several levels (Wilson et al. 2006). There seems to be a common understanding about the fact that unintended effects in genetically engineered plants can be expected in many cases (see Kuiper et al., 2001), but how to interpret these findings is a matter of dispute. Many changes in the genome and metabolome have also to be expected in conventional (and mutation) breeding. Several recent investigations compare these changes in transgenic and non transgenic plants. But in assessing its outcome one has to differentiate between several aspects. Some of those issues shall shortly be discussed here using a publication by Batista et al. (2008):

Batista et al. tried to compare the changes in gene activities in plants which had been subjected to mutation breeding and genetic engineering. In transgenic plants they found 2,318 additional changes in gene activity. The number of genes with a changed activity was reduced in the following generations but even in those plants some significant additional changes could be demonstrated.

Batista et al. demonstrate that in mutagenisised plants even more changes in gene activity can be observed. They thus also propose to investigate the risks of products derived from mutated plants. But

such a straight analogy between genetic manipulation and artificial mutation cannot be made. Mutation breeding is essentially based on evolutionary mechanisms: plants are permanently subjected to signals (such as UV sunlight) that can induce mutations. Thus the plants are trained to protect their genome; research shows that the number of mutations finally used is very minor.

Further, the change of gene activity in the follow up of a radiation cannot be seen as unexpected. It simply shows the plants' normal reaction (including repair mechanism) to an unspecific, untargeted stress factor. On the contrary, genetic engineering in plants aims at a specific manipulation in the plants' genome which cannot be controlled by the plant and uses genetic information that is not familiar with the metabolism of the plant. Thus the observed changes in gene activity of genetically engineered plants have other causes and so can result in other effects. All in all a multiple change in biological activism of genes is not surprising in mutagenizised seeds. But it is a matter of concern that in transgenic plants so many genes are affected by the introduction of new genetic information which is believed to be specific.

What is regarded as a normal mechanism in the gene regulation of plants in conventional cultivation (and basically in mutation breeding too) must in the case of direct intervention in the genome via genetic engineering be interpreted much more as disrupting its gene regulation. In any case the findings of Batista et al (2008) show that the assumptions of the EFSA, supposing changes in genetically engineered plants to be restricted only to the specific trait inserted, are not based on scientific facts.

1.4.4 What is biologically significant?

Recent findings about the complexity of gene function and genome regulation are not taken into account by the concepts of FAO/WHO (2000), Codex Alimentarius (2003) and the EFSA (2006). Their approaches make no difference between unintended effects observed in plants derived from conventional breeding and transgenic plants.

The presumption of similarity which is the starting point for risk assessment as performed by the EFSA prevents rigorous testing of genetically engineered plants with regard to their safety, predictability and reliability. Even in cases when significant differences between transgenic plants and their counterparts are observed, they are mostly dismissed by the EFSA as being not of "biological significance". Spök et al (2004) expose this problem:
"In compositional analysis, however, significant differences found are disregarded without attempts to verify or further investigate these differences in order to enhance the likelihood to detect unintended secondary effects."

Traavik (2008) raises the decisive question that could finally make the EFSA acknowledge a substantial difference:
"The concept enables the identification of potential differences between a GMO and its unmodified counterpart, and the differences should then be investigated further for potential adverse health and environmental effects. But how different can they be before becoming 'substantially different'?"

The hypothesis-driven approach chosen by the EFSA turns around the burden of proof: genetically engineered plants are assumed to be safe until the opposite is proven. In addition terms such as "biological significance" are established by the EFSA in a way that leaves a lot of space for speculation and interpretation and avoids any need for further and more detailed analyses.

Actual standards for risk assessment and monitoring in the EU

2.

Besides the debate about principles and concepts of risk assessment a decisive question is how the existing standards are implemented in practise. It was already mentioned that EFSA criteria leave a remarkable space for interpretation and even speculation. Examples of this will be described below. In fact in many cases the personal opinion of EFSA experts seems to be decisive in the question of how and if uncertainties shall be explored further. The guidelines as defined by the EFSA (2006) are anyway in most of its parts not mandatory and can be handled in different ways from case to case. Regulations for coherent 'step by step' procedures are missing, despite the fact they are required by European legislation (Directive 2001/18, recital 24). While the process for authorisation is indeed organised in several steps (first experimental field trials, before application for market authorisation), but the test criteria for the specific steps are poorly defined and the results not systematically integrated into risk assessment. A solution could be seen in the introduction of a new regime for risk analyses that gets applied even before field or feeding trials take place.

Feeding trials

2.1

Problems with the EFSA guidelines get particularly serious in the way the authority deals with feeding trials meant to investigate potential health effects as already mentioned above. The EFSA does not demand certain kinds of feeding studies be carried out regularly but decides from case to case (EFSA, 2007a, EFSA 2006)

By doing so it ignores that several studies concerned with feeding trials have revealed definite signs of negative effects on health (Ewen&Pusztai, 1999; Finamore et al 2008; Kroghsbo et al 2008; Malatesta et al 2002 und 2003; Vecchio et al, 2004; Prescott et al, 2005; Sagstad et al, 2007; Seralini et al, 2007; Valanta&Spök, 2008; Velimirov, et al 2008). While it should be acknowledged that not all aspects of the negative effects observed by these authors have been definitively assessed, the existing findings indicate that feeding trials with the whole plants seem to be quite reasonable and even necessary, before these products are authorised for food and feed. Several experts call for mandatory feeding trials. These should include testing with several generations and specific investigations of organs, the immune system and the reproductive system (Seralini et al, 2009, Spök et al 2004).

By analysing the EFSA's views it becomes evident that the authority in fact accepts dossiers with widely varying standards. The feeding trials accepted are substantially different in their methodology and aims. Only in some cases were feeding trials performed that concern potential health risks; in other cases only economically relevant parameters such as feed conversion in farm animals were investigated. Even in the case of the Bayer company's herbicide resistant Rice LLRice62, which is not meant mainly for feed (such as maize and soy) but for human consumption, the EFSA did not request specific feeding trials with the whole food in order to investigate potential health risks (see Table 1). More targeted investigations that might concern organs, the reproductive system or the immune system were in any case not requested by the EFSA.

Feeding trials with animals such as mammals are a matter of concern from an ethical perspective. Some of the tests proposed imply additional stress for the animals, beyond the uptake of certain feed under lab conditions. Since genetically engineered plants and food are rejected or at least seen as being controversial by most consumers in Europe, there is a possibility that animal trials will be conducted for products that will never become relevant for the EU market.

Superfluous feeding trials could, however, possibly be prevented (partially) by the EU Commission. The Commission, being the risk manager (see also below), may weigh up ethical, economical and scientific

questions within overarching analyses and decisions. To prevent unnecessary animal trials it could be the task of the EU Commission to only start a process for market authorisation if a substantial need for the product can be identified. Such "integrated" concepts, taking into account not only risk related issues, are proposed by Haslberger (2006) and Gesche&Haslberger (2006). Within such integrated concepts some detailed 'step by step' procedures can be defined that require certain mandatory checks before any feeding trials or releases take place. Some possible features of comprehensive testing are presented in section 6.

