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Free trade for 'high-risk biotech'?

Future of genetically engineered organisms, new synthetic genome technologies and the planned free trade agreement TTIP – a critical assessment

Dr. Christoph Then, Testbiotech
December 2013

The German version was prepared with the support of the Green Group in European Parliament

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Dr. Christoph Then, January 2014

This study was written for Martin Häusling, Green Party, Member of the European Parliament.
The English version edited and published by Testbiotech

Layout: Claudia Radig-Willy
Title graphics: Claudia Radig-Willy // elements partly from IStockfoto

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Content

Summary

This is a report on future developments in agro-biotechnology and genetic engineering. It focuses on the kinds of genetically engineered organisms for which market authorisation has been applied in the EU and those that are in the pipeline and might soon be on the market. Special attention has been given to new genome technologies. Furthermore, it includes a discussion of the potential influence of the planned free trade agreement (Transatlantic Trade and Investment Partnership, TTIP) on the authorisation of new genetically engineered organisms for use in agriculture and food production.

The majority of currently pending market applications are for genetically engineered plants with herbicide resistance and insecticidal toxicity. These same traits also appear in so-called stacked events, which are a combination of several genetically engineered plants in one event. The stacks of the highest order (so far) are plants that are resistant to up to four herbicides and at the same time produce half a dozen insecticidal toxins. Stacking such genes ultimately means pyramiding risks and uncertainties.

Some of the genetically engineered trees and animals that might be used in agriculture or forestry in the near future show a high potential for spreading uncontrollably in the environment. These risks are particularly relevant for planned field trials of genetically engineered olive flies and forest trees such as poplar.

In recent years, several new genome technologies have been developed that allow a radical transformation of the genome. These new technologies are summarised in this report as 'synthetic genome technologies'. They are already applied in practice without this being widely known. Not only are these new technologies associated with new risks but also with ethical problems concerning genetic identity and the integrity of living beings.

In the near future, it is to be expected that industry will want to market a larger number of risky new products for use in agriculture and food production in the EU. At the same, the new free trade agreement (TTIP) between EU and USA might facilitate placing such products on the market. This report presents some of the arguments used by the proponents of this policy who want to pave the way for the marketing of these products.

As the report shows, current developments are moving away from the traditional systems of breeding and agriculture and expanding into technologies that are complex, failure-prone and associated with a great number of uncertainties regarding risks. If society wants to allow the use of some of these technologies and applications there is no alternative but to strengthen the precautionary principle in parallel. This is the only way to deal with the many uncertainties and factual limits of knowledge in a rational way.

The report recommends

- strengthening the precautionary principle;
- extending ethical debates on the protection of genetic identity and integrity of living beings;
- a change in agricultural policy to include more comprehensive protection of the environment and enhancement of biodiversity

The implementation of these recommendations should have priority above further releases and market authorisations.

1. Introduction

Genetic engineering in agriculture and food production is a controversial issue. Whilst in countries such as the US, Argentina and Brazil genetically engineered plants are grown on large areas of land, in other regions there appears to be only a low level of confidence in the benefits and safety of these products.

Most of the products on the market at present are herbicide resistant (sometimes called tolerant) and insecticidal plants. Genetically engineered high-tech-monsters such as SmartStax maize, which is engineered to produce six insecticidal toxins and be resistant to two herbicides is just one example of the 'arms race' underway in the fields in the US. Insects and weeds are the 'enemies' that need to be controlled to continue this extreme form of industrial agriculture.

Agricultural policy in the EU differs from that in the US in that agriculture in the EU is meant to be sustainable, have multiple functionality and not only serve food production. In Europe, there are also many small structured agricultural landscapes, which are unlikely to benefit economically from practices such as streamlining herbicide applications, which are an issue in the US.

The EU also has different rules and regulations on risk assessment and labelling to those in the US. EU regulations require a centralised system for risk assessment and market authorisation of all genetically engineered organisms. Labelling is mandatory for food and feed derived from genetically engineered crop plants.

However, existing EU regulations are controversial amongst EU Member States. Several Member States are calling for much stricter implementation of current regulations for the protection of consumers and the environment whilst industry and the UK (as well as the US) have made complaints about barriers to freed trade. These controversies are now currently taking a new direction. In mid-2013, the US and the EU agreed upon starting negotiations for a new free trade agreement called the Transatlantic Trade and Investment Partnership (TTIP).

It appears that the market introduction of new genetically engineered organisms could feasibly be written into the planned TTIP. This report discusses some of the arguments brought forward by the proponents of this technology in their bid to change the standards of EU regulation in favour of the interests of industry and to pave the way for risky new products.

2. Agro-biotech: A toxic mix in the pipeline

49 genetically engineered crop plants (events) already have authorisation for import into the EU for use in food and feed. At present only one event – MON810 - is cultivated in a few countries. Plants authorised for import are mostly soybeans, maize, oilseed rape and cottonseeds. Nearly all of them are insecticidal and/or resistant to herbicides. Around half of the approved plants approved are so-called stacked events, which combine both traits. In November 2013, authorisation was approved for a maize called SmartStax, which is jointly produced by Monsanto and Dow AgroSciences. This maize produces six insecticidal proteins and is resistant to two herbicides.

Several other crop plants with similar qualities might be authorised in the near future. In the period up to December 2013, applications for the authorisation of a further 55 crop plants had been filed at the European Food Safety Authority (EFSA), nine of them were already in the advanced stages of risk assessment[1]. 48 events are herbicide resistant and 24 events produce insecticidal proteins. Eight plants have other traits such as altered quality in oil or higher tolerance to drought (see below).

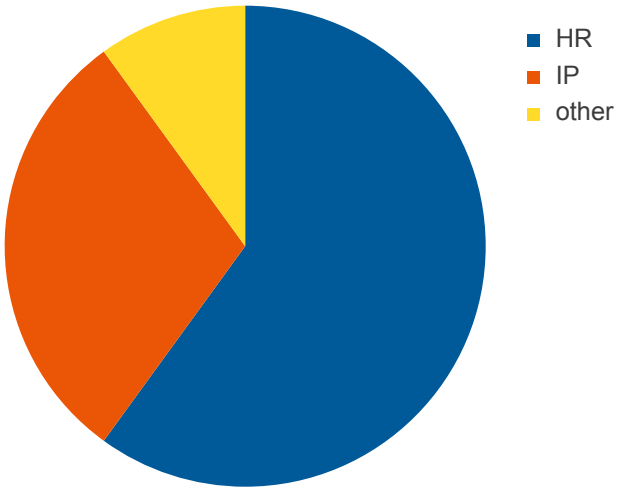

Figure 1: Overview of the traits of genetically engineered plants for which applications for market authorisation were filed in the EU up until December 2013. (HR: herbicide resistance; IP: insecticidal proteins).
Source: http://www.bfr.bund.de/cm/343/antraege-gvo-lm-fm-vo-1829.pdf

The highest numbers in terms of plant species are maize (24 applications), soybeans (16) and cotton seeds (12). Applications for cultivation in the EU have been filed for ten of the plants. Only a few months ago there were many more applications. Several EU applications for the cultivation of genetically engineered plants were withdrawn in 2013: BASF withdrew three applications for potatoes from the list, Monsanto withdrew five applications for maize and one for sugar beet. Despite several announcements in the media, Monsanto has not so far withdrawn all its EU applications for cultivation. Applications for glyphosate resistant Roundup Ready soybeans (40-3-2) and maize (NK603) were still pending at the time this report was finished.

1 www.bfr.bund.de/cm/343/antraege-gvo-lm-fm-vo-1829.pdf
http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

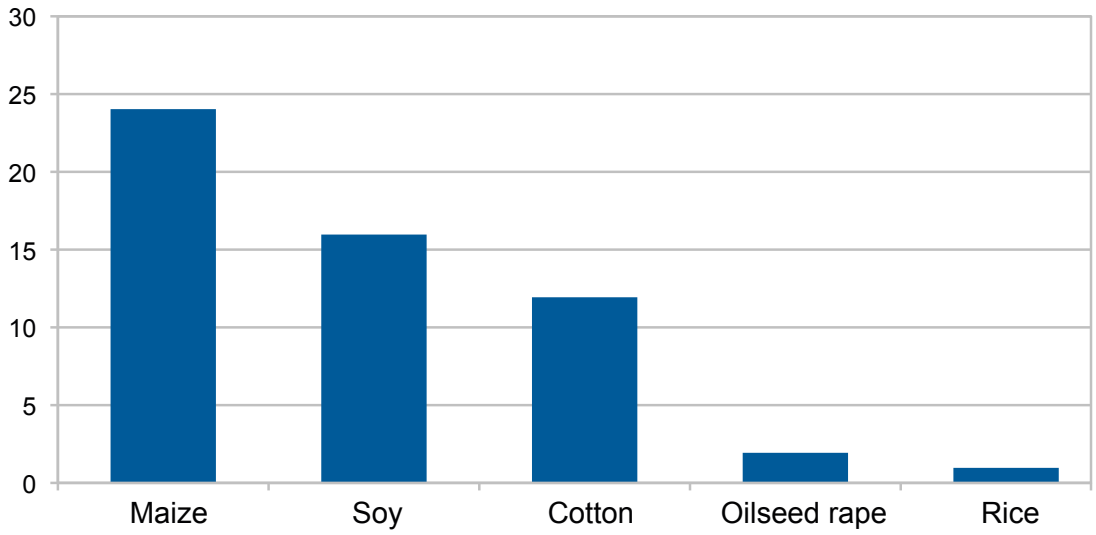

Figure 2: Overview of species of genetically engineered plants for which applications for market authorisation were filed in the EU in the period up to December 2013. Source: http://www.bfr.bund.de/cm/343/antraege-gvo-lm-fm-vo-1829.pdf