Table 1: Selected feeding studies as accepted by EFSA

Company/product	Trait	Duration, animal species	Issue in investigation
Bayer/LLRice62	Rice with herbicide tolerance	42 days, poultry 96 days, pigs	Feed conversion
Monsanto/MON863	Maize with Bt toxin	90 days, rats	Health risks
Monsanto/NK603	Maize with herbicide tolerance	90 days, rats	Health risks
Pioneer/1507	Maize with Bt toxin	90 days, rats	Health risks
Syngenta/ Bt11	Maize with Bt toxin	14 days, cows 14 days, poultry	Feed conversion

2.2 Ecological risk assessment

Despite the fact that most genetically engineered plants assessed by the EFSA have quite similar characteristics, the protocols for investigating their ecological risks differ quite substantially. The differences concern duration and number of experimental trials, the species investigated that might come into contact with the plants, the research protocols and the way the data about exposition are derived. In most cases the data as presented by industry are not suited for drawing final conclusions about the potential ecological risks of their transgenic plants. Lorch (2005), for example, found a long list of deficiencies in the Syngenta company's dossier of Bt11 maize dossier accepted by the EFSA for cultivation:

- during the trials filed, the features investigated were mainly relevant for agronomic and economical purposes but hardly for ecological risk assessment,
- most data were not derived under conditions as existing in Europe but were more relevant to the US, and many of the original data were never published and are not available to interested members of the public,
- the concentration of the Bt toxin varied across broad ranges but the reasons for this and the maximal variations were not investigated, and
- despite the fact that the plants not only produced an insecticide, but were also tolerant of a herbicide, no investigations were required about possible interactions.

According to official statements the EFSA so far does not have a coherent concept for ecological risk assessment. New guidelines will be proposed by the EFSA in March 2010 as requested by the EU Commisison.[10] The EFSA nevertheless keeps on presenting opinions about the cultivation of genetically engineered plants and their associated ecological risks even before these guidelines have been presented.

When investigating environmental risks there is a basic dilemma which is similar to ethical problems with animal feeding trials. Releases made to investigate potential ecological risks can in themselves already present ecological risks. In theory it is necessary to perform experimental field trials for several years in all the regions of the European Union which show specific ecological or climatic properties or other relevant environmental conditions, before the ecological consequences of commercial cultivation can be assessed.

10 http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/envir/104553.pdf

Thus strategies should be developed to avoid experimental field trials that would be made too early, too riskily and even unnecessarily. For this purpose comprehensive investigations in greenhouses, the laboratory or other systems that allow contained experimentation are the best options for obtaining more data about product quality and safety aspects. It is true that certain complex investigations can only be conducted in the open. But it is also true that certain information can in many cases only be obtained when work is done under conditions as apply in the lab, as these allow more precise test requirements to be met.

There are a whole number of tests that can usefully be conducted before any release trials. They include simulation of specific environmental conditions and exposition to certain stress factors that might alter the metabolism in cells and the concentration of key components in the plants. The potentials of these test systems are far from being explored by current risk assessment. Several of them will need to be elaborated further before they can be validated.

Most companies show an interest in releasing their genetically engineered plants into the environment as soon as possible. But under environmental conditions too many factors occur in parallel that cannot be investigated in detail. Thus it is current practice only to take into account very few indicators during field trials, with these then used to draw very general conclusions about the safety of the plants (a concept called the tiered approach by the EFSA). This might help companies to save money and time, but might become quite costly from the perspective of the precautionary principle.

Systematic testing which follows a true 'step by step' procedure, aiming first to conduct comprehensive investigations and assess a fixed set of data before any releases (or feeding trials) can take place, is not in place in the EU, despite being generally requested by Directive 2001/18. The authorities of the EU member states are not defining what has to be checked before (or during) experimental field trials. The data as made available by the companies are not subjected to an EU wide evaluation protocol.

Thus it is proposed here a new, transparent and clearly defined 'step by step' procedure be established, before market authorisation is requested and field trials take place or feeding trials are conducted. This procedure should involve the levels of both EU member states and the EU authorities and should also include assessment of ethical and socio-economical criteria (see section 6).

Monitoring

2.3

The deficiencies in risk assessment mentioned also impact the way monitoring is performed. EU regulations require post market monitoring of genetically engineered plants. According to Council decision 2002/81, genetically engineered plants (and derived products) also have to be monitored for potential health effects and ecological risks. On the aims of risk assessment:
"The environmental risk assessment aims, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct and indirect, immediate or delayed, on human health and the environment arising from its placing on the market. This assessment may also need to take account of potential long-term effects associated with the interaction with other organisms and the environment. The evaluation of such potential adverse effects should be founded on common methodology based on independently verifiable scientific evidence."
[...]
"Against this background, it is foreseen that the objectives of post-market monitoring, as detailed under Annex VII, are to:
- confirm that any assumptions regarding the occurrence and impact of potential adverse effects of the GMO or its use in the environmental risk assessment are correct, and
- identify the occurrence of adverse effects of the GMO or its use on human health or the environment which were not anticipated in the environmental risk assessment."

The way monitoring is actually performed depends essentially on the results of risk assessment. If no concrete risk is identified, monitoring might only be performed as 'general surveillance' without any specific scientific investigations. So the risk assessment and the system for monitoring move in circles. The risks of genetically engineered plants are not thoroughly investigated during risk assessment and therefore not subjected to detailed monitoring. One could say in summary that the aims of the EU regulations (to prioritise the precautionary principle) produce the opposite as a result of this system of self-reinforcing failures.

In fact the EFSA has not so far proposed case specific monitoring for any genetically engineered plant. The only exception to this is that during cultivation of Bt plants a case specific monitoring shall be established in order to observe the potential emergence of resistant pest insects. But this kind of monitoring is much more motivated by the economical interests of the seed companies (which might have to face falling turnover rates if their crops start failing) than by the need for a survey of ecological risks.

The EU Commission is well aware of current deficiencies in the monitoring of genetically engineered plants – at least with regard to potential health effects. As the Commission stated in 2005 (European Communities, 2005):
"As regards food safety, even if some GM products have been found to be safe and approved on a large scale..., the lack of general surveillance and consequently of any exposure data and assessment, means that there is no data whatsoever available on the consumption of these products – who has eaten what and when. Consequently, one can accept with a high degree of confidence that there is no acute toxicological risk posed by the relevant products, as this would probably not have gone undetected – even if one cannot rule out completely acute anaphylactic exceptional episodes. However, in the absence of exposure data in respect of chronic conditions that are common, such as allergy and cancer, there simply is no way of ascertaining whether the introduction of GM products has had any other effect on human health."[11]

The EFSA, too, admits (2007a) that no adequate systems for deriving relevant epidemiological data are currently established. But according to EU regulations, market authorisation of genetically engineered plants (and derived food and feed) is closely connected with the availability of effective monitoring systems.

The EFSA is not in fact responsible for deciding on how to monitor and survey potential risks (it can only make some proposals in the matter). Responsibility falls within the sector of risk management and political decision making, which in this case is part of the remit of the European Commission. As a conclusion one could question if the Commission is acting in accordance with European regulations if market access for genetically engineered food and feed is granted despite it being known that effective systems for monitoring its potential health effects are not available.

11 Paragraph 45, European Communities (2005)

New doubts about safety

3.

Given the deficiencies of existing risk assessment it is not surprising that even the safety of products that have already passed authorisation is still a matter of controversial discussions. This is most evident in the case of genetically engineered maize MON810, the cultivation of which is prohibited by a growing number of member states in the EU.

3.1

Plants producing insecticides

By 2009 the cultivation of insect resistant maize MON810 had been prohibited in a growing number of EU member states: Austria, France, Germany, Greece, Hungary and Luxembourg. So far this Bt toxin-producing maize is the only genetically engineered crop allowed to be commercially cultivated within the EU. It is grown on about 100,000 hectares in Spain.

A modified gene sequence from the Bacillus thuringensis soil organism was inserted into the plants by genetic engineering. This causes the Bt toxin to be produced in all parts of the plants. From there it is also emitted via pollen and parts of the plants into the environment and secreted by the roots into the soil. MON810 was granted market authorisation for the EU in 1998; this ended (according to EU regulations) in 2007. The US company filed an application for reauthorisation which was assessed and decided on in its favour by the EFSA in June 2009 (EFSA, 2009).

The German government prohibited the cultivation of MON810 in April 2009. It was argued that new publications showed negative effects on organisms such as ladybird larvae (Schmidt et al., 2008) and water fleas (Bøhn et al. 2008). An overview of recent scientific publications shows that the effects observed on these and other non-target organisms indicate a general problem with MON810 - there is growing evidence that the supposed selectivity of the toxin (which is meant to be active only on certain Lepidoptera larvae) is not in accordance with the scientific facts (Then&Brockmann, 2009).

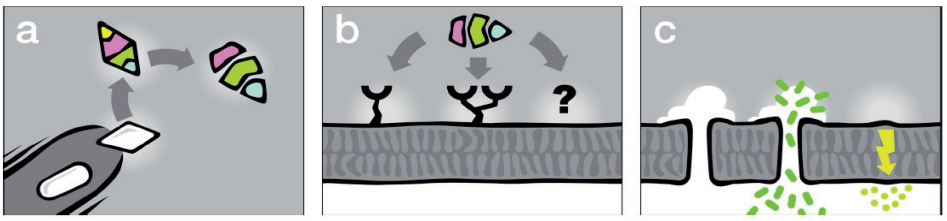
Because the natural occurring Bt toxins show a quite complex mode of action it was supposed that the toxins as produced in the plants can only fulfil their deadly mission under conditions as met in the gut of the larvae of certain insects (Lepidoptera). Specific receptors, described as 'target organisms', occurring in the gut of these pest insects (and in the case of MON810 the corn borer especially), are needed to activate the toxin. In contrast so called 'non-target organisms' are supposed not to be endangered because those receptors cannot be found. But this general assumption has to be reassessed in the light of recent publications:

- The toxin as produced in the plants is different in its structure from the natural occurring Bt toxin and thereby also changed in its biological activity (Hilbeck&Schmidt, 2006; Li et al., 2007).
- It seems premature to declare that the mode of action as described in target organism is the only way to initiate the toxic effects. Several publications show that a coherent theory for the mode of action of the Bt toxin (and the role of receptors) is missing. The different existing models are partially complementary but also contradictory to each other (Pigott&Ellar, 2007).
- Inference and synergies with external factors which can enhance the toxicity of the toxins have so far not been assessed. Recent research shows that the selectivity and the efficacy of the Bt toxins can be quite substantially influenced by external factors (Kaatz, 2005, Kramarz et al. 2007, Broderick et al., 2009, Then, 2009b). These potential risky synergies are also discussed in the interview with a honey bee expert in the next section.

These aspects are very relevant in the risk assessment of Bt plants such as MON810, but are ignored by the EFSA in their recent assessment of the application for reauthorisation of MON810 (EFSA, 2009).

The EFSA does not question the selectivity and mode of action of the Bt toxin as produced in the plants when listing various publications about effects on non-target organisms. Figure 1 gives an overview of some of the questions concerning the mechanisms of Bt toxins (source: Then, 2009b). It shows that many decisive questions concerning the toxicity of Bt toxins still need to be answered.

Fig. 1: some theories for mode of action of Bt -toxin (Cry1Ab)



(a): The inactive form of the protoxin is produced by Bacillus thuringiensis. In the gut of the insect larvae it is transformed to a solubilised active toxin which is shorter than the protoxin. For this process of activation an alkaline pH and certain enzymes are needed. These steps are not necessary for Cry toxins as produced in genetically engineered plants which are already activated by the technical process and by plant enzymes. (b): Several types of midgut receptors are thought to be decisive for the binding of the toxins in cells and some experts question the role of receptors in general. (c) Several mechanisms are thought to be decisive in the last step of toxin reaction:.Models exists with and without pores in the pithelial cells and with and without involving gut bacteria (source: Then, 2009b)

Another detail in the EFSA's recent opinion on MON810 (EFSA, 2009) is quite typical of the way the authority deals with uncertainties. Rosati et al. (2008) report that at the border between the normal maize genome and the newly inserted gene sequence a hybridisation of the DNA takes place leading to unexpected biological activity. These hybrid genes could even cause the production of proteins that have no similarity with known plant compounds. The EFSA takes notice of the publication but does not see any need for further investigations:
"These putative recombinant proteins did not show homology with any known protein and do not raise any new safety concerns."

It looks as if just because the properties of the new putative proteins are not known, the EFSA considers them as being safe (see also Cotter&Mueller, 2009). This is a typical example showing how biased the EFSA is in dealing with uncertainties that show up during risk assessment of genetically engineered plants. Uncertainties are mostly judged as indicating no or only minor risks because of the underlying hypothesis that defines transgenic plants as being comparable (or one could say similar) to conventional plants which have a history of safe use.

3.2 Herbicide-tolerant plants

Transgenic plants tolerating the glyphosate (brand name: Roundup) herbicide are grown in several regions of the world. The impact of the herbicide is increasingly cause for debate. The amount of this herbicide used has been rising for years, since more and more weeds show some tolerance against glyphosate and higher dosages are needed to treat them effectively (Service, 2007). As more is used, residues of the herbicide in the plants are also likely to increase, and some countries have already changed the level of acceptable uptake in food. At the same time more and more publications show that the mixture of the herbicide as it used in Roundup can cause negative effects on human embryos (Benachour&Séralini 2008) and the reproductive system (Gasnier et al, 2009).

This has been a matter for political discussions in Argentina, in particular, where about 100% of soybeans cultivated are herbicide-tolerant to glyphosate. After reports that glyphosate is more highly toxic for amphibians than previously thought were published thereglyphosate, health risks were also newly discussed. A group of attorneys active on environmental questions started a legal procedure to withdraw the authorisation of the herbicide.[12] Other environmental impacts of the large scale cultivation

12 Webber, J., Weitzman, H., 2009, Argentina pressed to ban crop chemical after health concerns, Financial

of the herbicide-tolerant soybeans have also been reported – impacts on soil organisms and the lower availability of essential soil minerals and aquatic systems (see overview Mertens, 2008).

The increase in herbicide-tolerant weeds has given reason for several companies to go for the production of further herbicide tolerant plants that can resist other chemicals (Service, 2007). Indeed new competition in the fields that is likely to result in the usage of chemicals with a higher toxicity being applied on large scale has started. This can be seen for example by the plans of US company, Dow AgroSciences, for arming soy plants with resistance against the 2,4 D herbicide (2,4-Dichlorphenoxy).[13] This chemical is supposed to have much higher detrimental impact on environment and human health than the current use of glyphosate. 2,4 D was also a compound in Agent Orange, used in the Vietnam war to defoliate trees and severely damaging human health. All in all the use of herbicide tolerant plants does not lead to a reduction of the use of herbicides; on the contrary, thetoxic burden on human health and the environment will be increased.

3.3 'Stacked events' and interactions between transgenic plants

Genetically engineered plants that are manipulated to combine different gene constructs are called 'stacked events'. In 2009 a maize was authorised with eight different gene constructs in the US and Canada.[14] The plants are a joint production of Monsanto and Dow; they are sold under the brand name SmartStax and are supposed to be grown on several million acres within the next few years. The plants produce several insecticides and are tolerant of two herbicides.

The EU has also authorised several stacked events for import (such as NK603xMON810 and MON863x-MON810). With positive opinion on Bt11 and 1507 maize the EFSA favours the cultivation of transgenic maize in the EU which combines insect resistance and herbicide tolerance (EFSA 2005a and b).