Monsanto filed the highest number of applications (18), followed by Syngenta (11), Dow AgroSciences (9), DuPont/Pioneer (8) and Bayer (8). Monsanto, Dow AgroSciencies and DuPont/ Pioneer have filed some of the applications in cooperation. For example, applications filed by Dow AgroSciences also cover plants originally produced by Monsanto (and DuPont/Pioneer).

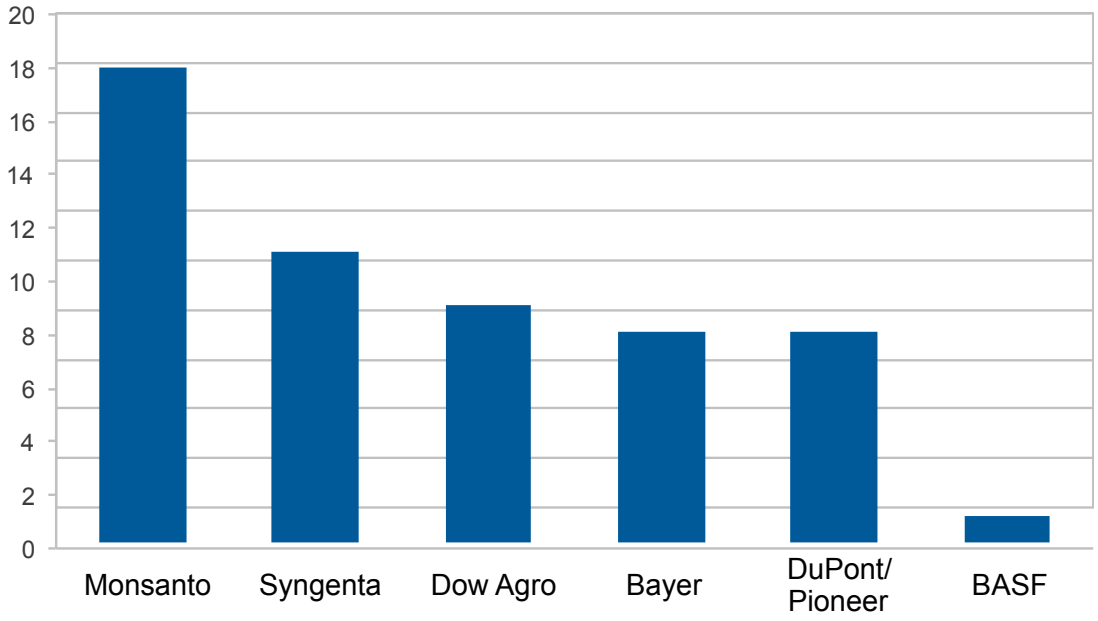

Figure 3: Overview, number of EU applications per company up until December 2013.
Source: http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

As mentioned, a large number (48) of the applications are for genetically engineered plants that are resistant to herbicides. Up to nine herbicides (or groups of herbicides) are relevant for this group of plants. Most of the applications are for plants resistant to glyphosate (34 applications), followed by plants resistant to glufosinate(24). Other applications are for plants resistant to 2,4-D (6), AOPPs (3)[2], dicamba (3), ALS inhibitors (3), imidazolinone, isoxaflutole and mesotrione. Some of these herbicids are known to be highly toxic (such as glufosinate, quizalofop from the group of AOPPs and isoxaflutole). Many of the plants have been engineered to be resistant to two herbicides, some stacked events tolerate a mixture of three or four herbicides.

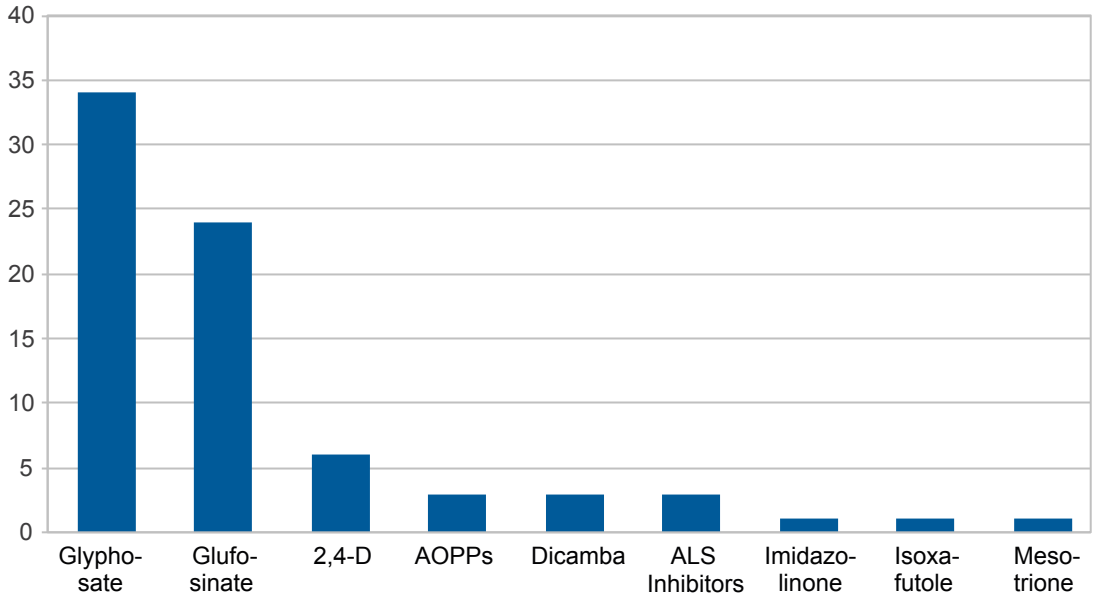

Figure 4: Overview of the number of genetically engineered plants for which applications were filed in the EU (up until December 2013) that are resistant to various (groups of) herbicides.
Source: http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

There is a strikingly high number of 25 stacked events out of the total of 55 applications. The highest number in terms of stacking is a combination of six different genetically engineered plants (SmartStax is a combination of four).

2 also known as ACCase Inhibitors or FOP-herbicides

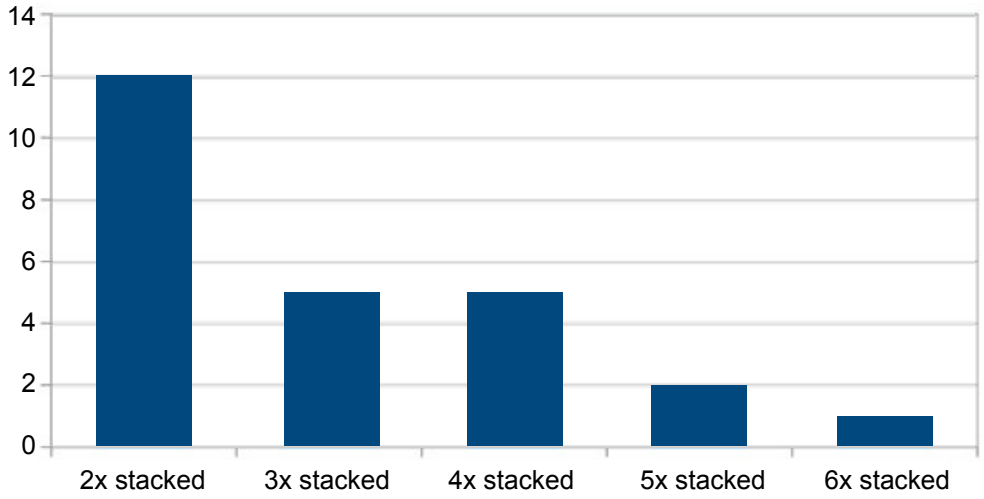

Figure 5: Overview of the number of stacked events of genetically engineered plants that have had applications filed for market authorisation in the EU up until December 2013.
Source: http://www.bfr.bund.de/cm/343/antraege-gvo-lm-fm-vo-1829.pdf

Dow AgroSciences and Syngenta have the highest number of stacked events and combinations of traits from genetically engineered plants. Dow AgroSciences and Monsanto jointly developed stacked events that include a crossing of SmartStax with another plant (DAS 40278-9) that makes it resistant to two herbicides at once. The resulting product can be called **"SmartStax +"**. This maize produces six insecticides (one of which was developed by using synthetic DNA which has no natural prototype) and is engineered to be resistant to four herbicides (glyphosate, glufosinate, 2,4-D and AOPPs).