The EFSA guidelines for the risk assessment of stacked events do not foresee specific investigations to identify unintended interactions between the different gene constructs and their products (EFSA 2007b). The EFSA assumes that in most cases the assessment of each of the single constructs will be sufficient. The authority is aware of potential interactions between the different events (EFSA 2007b) but concludes that field trials that have already been performed for one year will be enough to identify unintended effects. In doing so it is in the main following the industry's guidelines. Monsanto for example refers to the notion that experience with conventional cultivation should be drawn on in dealing with plants and stacked events.
"An important point for our work on stacked events is that conventional breeding is not necessarily safe, but it has a history of safety developed over time. In addition, we can use our knowledge of breeding to produce stacked events that meet criteria of acceptable safety (as safe as)."[15]

The Austrian authorities are among others who have assessed this approach by the industry, which is in the main also applied by the EFSA, as inadequate (Spök et al., 2007). The EFSA is in principle bound by law to examine, and also take account in its monitoring, interactions between plants and cumulative effects when dealing with genetically engineered plants. This can be seen from Directive 2001/18:

Times, May 29 2009, http://www.ft.com/cms/s/0/3d74344c-4be8-11de-b827-00144feabdc0.html?nclick_check=1, Argentinien: Kranke Dörfer, Gesundheitskrise durch herbizidintensive Sojaproduktion, 5.03.2009, BUENOS AIRES, IPS EUROPA, http://www.ipseuropa.org/index.php, ARGENTINA: Soy - High Profits Now, Hell to Pay Later (29.07.2009, Buenos Aires, IPS International) http://www.ipsnews.net/news.asp?idnews=43353

13 http://www.gmfreeze.org/page.asp?id=385&iType

14 http://www.bloomberg.com/apps/news?pid=20601103&sid=a57J5HHLMOg4

15 Thomas Nickson, Monsanto Company, USA, 2009-07-10, http://bch.cbd.int/onlineconferences/stacked2_ra.shtml?threadid=1214

"A case-by-case environmental risk assessment should always be carried out prior to a release. It should also take due account of potential cumulative long-term effects associated with the interaction with other GMOs and the environment." (recital 19)
and
"Monitoring of potential cumulative long-term effects should be considered as a compulsory part of the monitoring plan." (recital 20)

Annex II of the 2001 Directive also explicitly mentions interactions between genetic engineered plants and cumulative effects. Cumulative effects and potential interactions have to be taken into account as well in the parallel cultivation and imports of different genetically engineered plants and in the case of stacked events in single transgenic plants. As already mentioned it is known that synergies can emerge between different Bt toxins (Schnepf et al, 1998). Investigations by Kramarz (2007) and Kaatz (2005) show that synergies and interactions with external factors can make Bt toxins toxic in non-target organisms. Further, there are concerns that combined cultivation of Bt plants can cause cross resistance in pest insects (Tabashnik et al, 1997 and 2009). This means the EFSA would have to consider possible interactions between MON810, Bt11 and maize 1507 and their Bt toxins if these transgenic plants are grown or fed to animals in any combination. The same is true for stacked events such as MON863x-MON810.

Interference between Bt producing plants and the use of chemicals (herbicides, pesticides) is demonstrated as well. It has been published that the additional use of insecticides impacts the concentration of Bt toxins in the plants (Griffiths et al, 2006). Further, if Bt toxins are used in combination with herbicides such as glyphosate and glufosinate, the herbicidal residues in the soil will decrease slower (Accinelli et al. 2004). The potential interactions between events conferring herbicide tolerance and insect resistance are relevant for several genetically engineered plants such as Bt11, maize 1507, NK603xMon810 and SmartStax.

According to a report by the EU Joint Research Centre (JRC, 2009) it can be expected that more than 100 different events might be introduced into markets (or have authorisation applied for) in the next few years until 2015, and that several hundreds or even thousands of possibilities will be created for combining these events in stacked plants. According to EFSA standards detailed analyses of potential interactions or cumulative effects will only occur in some rare cases. The arguments presented above imply these standards should be seen as conflicting with current EU regulations such as Directive 2001/18.

3.4 General risks from genetically engineered plants

Risks from genetically plants depend not only on certain traits or events, but are inherently caused by the method of their production. While it is tru that risk assessment has to be performed on case by case studies, it also cannot be denied that there are certain risks that are typical just for transgenic plants.

3.4.1 Risks to immune system

Prescott et al (2005)'s publication shows that the technology of invasive gene transfer can cause severe risks to human health. A gene sequence from beans was transferred into peas. Investigations with the transgenic peas resulted in a severe reaction of the immune system in mice. Interestingly the transgenic peas were tested before on rats, pigs and poultry without showing these detrimental effects. Only testing specifically in mice revealed the immunotoxilogical reaction. Valenta &Spök (2008) evaluate the findings once more and identify some methodological deficiencies by the experiments as performed by Prescott et al (2005). They discuss the possibility that additional proteins that might have contributed

to the immune reaction were produced in the peas. They conclude that the causes of the observed effect are not known in detail (therefore it is not clear to what extent the protein from the bean bears a specific immanent risk) and explain that in the light of these findings the guidelines for risk assessment in the EU should be revised:
"On the other hand, the Prescott study clearly shows that a transgenic protein can induce under certain conditions an unwanted immune response leading to organ pathology and certain experiments demonstrate that exposure to the transgenic protein can increase the immunogenicity of other unrelated proteins which are administered together with the transgenic protein, a finding which would not be detected by current risk assessment procedures. In this context the Prescott study indicates a strong need for reconsidering the current approach to GM allergenicity assessment."

So far there are no standardised methods for testing for immune reactions to transgenic plants (EFSA, 2007a). This should certainly be a matter of concern, because there are several other publications besides Prescott (2005) and Valenta&Spök (2008) which show specific risks just at this point (Finamore et al., 2008; Kroghsbo et al.,2008; Sagstad et al., 2007).

How the environment impacts transgenic plants and the introduction of crash tests

3.4.2

Findings in genetically engineered maize and cotton producing the Bt toxin show that its associated risks are dynamic and subject to environmental conditions. Interference from light, fertilizer and climate can affect the Bt content in maize MON810 substantially (see table 2). Further factors in the plants seem to play a role because significant differences between maize plants grown side aside in one field have also been observed (Lorch&Then, 2007). All in all there are not yet enough results published to judge the real range of possible variations of Bt content in transgenic plants. In addition the methodology and protocols used for measuring Bt content are not standardised and thus the results can hardly be compared in many cases (see Then&Lorch, 2008).

Table 2: factors impacting Bt content in MON810 maize (source: Then & Lorch 2008)

Author	Factors	Impact
Abel and Adamczyk (2004)	photosynthesis	Bt content and photosynthesis are correlated
Bruns and Abel (2007)	nitrogen fertiliser	Bt content and nitrogen fertiliser are correlated
Griffiths et al. (2006)	soil quality	can increase or decrease Bt content
Griffiths et al. (2006)	pesticide use	spraying of insecticide (pyretroid, Decis) increases Bt content in leaves and roots
Griffiths et al. (2006)	growing process	Bt content increases towards flowering
Nguyen and Jehle (2007)	climate zone / regional factors	significant difference
Nguyen and Jehle (2007)	growing process	Bt content in leaves increases during growing season
Nguyen and Jehle (2007)	epigenetic effects	unclear
Nguyen and Jehle (2007)	genetic background of different varieties	unclear
Nguyen and Jehle (2007)	genetic instability	unclear

It is also known from experience with genetically engineered cotton (Chen et al., 2005) and soy (Coghlan, 1999, Gertz et al., 1999) that transgenic plants react to climate conditions. Furthermore, investigations on genetically engineered potatoes show that under stress conditions these plants reveal

unexpected reactions which are not detected under 'normal' conditions. Matthews et al (2005) subjected genetically engineered plants to several biotic (such as infections) and abiotic stress factors. They found several differences between the potatoes in the formation of of defending compounds. Their conclusion reads:

"Transgenic and nontransgenic potato lines were exposed to a range of biotic and abiotic stresses and a range of environmental conditions in the field and during storage. After the stress had taken effect, a comparison was made between the two groups of the potato glycoalkaloid and sesquiterpene levels. Significant differences were observed in the levels of both in the transgenic and control material and in infected and non-infected material."

The EFSA does not request any data on the potential (extreme) impact of environmental conditions on transgenic plants. While it is interested in some information about the genetic stability of the artificially introduced gene construct over a period of several generations, the EFSA does not define any external conditions which should be met for testing stability. The question of how the metabolism of the plants might react to climate stressing, for example – an issue which seems to be quite relevant in the context of ongoing climate change – is not part of the risk assessment. Because genetically engineered plants have to be seen as technically derived products, it is quite plausible that specific crash tests might reveal some limits of their genetic and metabolic stability. In the report as presented here it is suggested specific tests – 'crash tests', as they are called - be introduced for measuring the impact of defined environmental conditions on genetically engineered plants (see section 6).

Introducing such tests would make it possible to generate a great deal more basic data on each product than at present before they are released or applications for approval are made. The stability of transgenic plants and possible changes in their metabolisms can only be determined with defined stress conditions in a contained system. This kind of controlled test (crash test) would not only provide data on the concentration of critical compounds such as Bt insecticide, it would also allow observation of the plant's own compounds whose concentration may inadvertently have been influenced by the introduction of an additional gene.

There are now a number of new test procedures developed in recent years which can be used. For example, so-called microarrays allow simultaneous measurement and compilation of metabolic profiles of several gene activities. These tests are carried out internally by various companies but the results are hardly ever published. The EFSA believes these investigations to be important but does not consider them to be ready to be put into practice, although such procedures have been available for years now (EFSA 2007a).

Besides these newer methods of investigation there are many other ways of determining changes in the compounds of genetically engineered plants such as the content of Bt toxins. This does, however, necessitate an agreement between laboratories on the relevant standards.

Only when the data is presented can useful hypotheses be formulated to describe how plants behave under changing or extreme environmental conditions, the consequences for plants and the risks involved.

How independent are public research and the authorities?

4.

In the EU the promotion of independent research on genetically engineered organisms is safeguarded by Directive 2001/18:
"Member States and the Commission should ensure that systematic and independent research on the potential risks involved in the deliberate release or the placing on the market of GMOs is conducted. The necessary resources should be secured for such research by Member States and the Community in accordance with their budgetary procedures."

Despite this there have been many complaints in the last few years that independent research in Europe is systematically hampered by several mechanisms.[16] This problem was recently brought up in an interview conducted by Christof Potthof with a German honey bee expert, Hans-Hinrich Kaatz. The scientist had disturbingly realised that staff of the US company Monsanto knew about a decision by Nature magazine to reject his publications before he the author was contacted. Parts of the interview are documented below.[17]

In 2009 statements that public research is systematically hampered by seed companies were published in the US. 26 scientists from 16 US states in which genetically engineered maize is commercially grown filed a complaint at the EPA. They reported that the industry was denying access to necessary research material by abusing intellectual property rights.[18] Under these conditions truly independent research cannot be conducted and important questions concerning the impact of the cultivation of transgenic plants cannot be investigated[19]:
"Technology/stewardship agreements required for the purchase of genetically modified seed explicitly prohibit research. These agreements inhibit public scientists from pursuing their mandated role on behalf of the public good unless the research is approved by industry. As a result of restricted access, no truly independent research can be legally conducted on many critical questions regarding the technology, its performance, its management implications, IRM, and its interactions with insect biology. Consequently, data flowing to an EPA Scientific Advisory Panel from the public sector is unduly limited."

The editors of Scientific American Magazine report:
"But agritech companies such as Monsanto, Pioneer and Syngenta go further. For a decade their user agreements have explicitly forbidden the use of the seeds for any independent research. Under the threat of litigation, scientists cannot test a seed to explore the different conditions under which it thrives or fails. They cannot compare seeds from one company against those from another company. And perhaps most important, they cannot examine whether the genetically modified crops lead to unintended environmental side effects."[20]

These statements are especially relevant because in the debate about potential risks of transgenic plants the US is very often referred to as an example for how no adverse effects from large scale growing are so far known.

Scientists in Europe, too, complain of restrictions to access, or of even no access, to research material. Two different kinds of material are relevant here: Genetically engineered plants are covered by patent

16 Kleiner Käfer, große Fragen, Frankfurter Allgemeine Zeitung, 19. April 2009
17 Full version only in German: http://www.gen-ethisches-netzwerk.de/gid/194/kleiner-parasit-grosse-wirkung
18 New York Times 20.Feb. 2009: Crop Scientists Say Biotech Seed Companies Thwarting Research on GMO Safety, Ef ficacy, http://www.nytimes.com/2009/02/20/business/20crop.html
19 http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=090000648084de39
20 Do Seed Companies Control GM Crop Research? Scientific American Magazine - August 13, 2009 http://www.scientifi camerican.com/article.cfm?id=do-seed-companies-control-gm-crop-research&print=true

law, which is the basis for written agreements required for their purchase. Secondly, there is the material needed to make comparisons between the transgenic plant and its conventional counterpart, the so called isogenic lines, access to which is even more difficult. These plants are the closest 'relatives' to the genetically engineered plants and a prerequisite for assessments that aim to investigate substantial equivalence.

Independent researchers also report difficulties in publishing their findings if these are in contradiction to the interests of the industry. An example of these complications is the history of a publication about research on transgenic seed contamination of maize landraces in Mexico, one of the centres of origin of maize biodiversity. As long ago as 2001 initial findings were published about contamination in regions where seed propagation of local varieties takes place (Qist&Chapela, 2001). These findings were challenged by many sides and even scientists involved were afraid of becoming removed from their public institutions in the US. Some contamination was again detected in 2008. But the Proceedings of the National Academy of Sciences magazine rejected publishing these results, because it was afraid that further political debates might arise (Dalton, 2008). As a scientist, Alison Snow, from the US Columbus University wrote in an article for Molecular Biology magazine[21]:
"Furthermore, the politically sensitive nature of this information has made it difficult for researchers to publish their findings."

This case is not the only one. There are several publications that caused real hunts against their authors because their findings revealed potential risks from genetically engineered plants. For example, in September 2009, Nature magazine[22] reported about the case of Rosi-Marshall, which became the target of a campaign just because she described the impact of Bt plants on some water organisms (Rosi-Marshall et al., 2007):
"Behind the attacks are scientists who are determined to prevent papers they deem to have scientific flaws from influencing policy-makers. When a paper comes out in which they see problems, they react quickly, criticize the work in public forums, write rebuttal letters, and send them to policy-makers, funding agencies and journal editors."