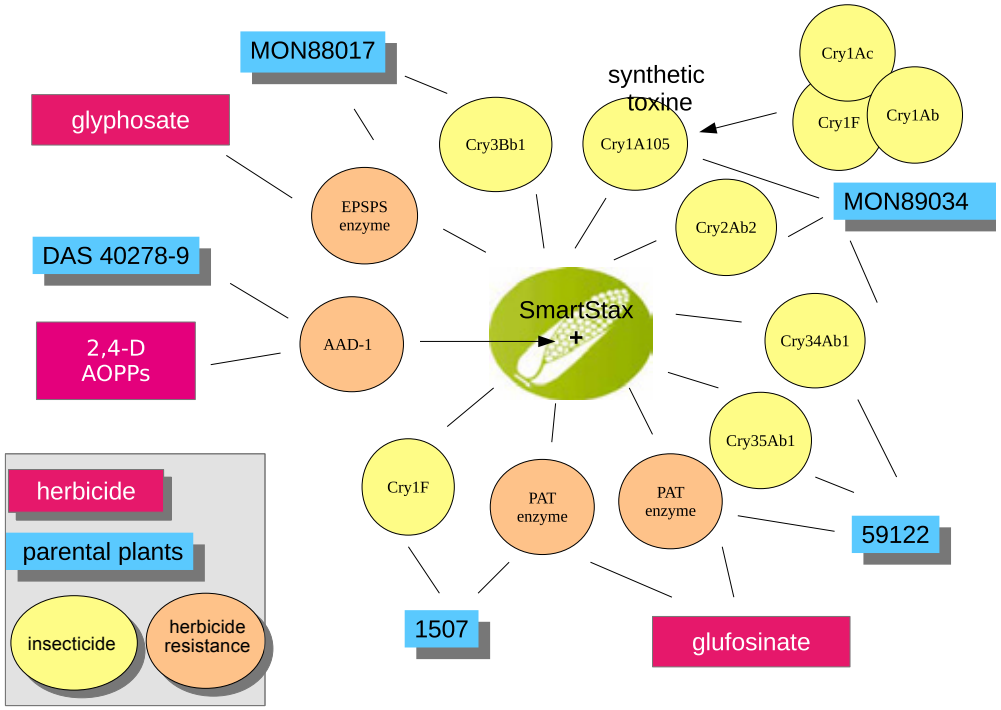

Figure 6: Overview of traits included in genetically engineered maize **"SmartStax +"**, which was developed by Monsanto and Dow AgroSciences by crossing five genetically engineered plants. It produces six insecticidal proteins and is resistant to four herbicides. Source: http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

Syngenta has filed an application for marketing a maize variety which is produced by crossing six genetically engineered plants. This product is designated **"Syngenta Six"** in this report. It is resistant to glyphosate and glufosinate and produces four insecticides, at least one of them based on synthetic DNA. Two of the toxins are part of the group of VIP toxins[3]. So far information on risk assessment of this maize has only appeared in very few publications, thus uncertainties regarding impact on health and environment are particularly high.

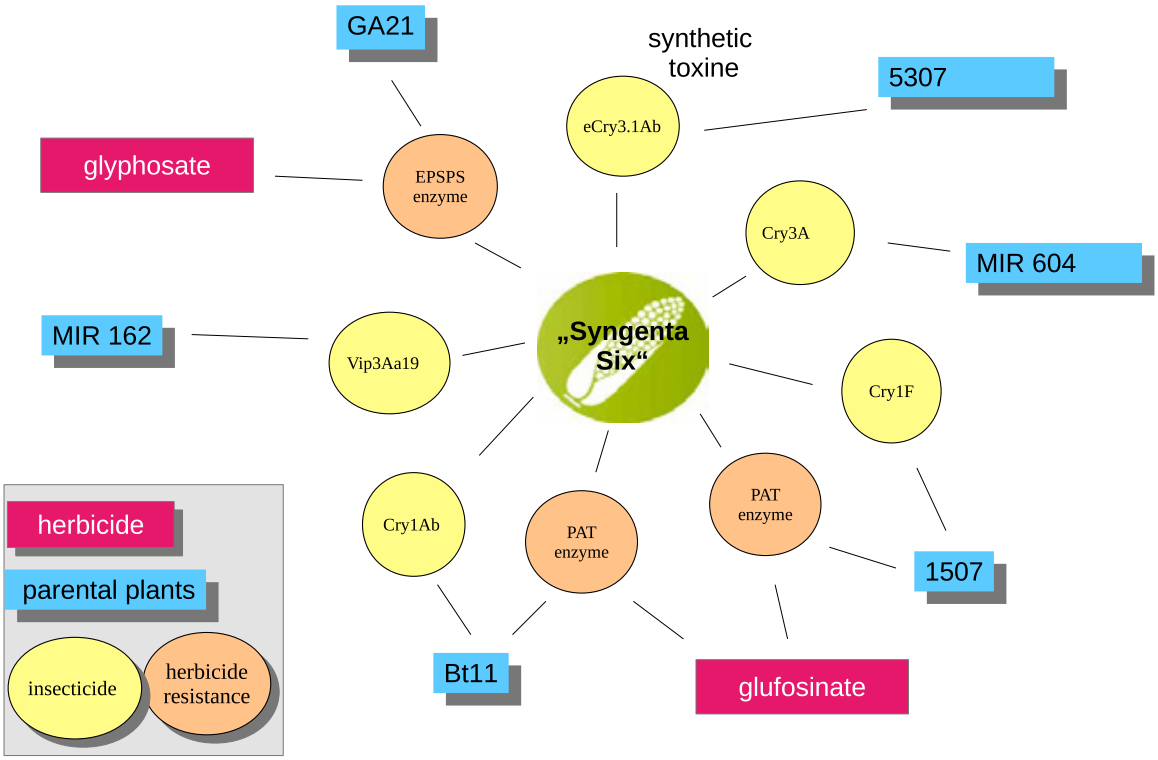

Figure 7: Overview of traits included in the genetically engineered maize "Syngenta Six" which was produced by Syngenta by crossing of six genetically engineered plants. The maize produces five insecticidal proteins and is resistant to two herbicides. Source: http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

Experimental field trials and new traits in genetically engineered plants

The EU database listed 2709 experimental field trials with genetically engineered organisms up until April 2012. Most of them were with plants for food and feed, around 80 field trials were with genetically engineered trees. There were also several trials with genetically engineered microorganisms. Nonetheless, the overall number of experimental field trials in the EU has been decreasing for several years.

3 These toxins originate from *Bacillus thuringiensis* as is the case with toxins produced in SmartStax. However, the mode of action of VIP toxins is different from that of toxins, which are members of the group of Cry toxins produced in SmartStax.

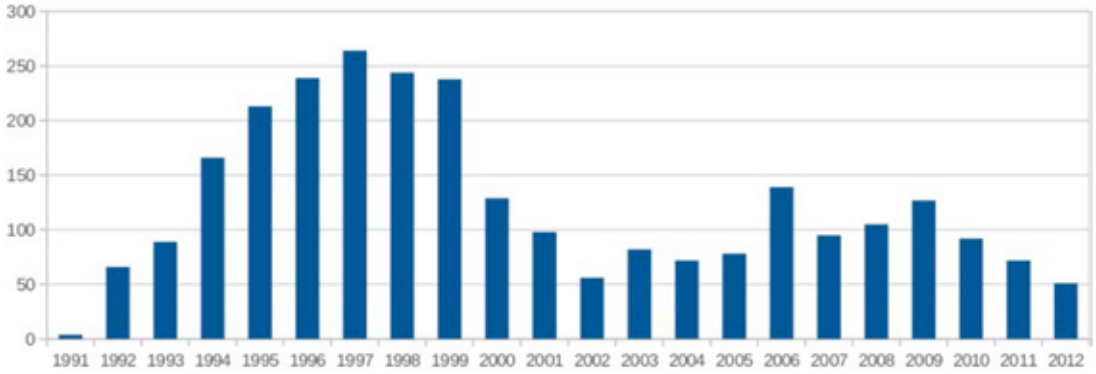

Figure 8: Number of experimental field trials with genetically engineered organisms in the EU per year.
mSource: http://gmoinfo.jrc.ec.europa.eu/overview/

The experimental field trials are mainly to examine herbicide resistant and insecticidal plants, changes in the metabolism of the plants (oil, starch and others) male sterility, resistance to virus, fungal diseases and others. The following table lists the ten plants species that were used most frequently in field trials so far.