4.1

An illustration: feeding trials with cows and the dairy industry

A research project involving feeding trials with the transgenic maize MON810 illustrates how difficult the conditions for independent research into risks in Germany are. Its results were presented by the Technical University of Munich (TUM) in 2009 (Meyer et al., 2009), in the midst of political discussions in Germany about the prohibition of the cultivation of MON810 maize. According to scientists involved in this feeding trial, which lasted 25 months, the findings can be taken as proof that the transgenic maize has no impact on lactating cows. It further highlighted that no residues from the transgenic maize could be detected in the animals' meat or milk. The study was presented to the press as the best study ever made:
"The study by Munich Technical University, the most detailed and most precise study ever conducted worldwide, has shown yet again that feeding with transgenic maize does not have any impact on the food chain."[23]

The results were also published in an international magazine (Steinke et al, 2009). The publication mentions that the findings are of robust quality because of the long duration of the feeding trials:
"Feeding Bt maize over a period of 25 months had no effects on the performance and metabolic parameters in this study. The statistical differences between isogenic and transgenic fed dairy cows (milk

21 Molecular Ecology, 2009, 18, 569–571
22 Waltz, E., 2009, Battlefield, Nature Vol 461/3 September 2009: 27-32
23 Prof. Dr. Wolfgang Herrmann, president of the Technical University Munich, quoted in Landshuter Zeitung, page 2, 7st Aprile, 2009, tranlation: authors

protein, milk fat and glucose) in the first lactation were not confirmed in the second lactation and are probably due to individual or physiological differences between animals."

But as a comparison between the results as presented in German (Meyer et al. 2009) and English (Steinke et al., 2009) shows (Then 2009 c), the international publication does not mention several relevant data and furthermore hides the fact that many animals were removed from the trials during them. Only one third of the cows (18 animals) were fed over a period of 25 months as stated by Steincke et al., 2009. The rest of the 54 cows were changed during the trials without concrete reasons or the exact timing of the substituting being made public. Despite the fact that changing the animals in this way is highly plausible as the main reason why significant results could not be confirmed over the whole period of the study, the official international publication does not mention this important fact.

Further analyses of the data shows that the study hardly allows any final conclusions to be made. As mentioned, the statistical figures do not show which animals took part in the feeding trials over which period of time. Specific and detailed investigations concerning certain organs, as well the examination of the calves, are missing. Further, it is not clear to which extent the Bt toxin was deactivated by the heating process performed for the preparation of the feedstuff. All in all the conclusions of Steincke et al (2009) and the presentation of the results in the press have to seen as being as inadequate and even misguiding.

The second part of the study, which aimed to detect residues (such as specific DNA) of the genetically engineered plants in animal products (especially milk), also has to be discussed in a critical way. The methods and protocols used are not in accordance with international standards and technically not sufficient for showing the highest likelihood of making such a detection successfully (Then, 2009c).

The project was funded partially by the dairy industry. Some of its members were repeatedly criticised by consumer and environmental organisations because they allowed the use of genetically engineered plants in their animal feed. Even before the trials were started, the leading scientist in the project signed a declaration stating that residues from genetically engineered plants cannot be found in animal products (see Then, 2009c). All in all this research project provides a lot of good reasons to raise doubts in the independence of public research.

Special agencies' network

4.2

In Germany the framing of public research and independence of the national authorities are subjects of general debate. There are several reasons for these discussions, which were presented in an overview in 2008 (Lorch&Then, 2008). Some examples of the connections between corporations and the authorities documented in that overview are listed here:

- A consulting agency which closely works with biotech industry officially presents the results of public risk research (www.biosicherheit.de).
- There are several reports that staff of the German authorities (Hans-Jörg Buhk and Detlef Bartsch) appeared in a Monsanto promotion video.
- German authority staff (Joachim Schiemann und Klaus Dieter Jany) were involved in patent applications on genetically engineered organism.
- German authority staff have been coordinating organisations (such as Wissenschaftlerkreis Grüne Gentechnik) that are supportive of the use of genetically engineered plants in agriculture.

Systematic analysis shows there to be a close interconnection between the authorities and consulting agencies in national and international institutions. Special mention can be made here - besides the German Wissenschaftlerkreis Grüne Gentechnik of the Public Research & Regulation Initiative lobbying

organisation as well as the EU's Biosafenet and Co-Extra projects BiosafenetCo-Extraand the International Society for Biosafety Research (ISBR). The German consulting agency Genius GmbH can be identified as one of the most active organisations promoting active networking between the authorities and corporations.

The report by Lorch&Then (2008) mentions the following activities of Genius GmbH: Genius is member of the BIO Deutschland national umbrella organisation and the European lobby organisation, the European Federation of Biotechnology. It has about 20 staff and its official annual turnover is about two million euro. Genius's customers are companies like Bayer, BASF, Monsanto and Syngenta, and also the European Commission, the German state of Hesse and the German ministry for education and research (BMBF). Public outreach often is presented indirectly: the consultancy edits the biosicherheit.de website on behalf of the BMBF and presents the outcome of publicly funded risk research – at a first glance the website looks like an official medium of the ministry.

A second project that aims at public outreach and is organised with the support of Genius is the "GMO Compass", which was first financed as a EU project (2005-07), then funded by EuropaBio (2007) and the German agriculture ministry (2007-2008). Other organisations involved in the project are the initiators of the transgen.de website, which was first financed by a consumer organisation and then partially financed by the biotech industry. Intended to be perceived as having a close relationship to a consumer organisation, GMO Compass gives the impression of being an unbiased institution. But the editing team is more or less identical to that of www.biosicherheit.de, describing themselves as "independent science journalists". Joachim Schiemann of the Julius Kühn institute (JKI) and former member of EFSA's GMO panel is also mentioned as are a member of GMO Compass' advisory team and the industrial umbrella organisation EuropaBio.

Projects such as biosicherheit.de and the GMO Compass can be seen as an exception in the activities of Genius GmbH. Mostly its members work as service-orientated consultants, very often in combination with members of the authorities. The JKI's Joachim Schiemann, in particular, is very often to be found in this connection.[24] Genius was active in the EU's Biosafenet project, its coordinator Joachim Schiemann. Genius staff are involved in the ISBR's internet presentation, while its former president was Schiemann.[25] Joachim Schiemann was a partner in the EU's Co-Extra project, with Genius working as an editorial office. Together with Schiemann and Jeremy Sweet (EFSA) Genius was also a member of the management board of Co-Extra. Joachim Schiemann was the German representative at the EU "Plants for the Future" strategy meeting and members of Genius were invited as experts. Genius was also active for the EFSA editing its publications such as the 2006 annual report.

Agencies such as Genius GmbH work like an intermediary between the authorities and industry; they lower the borders between public institutions and private interests and foster increasing intransparency in the way decisions are really taken where genetically engineered plants are concerned.

24 most details as found in the year 2008

25 Schiemann was followed by Patrick Rüdelsheim, former staff member of Plant Genetics Systems and Bayer Crop Science.

Interview by Christof Potthof with the bee researcher Hans-Hinrich Kaatz, University of Halle[26]

Introduction

In an investigation colonies of honey bees infected with the parasite nosema and fed with the pollen of the genetically modified maize MON810, collapsed much earlier than those colonies which were fed with conventional maize pollen. (.....)

What did you observe during the investigation?

In the first year of the field trial designed to last six weeks in that year, the honey bee colonies fed with the Bt maize pollen very clearly collapsed after three weeks. The effects were always the same in the Bt nets. I found this very unsettling because it was not what I had expected; all the previous data from other researchers, which is naturally not transferable, had suggested that the Bt toxin had no effect on honey bees. Then, of course, one has to think about why this should be. It was possible that the causes could be found in our methods; we had used a ten-fold higher concentration of the Bt toxin than there would have been in a natural environment i.e. the Bt content given as the content in the pollen of the genetically modified plants. Because we had not expected any effect we thought we would "use the ten-fold amount to be on the safe side. Also if we used the ten-fold amount and found nothing then we could put our minds at rest about the lower content in the plants." (.....)

Did you find any other clues when you examined the dead honey bees?

Well, of course, we asked ourselves what had happened to the bees. There were dead honey bees everywhere. We tried to find out which factors had caused their deaths. One possible factor was that affliction with nosema[27] was relatively high in the honey bee colonies. That was something we had not expected quite so strongly at that time in autumn. Basically we knew that the occurrence of nosema can be intensified under stress conditions.

If the higher occurrence of nosema is connected to stress then it should have appeared in the colonies without Bt.

Yes, that is how it was. We examined the control colonies without Bt and found no differences. But it was clearly observed that first of all only the Bt group of colonies collapsed and the control group collapsed later on. However, I need to repeat that we have no evidence. At the moment it is nothing more than a correlation, it could be coincidence.

But does it have statistical significance?

Yes. That is indisputable except that we could not clarify the cause. Interaction between microorganisms found in the digestive tract and the target cells for the toxin has been described in the literature. This has been observed in butterflies .... So thinking in this direction is not erroneous. (....)

Have co-factors been included in this type of investigation in the past?

No, the effect of co-factors has not really been taken into account. One has to say that this kind of investigation is a huge undertaking. In an investigation of a pesticide it is only the active agent factor that is examined. Clearly we need to be very careful here and look much more closely at this aspect in future. Other questions arise too: for instance, is the present testing procedure really adequate in its dimensions to include co-factors? If we actually find evidence that there is some interaction between the effects of co-factors then we need to get down to work. It is a relatively new view point. (...)

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26 Gen-ethischer Informationsdienst, GID, 194: page 5-9, http://www.gen-ethisches-netzwerk.de/gid/194/kleiner-parasit-grosse-wirkung

27 Nosema apsis is a parasite which causes a kind of dysentery in honey bees. It is a microsporidian and is now often classified as fungi.

In the past you have done other honey bee research. Can you tell us a little bit about this?
Before starting the project with the Bt plants we had already done some research on possible hazards to the health of honey bees due to genetically modified herbicide resistant oil-seed rape and maize plants. We did not find anything negative here. Apart from this we also investigated whether the genes that come from the pollen of the plants could be transferred to honey bees. This is called horizontal gene transfer. Our first step was to find out if genes from the plants could be transferred to the microorganisms in the digestive tract of the honey bees. Later on we aimed to determine how high the probability was that the honey bees incorporate the genes themselves. One must consider that the crossover of genes is one of the principal mechanisms of evolution. It happens in very many groups of organisms. It was more a fundamental question of scientific principles than a practical problem. We cultivated the microorganisms with the pollen and the result was that the microorganisms had indeed taken up the pat gene.[28] In the debate on genetic engineering it had always been said that one thing that could never happen was the horizontal transfer of newly inserted genes. We presented the results to the Nature journal and got two expert opinions. One was very positive, thinking it could be published immediately. The other thought we should do an additional analysis, a so-called Southern blot which would further verify our results. Then he would back publication. We said, "We'll do that." We did the Southern blot and submitted the article again in the belief that there was now nothing in our way. For a long time we heard nothing at all from the editorial team at Nature but in the meantime we were visited by a ZDF (German public television channel) team who asked us about our research. At the time we told them that nothing could be broadcast until an agreement had been reached with Nature and the article had been published. They nevertheless did broadcast a television programme. It was even on the news – all before we had had a final decision from *Nature*. We intervened strongly whereupon one of the ZDF team said, "Wait a minute, don't you know that your article has been rejected." Until that moment we had had no idea. When we asked him how he knew he said that he had spoken to some people at Monsanto and they had told him. Naturally I was shocked. It is good that they get to know these things, but I find it awful that they should know before the authors know.

How extraordinary!
Well, you know that when the person making the decision has contacts to Monsanto says something ... good. But the editorial team – since they were the only ones to have had both reports - that they pass this on, I find that very annoying. Such a highly respected journal. They shouldn't need to do that. In fact such a review process should first and foremost be.....(falters)

....discreet?
....very discreet.

You probably don't know the names of either of these editors, do you?
No.

Do they know your name?
Yes, they get the paper and then of course they know the names of the authors. It is not anonymous. Unless you insist. Sometimes that happens. In sensitive cases. I didn't think our data was so sensitive. We have repeated the experiment. And we have been able to prove that horizontal transfer occurs with a whole series of microorganisms of different kinds.
(....)

Were your findings published somewhere else later on?
No, not yet. Since they are something no one wants to hear it is difficult to find an adequate place for them. (....)

28 The pat gene in genetically engineered plants mediates a tolerance to the herbicide agent containing glufosinate

Political responsibilities

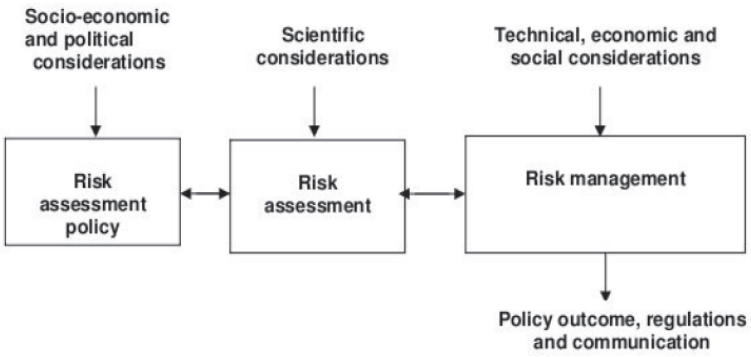
5.

The European Union has fixed high standards in its regulations for protecting consumers and the environment (Regulation 178/2002, Directive 2001/18, Regulation 1829/2003). A majority of EU member states currently seems to be convinced that these standards are not met by the practice for authorising transgenic plants. Since the EFSA started its work, none of its opinions about risk assessments of genetically engineered plants has been accepted by the necessary majority of EU member states. On thecontrary, a majority has even voted against the EFSA's opinions in several cases.

In 2009 the EU Commission came up with a statement that it is no longer going to authorise transgenic plants without having the support of the EU member states. The reason for this announcement is a genetically engineered BASF company potato called Amflora. The EFSA and EU Commission already declared their consent to its authorisation but no majority was reached in the EU Council. The EU Commission has in similar situations so far not hesitated to grant market authorisation. But this was not the case with Amflora; instead the Commission explained it was not going to proceed with the case if the member states opposed the authorisation.[29]

Unlike in the US, in the EU there is a legal distinction between the institutions that conduct scientific risk assessment (the responsibility of the EFSA) and those which decide about the overall risk analyses and risk management. These decisions are taken at the political level. Thus the European Commission and EU Council of member states are the ones to decide about market authorisation (see also Then&Lorch, 2008b). The connections between risk assessment (EFSA), risk communication (EFSA) and risk management and risk analysis (political decision) can be summarised as shown in Figure 2:

Fig. 2 : "Risk assessment policies"[30]



The EFSA's work is confined to scientific risk assessment. The basic requirements of risk assessment policy, on the other hand, are matters for political decision (by the EU Commission or EU member states), as is the subsequent risk management on which the decision on a product's authorisation made.

In taking its decision on market authorisation, the EU Commission not only has to refer to scientific findings, it should also take into account ethical and socio-economical considerations. The precautionary principle has above all a high priority. Regulation 178/2002 defines risk analysis and risk management as follows:
"'risk analysis' means a process consisting of three interconnected components: risk assessment, risk management and risk communication;
'risk assessment' means a scientifically based process consisting of four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation;" (Regulation 178/2002, Art. 3.10-11).

29 TAZ, 19.6.2009
30 aus: JRC, 2008

On the specific balance between risk assessment and risk management it is stated:
"It is recognised that scientific risk assessment alone cannot, in some cases, provide all the information on which a risk management decision should be based, and that other factors relevant to the matter under consideration should legitimately be taken into account including societal, economic, traditional, ethical and environmental factors and the feasibility of controls." (Regulation 178/2002, recital 19)

In the light of this general framework and taking into account the details as presented in the parts above some recommendations are made for the EU's risk analyses as follows.