Plants species	Number of experimental field trials in the EU
Maize	936
Oilseed rape	381
Potato	307
Sugar beets	282
Cotton	91
Tomato	75
Tobacco	61
Rice	36
Wheat	36
Chicory	31

Table 1: Plant species used most frequently in field trials in the EU up until 2012.
Source: http://gmoinfo.jrc.ec.europa.eu/overview

Very few applications for market authorisation are actually filed in the EU for plants from these field trials. Only a very few have traits that are not related to herbicide resistance and/or insecticidal proteins. Amongst these plants are potatoes produced by BASF which have been engineered to be resistant to a fungal disease called phytophthora. Because this fungal disease showed extreme potential for adaptability, doubts remained whether these potatoes would indeed be resistant under practical conditions. BASF withdrew its application at the beginning of 2013 (see above).

Monsanto and BASF jointly developed a drought tolerant maize which has been grown in the US since 2012/2013 and is now about to be imported into the EU. It is doubtful whether this maize can do any better than conventionally bred maize. For example, Syngenta also sells a drought tolerant maize

in the US derived from traditional breeding which performs at least as good as Monsanto´s genetically engineered maize (see for example Gurian-Sherman, 2012). Furthermore, Monsanto has filed an application for the import of genetically engineered soybeans with an altered composition in fatty acids (MON87705) which is in an advanced stage of authorisation process.

Overall, the variations in the technical quality (traits) of genetically plants remain rather limited. According to information from industry, plants with herbicide resistance and insecticidal proteins will remain dominant in the coming years (Stein & Rodríguez-Cerezo, 2009). The number of stacked events is expected to see to the strongest increase.

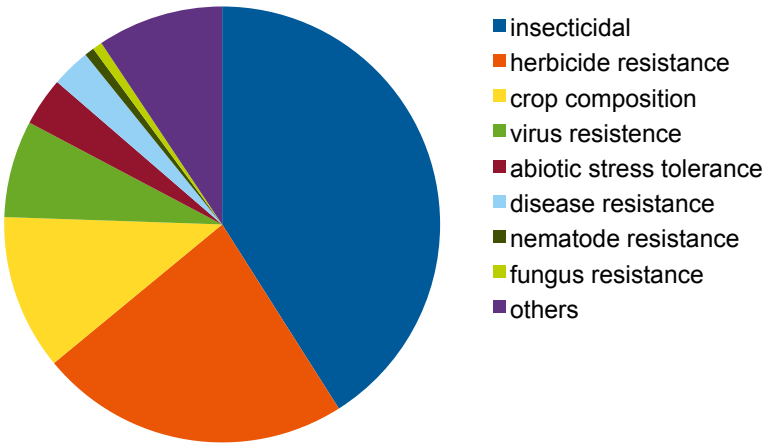

Figure 9:
Predicted development of genetically engineered traits in crop plants ready for market authorisation by 2015, according to data from industry (source: Stein & Rodríguez-Cerezo, 2009).

Figure 10: Theoretical combinations to produce new GM maize by stacking

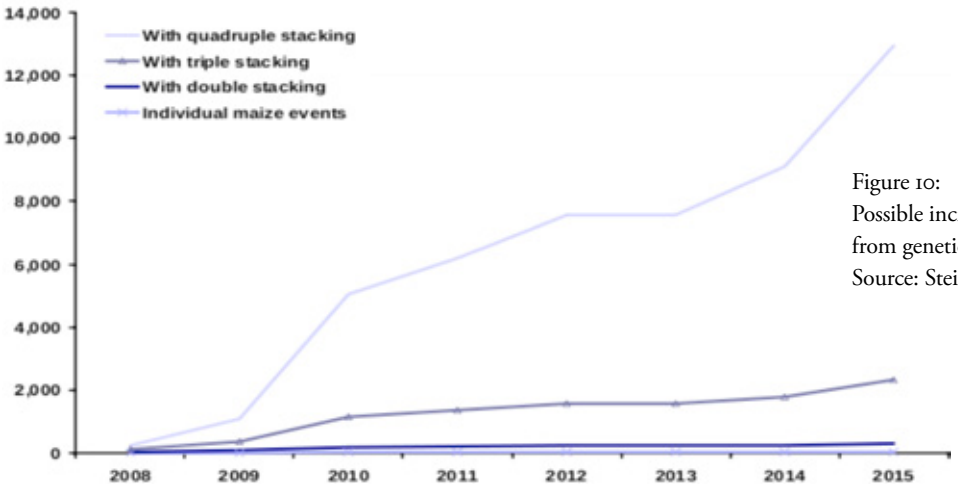

Figure 10:
Possible increase of stacked events produced from genetically engineered plants by 2015. Source: Stein & Rodríguez-Cerezo, 2009

If these data are compared with the original prognosis made by industry, it is evident that agro-biotechnology has clearly failed to fulfil expectations. This is evident when a comparison is made with data from industry, collected by the OECD and published in 1992 (OECD, 1992). According to this data, genetically engineered plants adapted to climate change and producing higher yields should have already been on the market for several years.

Table 2: prognosis for the development in agro biotechnology OECD 1992

1990-1993	Herbicide and insect resistance
1993-1996	Improved quality in processing
1996-1999	Industrial production of pharmaceutical products
1999-2003	Improved tolerance to environmental stress conditions
2003-2006	Higher yield

Increasing risks

Even if the number of genetically engineered plants with new traits is rather limited, maize with drought resistance or soybeans with an altered oil quality still raise new questions in risk assessment.

The higher tolerance to drought in maize MON 87460 is based upon proteins that normally are produced in bacteria under stress conditions. These proteins are produced permanently in the genetically engineered plants – even when the plants are not under this kind of stress. This new protein can impact plant metabolism in various ways. The data from field trials with these plants show several significant changes in the composition of the plant components[4].

The change in oil quality in genetically engineered Monsanto soybean MON87705 is based on manipulation of the plant by RNA interference (RNAi). The RNA interacts with plant gene regulation and blocks the production of a specific enzyme. In regard to risk assessment it is important to take into account that some kinds of RNA, called double stranded RNA (dsRNA), can pass into the human gut and enter the blood stream. This observation is relevant because dsRNA can interfere with gene regulation in humans and animals[5] (see below).

Pending applications filed for genetically engineered plants engineered to have herbicide resistance and at the same time produce an assortment of insecticidal toxins are a further reason for growing concern. In the following summary, we have set out some of the risks mostly to human health (Bt plants, herbicide resistant plants and transfer of biological active substances).

4 www.testbiotech.de/node/754
5 www.testbiotech.de/node/745

Case study: Bt toxins

Toxins produced by genetically engineered plants originate from soil bacteria called *Bacillus thuringiensis*, and are therefore known as Bt toxins. There are several hundred toxins present in these bacteria. More than a dozen of them are used in genetically engineered plants. Each of the toxins is different in its mode of action and they are therefore classified according their toxicity to specific groups of insects, such as beetles, butterflies or flies. Currently scientists do not know the all details of the specific modes of action and differences between the Bt toxins. There are even some contradictions in the way the toxicity is explained (see for example Pigeot & Ellar, 2007). For most toxins, there have been no detailed investigations into specific modes of action. Therefore, selectivity is questionable and there remains the possibility that these toxins may have adverse effects on many more organisms than assumed so far (see van Frankenhuyzen, 2009). The fact that the DNA, which is the basis for production of the toxins, is substantially altered before being inserted into the plants must also be taken into account. In some cases, the DNA is artificially synthesised, which means there is no natural form of the toxins in existence. This adds even further uncertainties for risk assessment.

Essentially the mode of action of each of the Bt toxins should be investigated to assess its potential impact on health and the environment, its interactions with other stressors and its persistence in the environment. However, for the most part, there is no reliable data available on the toxins used in the plants. There is further no reliable data about the content of the toxins in the plants because there are no sufficiently evaluated and established methods for determining the Bt toxin expression in the plants. (see Székács et al., 2011). What is known is that the content of Bt toxins can vary substantially under changing environmental conditions (see Then & Lorch, 2008).

The Bt toxins could impact on health in several ways and there are numerous indications that Bt toxins can have adverse effects on the health of humans and livestock (Thomas and Ellar, 1983; Shimada et al., 2003; Huffmann et al., 2004; Ito et al., 2004; Mesnage et al., 2012; Bondzio et al., 2013). In addition, interaction with other stressors such as herbicides can enhance toxicity (see for example Kramarz et al., 2007 and Then, 2010c).