Some recommendations

6.

(1) Risk assessment of genetically engineered plants should be conducted without preconditions such as assumptions of similarity (familiarity, substantial equivalence) between transgenic plants and plants derived from conventional breeding. The comparison between genetically engineered and conventionally bred plants is an essential tool in risk assessment, but substantial equivalence and familiarity cannot serve as a basic approach or starting point. Transgenic plants have to be seen as technically derived products with specific risks and have to be subjected to comprehensive risk assessment per se.

(2) Before the applications for market authorisation are filed, a mandatory step by step procedure with sufficiently defined criteria should be introduced. To avoid unnecessary feeding trials and field trials, testing in contained systems should be given more weight. This new step by step procedure could part of an integrated risk analysis which requires closer cooperation between EU member states, the EU Commission and EFSA and also encompasses ethical, socio-economical and risk related issues (see for example Haslberger, 2006; Gesche &Haslberger, 2006).

Possible tests which should be performed in an early step of risk analysis are stress exposures of transgenic plants under defined conditions (crash tests), profiling metabolic compounds under different stages of plant growth and environmental conditions, simulations of different ecological systems and interactions with different external factors. Before feeding and/or field trials take place, socio- economic and ethical questions should be assessed according to defined criteria. Table 3 tries to give an overview of the early stages of a new step by step procedure for risk analysis.

These investigations result in data which allow a first insight into the stability and predictability of the transgenic plants as well as the formulation of initial hypotheses on the possible effects on particular organisms and and ecological systems. Investigations like field and feeding trials cannot be fully replaced by these early step in the risk analysis. To avoid unnecessary trials which are of ethical and ecological concern, it is important to perform the testing as proposed in Table 3 in the framework of an integrated risk analysis which also takes socio-economic and ethical criteria into account as a prerequisite for further investigations. These requirements of integrated risk analysis should become a mandatory part of market authorisation procedures.

(3) To support independent risk research, unrestricted access to research material has to be provided. This access has to be guaranteed at the filing date of applications for experimental field trials at the latest. In addition companies should pay at fixed rates into a publicly organised fund which can be used as financial resources for independent research projects. The spending of these funds has to be organised in an independent and transparent manner and involve a range of different research groups.

(4) Clearly defined rules for the selection of potential staff members of the authorities and other experts involved and their code of conduct have to be developed, as do mechanisms that serve to provide absolute transparency about their contacts with industry, to foster the independence of EU authorities.

(5) A system that enables effective monitoring of potential health effects at consumer level is a prerequisite for any authorisation is. Regarding risks to the environment, case-specific monitoring is necessary in any case as soon as a risk potential can be scientifically described. This always should be the case, for example, if plants produce toxic compounds such as Bt insecticides. Further, in view of the general risks from genetically engineered plants, there are good reasons to apply case specific monitoring as a rule, even if just to confirm that no risks can be identified. The existing networks and proposed systems of ‘general surveillance’ are not sufficient to examine risk assessment findings after market authorisation has been given.

Table 3: Step by step procedure for early stages of integrated risk analysis of genetically engineered plants

System	Subject of investigation	Comments
Laboratory	Identification of the localisation of insertion of the artificial gene construct, of possible open reading frames and the exact sequence of the inserted gene. Screening of gene activity and metabolites. Screening for rearrangements, deletions, inversions, and additional parts of the transferred gene sequence or its backbone DNA. Determination of the gene expression under different stages of plant growth.	This level of risk assessment is only partially fulfilled by the EFSA and national authorities. Some methods suited to measuring the metabolism in the plants should be developed further to get evaluated and standardised protocols.
Contained systems (1): Impact of different environments on the transgenic plants	Various stress tests (or crash tests), to measure genetic stability and changes in metabolism under changing conditions (such as soil and climate) or extreme conditions (such as drought or saline soils).	So far no such testing is required by authorities .
Contained systems (2): Impact of transgenic plants on various defined ecological systems	Exposure of several test organisms (such as soil bacteria) with and without integrated food webs, simulation of interaction with external factors or other genetically engineered plants.	So far no systematic, comprehensive testing is required
Decision of the risk manager (political level) about experimental field trials and feeding trials.	On the basis of the generated data and in awareness of ethical and socio-economic questions the risk management takes a decision on whether experimental field trials and feeding trials can be allowed and what exactly should be investigated during those trials.	If the EU authorities cooperate closer on the basis of an integrated approach to risk analyses, unnecessary field and feeding trials might be avoided.

(6) Plants that contain stacked events have to be subjected to a comprehensive examination as complete new applications even if the different events have already passed risk assessment. If new transgenic plants are authorised, interactions with other genetically engineered plants already on the market have to be assessed.

Even if substantially improved concepts for risk assessment apply, it cannot be expected that the risks from genetically engineered plants can be controlled or excluded. This dilemma should be communicated quite openly. The technical manipulation of the plants' genome might no longer be seen as a big technical challenge - but insight into the complexity and possible impacts has increased substantially in the last few years. It is already evident that even today it is a matter of open discussion whether there is a generally authoritative definition of what a gene is (Pearson, 2006). Perceptions and defitions will differ – depending on the context.

The increasing knowledge about the complexity of genome regulation is a strong argument for promoting conventional breeding concepts such as marker assisted selection. These new concepts in conventional breeding apply recent findings in molecular biology but not invasive methods for technical manipulation of genetic information. For the future of plant breeding the usage of the whole range of existing biodiversity will be much more relevant than the methods of transferring isolated gene sequences. Besides unanswered questions about the true risk from transgenic plants, success in recent conventional breeding also provides strong arguments for a change of paradigm which has been on its way for some years already – even in some of the bigger seed companies.

The shift of paradigm can be traced to patent applications by companies such as Monsanto. As is written in its patent application WO2004053055, which claims unintended effects (!) in genetically engineered plants:
"Nonetheless, the frequency of success of enhancing the transgenic plant is low due to a number of factors including the low predictability of the effects of a specific gene on the plant's growth, development and environmental response, the low frequency of maize transformation, the lack of highly predictable control of the gene once introduced into the genome, and other undesirable effects of the transformation event and tissue culture process."

All in all it is time for a fundamental rethink of risk assessment and usage of genetically engineered plants in agriculture and food production.

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Concluding remarks

Testbiotech e.V. was founded by a group of experts in 2008 and this report is its public debut. TestBioTech supports independent research and public debate on the effects of biotechnology. It is an organisation which sees itself as an interface between science and society with a intermediary role between the public, research and politics. Its main concerns are the ecological, social and ethical consequences of biotechnology, particularly the application of genetic engineering in agriculture. TestBioTech supports independent risk research.

In recent years the team at Testbiotech have worked on and acquired expertise in various aspects of modern biotechnology, some of which has been factored into this report.

Christoph Then has amongst other things recently worked on risk assessment for genetically engineered plants which produce the Bt insecticide. His contributions have been published in the scientific media (Then, 2009b, Then & Lorch, 2008a) and cited in discussions on science and politics by various non-governmental organisations (Then 2009a, 2009c, Then & Brockman, 2009). His book Dolly ist tot ("Dolly is Dead") was published in 2008 by Rotpunktverlag publishers in Zurich.

Christof Potthof works for the Gen-ethischen Netzwerk network (www.gen-ethisches-netzwerk.de) and is the editor for the Gen-ethischen Informationsdienst service GID. His contributions focus on the scientific, political and economic fields of agro-genetic engineering. His interview with Professor Hans-Hinrich Kaatz appeared in GID 194. It deals with the problems of independent risk research in Germany and appears here in extracts.

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Risk analysis of genetically engineered plants within the European Union

A report by Testbiotech e.V.
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