Further, Bt toxins can also enhance immune reactions (Esquivel-Pérez and Moreno-Fierros, 2005; Moreno-Fierros et al., 2003; Vásquez et al., 1999; Vásquez-Padrón et al., 1999; Vásquez et al., 2000; Verdin-Terán al., 2009). Some of them are even used in vaccines as an adjuvant. In feeding trials with genetically engineered plants, immune reactions were observed in several animal species (mice, rats, pigs and fish, see Sagstad et al., 2007, Frøystad-Saugen, 2008, Walsh et al., 2011, Finamore et al., 2008, Kroghsbo et al., 2008, Adel-Patient et al., 2011; Carman et al., 2013). Therefore, it has to be concluded that the immune system can identify genetically engineered plants and react to them.

EFSA has in the meantime deemed it necessary to investigate this problem. In December 2013, a report from the University of Manchester was published which was commissioned by EFSA (Mills et al., 2013a and 2013b). It is a report on health risks due to adverse immune system reactions to foods, which are relevant for adjuvant effects as discussed (Mills et al., 2013a). Further, it shows that in vitro tests used so far are not likely to provide reliable results for digestibility (Mills et al., 2013b). Presently the EFSA view is that the Bt toxin is degraded rapidly but empirical investigations have shown the oppo-

site to be the case (Chowdhury et al., 2003; as Walsh et al., 2011). As a result, it has to be assumed that that Bt toxins are not degraded quickly in the gut but can persist in large amounts during digestion (Chowdhury et al., 2003; Walsh et al., 2011). This means that there is enough time during digestion for the Bt toxins to have an effect on health and interact with various food compounds. In addition, allergies to other food components might be induced or enhanced.

The risks and uncertainties of Bt toxins are increased by the new genetically engineered plants pending for authorisation: In the stacked events there is a much higher concentration of Bt toxins than in the plants producing just single toxins. Stacking those genes means pyramiding uncertainties.

Case study: Herbicide resistance

The increase use of herbicide tolerant plants can also be expected to bring a substantial increase in risks. Several herbicides such as glyphosate and 2,4-D pose considerable risks for farmers, rural communities and ecosystems if applied in high concentrations. For example, the overuse of glyphosate in Argentina is said to have had a detrimental impacton human health[6].

Regarding 2,4-D, there are recent reports of contamination with dioxins and it is suspected that uptake via dermal contact is far easier than assumed so far by the regulators (Neumeister, 2013). Similarly to dicamba, 2,4-D is very easily spread by the wind to neighbouring fields and can have adverse effect on conventional crop plants even at low dosages (Mortensen, 2012).

The use of herbicide resistant plants changes the pattern of exposure with residues from spraying: In conventional agriculture, crops should only sprayed when weed problems exceed a certain threshold or there is pest infestation. Therefore the concentration and the chemical composition of the residues will be dependent on the specific situation in the fields. This is different with the application of complementary herbicides on herbicide resistant plants. In these plants, one can regularly expect residues from the complementary herbicide, sometimes in high concentrations[7].

The impact of continuous exposure to specific chemical substances can be assumed to be different when compared to that of exposure to varying substances. This difference is likely to be relevant in the case of micro-organisms in the gut. There are investigations showing glyphosate can cause changes in the composition of gut bacteria that can be associated with adverse health impacts (Shehata et al., 2012; Krüger et al., 2013). These observations are a matter of particular concern if there is continuous exposure to glyphosate via the food chain.

Some of the new traits inserted in genetically engineered plants cause an increase in substances that stem from the degradation of the herbicides in the plants that might even have a higher toxicity than the original herbicide. For example, in Monsanto´s soybean MON87708, dicamba is metabolised to 3,6-dichlorosalicylic acid (DCSA) and formaldehyde in the plants (EFSA, 2013 a). These residues not only raise concerns about health but can, for example, also interact with residues from other herbicides

6 www.boston.com/bigpicture/2013/10/agrochemical_spraying_in_argen.html

7 See for example: www.testbiotech.de/en/node/926

Interactions between residues from spraying and plant compounds can also be relevant for risk assessment. There are indications that mixtures of glyphosate act in a similar way to hormones (see for example Gasnier et al., 2009; Thongprakaisang et al., 2013). Soybeans produce estrogen-like compounds, but there has been no investigation into whether this can lead to synergistic or additive hormonal effects in the body when soybeans and glyphosate are continuously consumed in combination (as is the case when genetically engineered soybeans are part of the food chain).

Case study: The transfer of biologically active substances (RNA and DNA)

The DNA inserted into the plants is a further relevant issue. Just a short time ago it became evident that biologically active substances in the plants, in particular the so-called double stranded RNA (dsRNA) plants, can be transferred to humans (and animals) at the consumption stage. These substances can leave the gut and enter the bloodstream and then interfere with gene regulation in humans (and animal) cells (Zhang et al., 2012). So far, this issue has been left aside in the risk assessment of genetically engineered plants. However, it has to be assumed that changes in the dsRNA content are inevitable if RNA interference is used to change the oil composition in the plants, as is the case with MON87705 (see above). In general, new dsRNA should always be taken into account during risk assessment (see Heinemann, 2013).

Furthermore, the risk of humans taking up biologically functional DNA sequences from the gut during digestion might have been underestimated so far. In 2013, Spisak et al. published a study showing that, in humans, DNA sequences can be absorbed from the gut when they are still biologically functional. The rate of DNA transfer seems to be dependent on the health status of the individual. There have been no systematic investigations into the extent of which DNA from genetically engineered plants can be taken up from the human gut, and what impact it could have. Thus far it has been concluded from the outcome of feeding trials with animals that DNA is broken down quickly during digestion into particles that are no longer of biological relevance (see EFSA, 2007; Mazza et al., 2005).

3. Genetically engineered trees: Risk without control

Around 80 experimental field trials with trees have been registered[8] in the EU. The countries concerned are Spain, France, Sweden and Finland. While in the US, virus papaya trees are commercially grown in Hawaii, and cold-tolerant eucalyptus trees might be deregulated (Barker, 2013), there are no applications pending for market authorisation in the EU.

Figure 11: Experimental field trials with genetically engineered trees in the EU Source: www.gmtreewatch.org

In the EU, most field trials were with poplar trees which are of huge interest to industry (see below). Genetically engineered trees that produce Bt toxins have been grown commercially in China for many years (Then & Hamberger, 2010). Many of the field trials in the EU are with fruit trees, particularly apple trees, but also pear, plum and cherry trees are registered in the EU database[9].

8 http://gmoinfo.jrc.ec.europa.eu
9 http://gmoinfo.jrc.ec.europa.eu

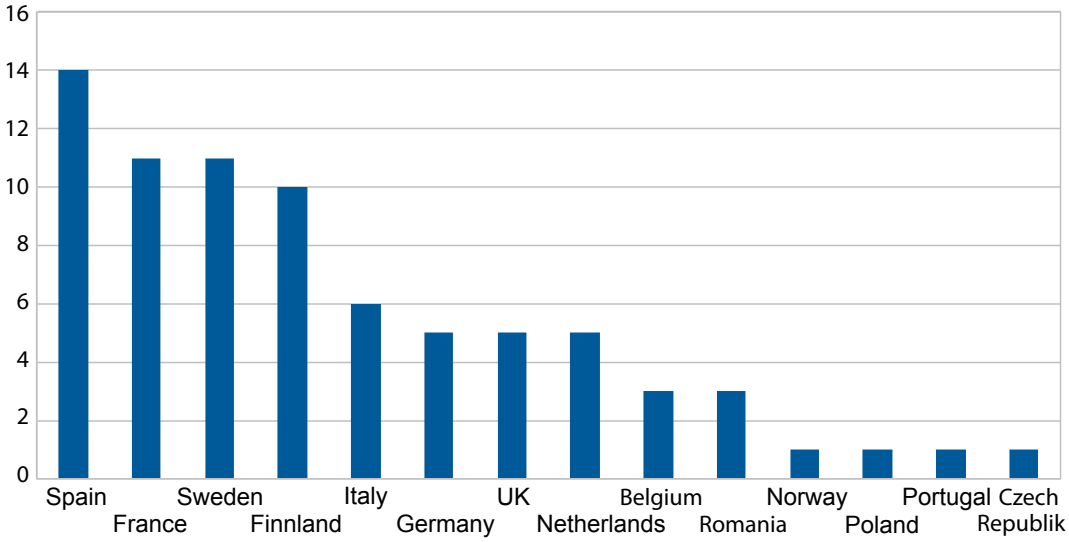

Figure 12: Overview of EU countries where experimental field trials with genetically engineered trees were registered.
Source: http://gmoinfo.jrc.ec.europa.eu

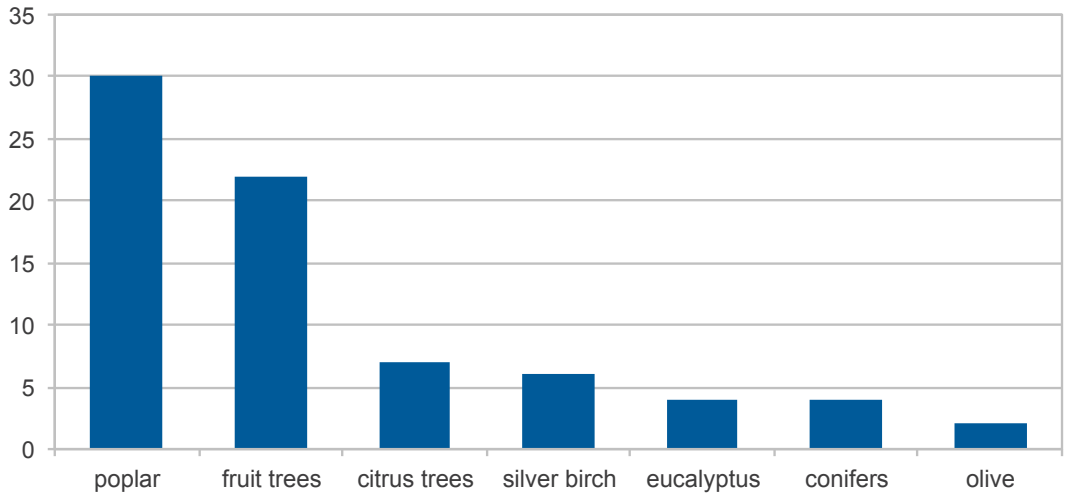

Figure 13: Overview of tree species that were used in experimental field trials in the EU.
Source: http://gmoinfo.jrc.ec.europa.eu

The field trials in the EU were designed to test various traits of the genetically engineered trees, especially resistance to diseases (such as viruses, fungi and bacteria) although some examined traits of interest to the wood industry (such as content of lignin and growth). Herbicide resistance has so far only played a minor role[10].

10 NGO Database Gmtreewatch.org gives a good overview, even though not all field trials are registered.

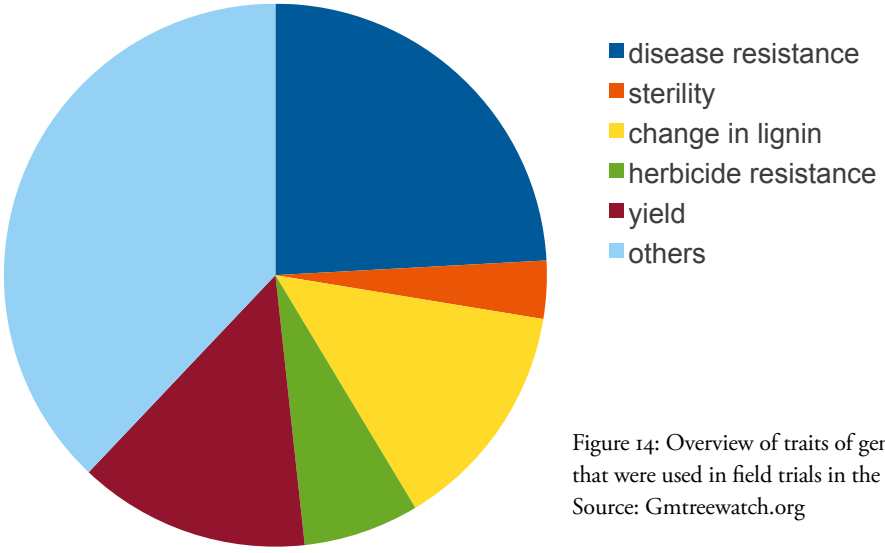

Figure 14: Overview of traits of genetically engineered trees that were used in field trials in the EU.
Source: Gmtreewatch.org

The risks of genetically engineered trees are generally different from those of genetically engineered crop plants:

- Trees do not grow in fields. They grow in complex and vulnerable ecosystems such as forest and pasture landscapes. There is a particular risk of uncontrolled spread of the transgenes within these ecosystems.
- The long lifecycle and genetic variability facilitate genetic instabilities and unexpected effects.
- Because trees live for a long time they can also have an impact on soil, the food web and forest ecosystems over long periods.
- Trees have an extreme potential to proliferate in the environment. Some tree species produce enormous amounts of pollen and seed which can be transported over many kilometres. Several species can also propagate via shoots and broken or cut twigs.

Poplar trees are the most commonly used trees in forest bio-tech and a good example of the potential for uncontrolled spread into the environment. The trees each produce around 25-50 million seeds per year. According to Rathmacher et al. (2010), there is proof of seeds being transferred over distances of up to two kilometres and pollen over eight kilometres. Dispersal is further fostered by rivers, which can transport seeds, twigs and roots over many kilometres. In addition, poplars can mix with other poplar species and render hybrids as well as propagate through cuttings. After a poplar tree is cut down new shoots come up from the roots over several years. In particular, there is no way to control the spatio-temporal dimension in the commercial cultivation of genetically engineered poplar trees in, for example, China where more than a million trees have been grown over the last ten or more years. If adverse effects do become noticeable in ecological systems or if transgenes escape into wild populations of poplar trees, there is hardly any effective action that can be taken to prevent permanent damage (see Then & Hamberger, 2010).

The Chinese example does not appear to be deterring other interested parties Especially ArborGen is pushing for the commercialisation of genetically engineered eucalyptus trees in the US (Barker, 2013). Further, there are plans to release genetically engineered poplar trees with an altered wood composition in Belgium over a period of several years[11].

11 http://www.bio-council.be/docs/BAC_2013_0580_CONS_rev0410.pdf

4. Genetically engineered animals: Going beyond boundaries

Genetic engineering of animals started about 40 years ago; transgenic mice were first produced in 1974. So far, however, unlike animals used in laboratories, there has been no commercialisation of genetically engineered animals for food and feed production. This might change very soon: Genetically engineered salmon produced by Aquabounty might be allowed for marketing in the US very soon. In the EU there has been some movement in regard to marketing authorisation for genetically engineered animals. In 2012 the European Food Safety Authority EFSA published a Guidance on the risk assessment of food derived from genetically engineered animals (EFSA, 2012). It was followed by a Guidance for the environmental risk assessment of genetically engineered animals for food production (EFSA, 2013b). Currently, EFSA (2013b) is looking at the risks of releasing genetically engineered fish and insects. It seems unlikely that cows, pigs or sheep will be the first genetically engineered animals to be used for agricultural purposes, but salmon produced by the US company, Aquabounty (as mentioned) and insects from the UK company, Oxitec are being considered. Initial applications for experimental releases of genetically engineered olive flies in Spain and Italy were first made public in 2013[12]. The following table provides an overview of the developments concerning genetically engineered animals.

Table 3: chronological overview on development of genetically engineered animals.

1974:	First transgenic mice
1985:	First transgenic sheep and pigs
1988:	First US patent granted on genetically engineered mammals („oncomouse");
1990:	„Bull Herman" is born, its female offspring are supposed to give humanised milk (with lactoferrin);
1992:	First European patent granted on genetically engineered mammals („oncomouse"); Aquabounty applies for patent on its fast-growing salmon;
1997:	Cloned sheep „Dolly" is presented to the public;
2001:	Patent on fast-growing salmon granted in Europe (EP 578653);
2007:	European patent granted on genetically engineered dairy cows (EP 1330552);
2010:	Meat from descendants of cloned animals is found in UK supermarkets;
2012/13:	EFSA publishes Guidances for risk assessment of genetically engineered animals for food production.

12 www.testbiotech.de/node/874

Fluorescent fly maggots

The UK company, Oxitec is currently developing genetically engineered insects for several applications. Mosquitos developed by Oxitec, engineered to mate with natural populations have been released in Brazil, Malaysia and the Caymans to combat Dengue fever. Specific mechanisms will allegedly prevent the uncontrolled spread of these insects. The mosquitos are genetically engineered to be dependent on antibiotics (tetracyclin) for their survival. The antibiotics are added to the feed in the laboratory, and once released into the environment the insects will supposedly die within a short time. But there are reports showing that some of the insects are surviving (for overview see: Wallace, 2012).

In the EU, Oxitec applied for permission to carry out field trials in Spain and Italy [13] with genetically engineered olive flies. The male flies are manipulated in a way that their female descendants are sterile. However, the survival rate of the males is unchanged. The plan was to contain the flies with nets. But according to the application filed by Oxitec, they could not completely exclude some insects escaping[14]. Olive flies are known to be invasive, they proliferate in the environment and can fly over distances of several kilometres. Thus it has to assumed, that these genetically engineered olive flies can spread throughout the whole Mediterranean region, where they live. As long as the natural populations of olive flies do not collapse, the genetically engineered flies are likely to survive as well. The spread of these flies in the environment might be detected easily because their maggots are manipulated to be fluorescent, but their proliferation cannot be stopped. Oxitec announced its withdrawal of the application at the end of 2013, but at the same time announced that it intends to file a new application soon.

Oxitec has ties with the biotech company Syngenta and employs several former Syngenta members of staff at management level. Syngenta also provided direct financial support. Oxitec's own view is that it hopes to overcome opposition to genetically engineered food by engineering pest insects rather than crops (see Wallace, 2012). In parallel Oxitec is trying to convince the EU that the manipulated larvae living in the olives should be seen as an inevitable adventitious ingredient that does not need to be authorised or labelled (see Wallace, 2012). If this were to be accepted is in this form, it would constitute a violation of current EU regulations.

Monsanto acting as 'godfather' for Frankenstein-salmon

The genetically engineered salmon developed by the US company, Aquabounty produce additional growth hormones and therefore grow faster than native salmon. There are concerns that the GE salmon could escape into the environment (despite intended containment) and spread into wild populations. In 2013, a paper was published showing that the GE salmon could mate with brown trout. Faster growth and larger size with higher fitness could, however, lead to the replacement of wild populations. Further, the salmon are genetically engineered to be tolerant to cold[15]. In a worst case scenario, higher fitness in the transgenic salmon might possibly cause the wild populations to collapse.

13 www.testbiotech.de/node/874

14 http://gmoinfo.jrc.ec.europa.eu/gmo_report.aspx?CurNot=B/ES/13/07

15 Süddeutsche Zeitung, 2.12.2013

This would also impact wider parts of the food web. It is for this reason that many civil society organisations have, for some years, been actively trying to protect consumers and the environment by preventing the approval of these GE salmon. In 2013, the Canadian government allowed the production of fertilised eggs from the transgenic salmon and their export to Panama for breeding purposes[16].

Although the patent on the GE salmon has now expired and Aquabounty almost went bankrupt, new investors have been found. The US company Intrexon has held an approximately 50% share in Aquabounty[17] since 2012.The management of Intrexon has strong links with Monsanto, for example, Robert B. Shapiro, a former Monsanto executive is now active at Intrexon[18]. The Intrexon department "Animal Sciences and Agricultural Biotechnology Division" is led by a former Monsanto member of staff member. In 2012, Intrexon was highly criticised publicly because it holds European patents on genetically engineered chimpanzees[19]. It is evident from the text of the patents that Intrexon is not only interested in pharmaceutical research. Its patents on mammals which are engineered with insecticidal DNA to control gene regulation (EP 1456346 & EP 1572862) claim "a mouse, a rat, a rabbit, a cat, a dog, a bovine, a goat, a pig, a horse, a sheep, a monkey, and a chimpanzee".

Frankenstein-camels and enviropigs

There are currently other projects to produce genetically engineered animals involving cows, goats and even camels that are manipulated to produce humanised milk. There have been media reports on this issue from Argentina[20], China[21], Saudi Arabia [22] and the US[23]. It is an idea that has already been promoted for several years: The first genetically engineered bull which was born in the Netherlands in 1990 and called "Bull Herman" by the media[24], was supposed to produce cows with humanised milk. There is however, considerable room for doubt about whether the world is ready to embrace human breast milk produced by 'Frankenstein-camels'

Enviropigs that were created in Canada produce an enzyme in their saliva (phytase) meant to enhance the uptake of phospor from feed. If and when these pigs will enter the market is unclear. They were developed more than ten years ago. In 2012 the project was stopped due to financial problems[25].

16 http://www.gazette.gc.ca/rp-pr/p1/2013/2013-11-23/pdf/g1-14747.pdf
17 http://globenewswire.com/news-release/2012/10/31/501471/10010606/en/Intrexon-to-Acquire-48-Stake-in-AquaBounty-Technologies.html
18 www.dna.com/Shapiro
19 www.testbiotech.de/node/738
20 www.heraldsun.com.au/news/breaking-news/lab-clones-cow-to-produce-human-milk/story-e6frf-7jx-1226072890692
21 www.telegraph.co.uk/earth/agriculture/geneticmodification/8423536/Genetically-modified-cows-produce-human-milk.html
22 http://www.thenational.ae/news/uae-news/genetically-modified-camels-to-act-like-pharmacies
23 http://news.ucdavis.edu/search/news_detail.lasso?id=10528
24 http://de.wikipedia.org/wiki/Herman_%28Stier%29
25 http://www.spiegel.de/wissenschaft/natur/aus-fuer-enviropig-kanadier-wollen-transgene-schweine-nicht-a-825724.html

Risks of genetically engineered animals

In 2012, EFSA published an initial Guidance for the risk assessment of food from genetically engineered animals (EFSA, 2012). In 2013, it was followed by Guidance on the environmental risk assessment for the release of genetically animals (EFSA, 2013b). The EFSA approach to the risk assessment of genetically engineered animals is more or less the same as that for genetically engineered plants. In the case of the animals it foresees a "comparative risk assessment". Genetically engineered animals or products from these animals are compared with conventionally bred animals or products derived thereof. In general, if there are no striking differences apparent at first sight, the genetically engineered animals will be considered as "substantially equivalent" and safe.

But even EFSA is aware of several gaps in knowledge and problems. Generally, risk assessment of genetically engineered animals is considered to be more complex than risk assessment of plants. Some examples:

- Several animal species cannot be properly controlled in their spatio-temporal dimensions. Animals that move around in the environment will come into contact with various environmental conditions whereas crop plants are supposed to remain in the field.
- Animal excrement and potential pathogens have to be considered since they can be distributed in the environment by the animals. Several pathogens that impact poultry, pigs or cattle also can cause health problems in humans. If the immune system of the genetically engineered animals is impaired, the number of risky pathogens can soar.
- Unexpected side effects of genetic engineering can also cause a change in the behaviour of the animals (being more aggressive or more invasive).

EFSA itself states that there are no long-term studies and there are many risks that cannot be practically assessed before an animal is released (EFSA, 2013b). Nevertheless, it is still of the opinion that risk assessment will be possible by comparison with other animals or computer modelling. Given this viewpoint it seems unlikely that EFSA risk assessment will be of a sufficiently high standard.

Genetic engineering and animal welfare

Each technical step in genetic engineering such as insertion of the DNA into the cells, the propagation of cells in the laboratory or the cloning of genetically engineered animals can cause unintended changes in the DNA or disturbances of the (epigenetic) genome regulation in the animals. This is shown, for example, in publications reporting on livestock cloning: The percentage of animals dying or left with severe illness is high. In many cases, the success rate is no more than 5 percent (for overview see Then & Tippe, 2010).

Neither can genetic engineering in animals be considered neutral from an ethical point of view. Rather, in many cases, a severe impact on animal health is only to be expected. This is further evident in a publication by scientists involved in the creation of the first transgenic bull called Herman (see above) (van Reenen et al., 2001):

"(...) there are convincing arguments to support the idea that treatments imposed in the context of farm animal transgenesis are by no means biologically neutral in their effects on animal health and welfare. On the contrary, several treatments seem to directly threaten the pre- and postnatal survival of transgenic farm animals, and there is every reason to assume that overt pathogenicity and lethality merely represent the very extremes of a wide range of possible detrimental effects of experimental manipulations and phenotypic changes related to transgenesis on animal health and welfare."

These problems are being exacerbated by new methods in synthetic biology (see below) which allow for radical changes in the genome of mammals. Some companies seem to be ready to try anything that is technically possible and profitable. Intrexon, for example, sees itself as "a leader in synthetic biology". According to the Intrexon website, their business is about to take control of the biological functions of all kinds of species[26]:

"Intrexon Corporation is …. focused on the industrial engineering of synthetic biology. …. across multiple industry sectors, including: human therapeutics, protein production, industrial products, agricultural biotechnology, and animal science. The company's advanced bioindustrial engineering platform enables (….) unprecedented control over the function and output of living cells."

There is a manifest need for in-depth discussion of ethical boundaries especially in light of new technologies that are becoming available (see below) not only to introduce new DNA sequences but also to manipulate large parts of the genome. These are technologies that allow substantial changes in the genetic identity of mammals and as such should raise ethical concerns even if suffering and pain cannot be observed. Patents belonging to Intrexon claiming chimpanzees manipulated with DNA originating from insects might just be a foretaste of things to come.

26 www.dna.com

5. Synthetic genome technologies

In recent years several new technologies have emerged that allow technical intervention in the genome. Synthetic biology has received a lot of public attention. Within this discipline there have been several attempts to create living organisms with new properties and even create artificial life. So far, attempts to create completely new life forms have not been successful. Nevertheless, the technical possibilities of synthetic biology are far reaching: It allows fast sequencing of large amounts of DNA and the re-synthesis and radical alteration of DNA.

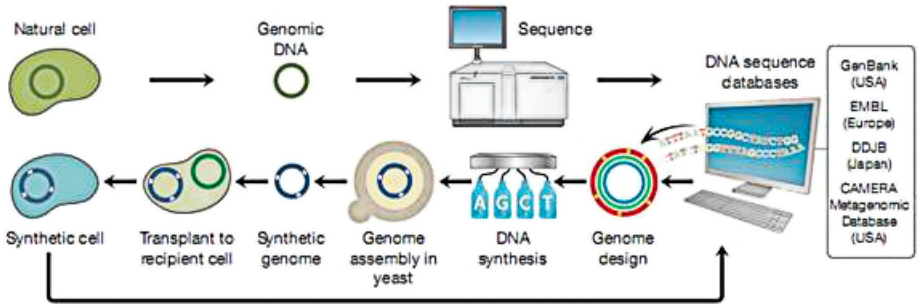

Figure 15: DNA-sequencing and DNA synthesis go hand in hand.
Source: US PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

In 2010, a microorganism with a completely re-synthesised genome was presented to the public for the first time (Gibson et al., 2010). The genome of this organism is not completely new, its DNA was digitally made on the computer and re-synthesised in the laboratory. This experiment was conducted by scientists working with Craig Venter and presented to the global media as a huge scientific success. As the media release[27] from the Craig Venter Institute reads:

[This] "is the proof of principle that genomes can be designed in the computer, chemically made in the laboratory and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome."

As previously mentioned, synthetic biology is not only able the re-synthesise the DNA of existing life forms but also to radically alter their genome. These new technologies enabling the extreme alteration of DNA are known collectively as 'Synthetic Genome Technologies'[28]. They are technically very different in comparison to the methods currently known by the wider public as genetic engineering.

27 Craig Venter Institute media release, 20 Mai 2010, Ref: Gibson, D. G. et al., (2010) „Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome", Science, www.jcvi.org/cms/press/press-releases/full-text/article/first-self-replicating-synthetic-bacterial-cell-constructed-by-j-craig-venter-institute-researcher/

28 In this context this wording seems to be more precise than synthetic biology which also is used in the context of carrying out experiments with cell systems.

With these technologies:

- It is not necessary to isolate DNA from living beings, the DNA can be directly synthesised in the laboratory.
- The DNA which is transferred does not depend on naturally existing genomes, it can be designed in the laboratory or be a combination of DNA from various organisms.
- Some applications do not require the transfer of isolated DNA, but enable direct alteration of the genome in the cells.
- The technical possibilities to change regulation of the natural genome without changing the structure of the DNA are also increasing.

Several organisms derived from these technologies have already been commercialised or might be allowed on the market soon. Some examples:

- Maize SmartStax produces a toxin (Cry1A.105) on the basis of synthetic DNA
- The genome of the olive flies is a combination of DNA from other insects, marine organisms, bacteria and viruses and was realised by gene synthesis.
- Intrexon is relying on the methods of synthetic genome technologies to radically change the genome of mammals and other organisms.

Below we describe two methods used in synthetic genome technology to achieve far reaching changes in the genome. These are so-called gene scissors (nucleases) and oligonucleotides.

Genome-scissors (nucleases)

Nucleases are proteins (enzymes) used to break up DNA – that is why they are called genome scissors. Nucleases have been available technically for several years but were limited in the number of options for cutting the genome. Several nucleases have been developed over the last few years which allow the cutting of DNA and the insertion of new DNA in any position in the chromosomes. These new genome scissors are called TALEN (Transcription Activator-Like Effector Nucleases) or CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). They are a combination of a unit to recognize specific regions of the DNA and an enzyme to cut the DNA. By using TALEN or CRISPR, genes can be knocked out (silenced) and mutations or new DNA can be inserted.

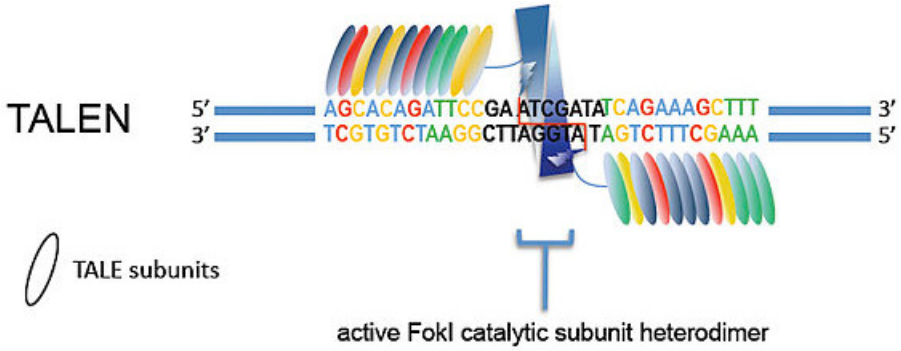

Figure 16: Genome scissors "TALEN" can recognise specific regions of DNA, cut DNA and also introduce new DNA sequences (source: http://en.wikipedia.org/wiki/Genome_editing, author seahorsecipmunk).

In August 2012, a German newspaper revealed that these technologies are about to be used in the plant breeding sector[29]. The article reported that big seed companies such as Syngenta, Monsanto, Bayer Crop Science and KWS Saatzucht AG already have licences to use TALEN technology. According to the newspaper, such plants are already being grown in the KWS greenhouses (Germany). It is not known whether any of the plants have been released into the environment. There is, however, a clear lack of regulation to ensure that these plants, which are genetically engineered organisms, undergo risk assessment (see below).

Alteration of DNA directly in the cells

Oligonucletids are also used in plant breeding. This method is based on using small parts of DNA (RNA) sequences (called oligonucleotids) which are synthesised according to naturally occurring templates (e.g. from plants). By synthesising the DNA it is altered in one detail, so for example the new DNA can be made resistant to herbicides. These short synthetic sequences are transferred into the cell to induce alteration of the plant´s own DNA at the region where the original template was sequenced. It is assumed the oligonukleotids do not become integrated into the plant´ s DNA. The detailed mechanisms are not known. It is believed that the plant's own repair mechanisms are the reason for adapting its genome to the synthetic DNA (Lusser et al., 2011).

29 Stollorz, Das Leben einmal neu redigiert, Frankfurter Allgemeine Sonntagszeitung, 26. August 2012, Nr. 34

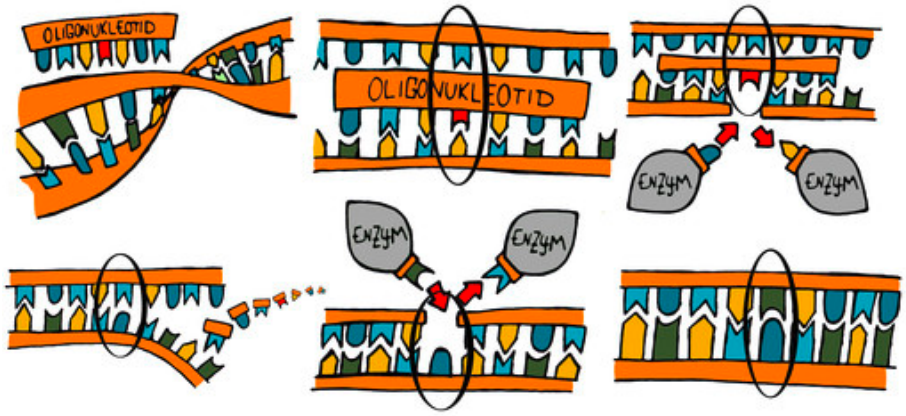

Figure 17: Model of the mode of action of oligonucleotides: 1. The oligonucleotid is inserted into cells 2. The oligonucleotid is fixed at the position with high similarity in the genome. 3. The difference between the plant´s genome and the oligonucleotide induces enzyme repair mechanisms in the cells, one strand of DNA is changed at the relevant position. 4. The oligonucleotid is removed from the plant´s DNA (mechanisms not known). 5. The difference between the two strands of DNA are repaired by the plant's own repair mechanism. 6. The specific alteration within the genome is achieved. Source: http://www.keine-gentechnik.de/dossiers/neue_technologien.html

According to statements of several experts (for example see ZKBS, 2012), this technology should be regarded as conventional (mutation) breeding and not as genetic engineering. This means that these plants will not be covered by regulation. Consequently, risks will not be examined, products will not be registered and no labelling will be required.

At first sight it appears to be correct that oligonucleotid technology can be used to achieve similar results to mutation breeding. However, on closer examination it is evident that it is fundamentally different to conventional (mutation) breeding. In conventional mutation breeding an unspecific stress triggers non-targeted changes in the plant´s DNA. Manipulation with oligonucletids, however, is an invasive method that aims to change the plants DNA very specifically. Oligonucleotid technology can cause off target effects. It is possible that there will be unintended changes in the plant's DNA or in the activity of the plant's own genes (see for example Vogel, 2012; Pauwels et al., 2013). So far, there has been no investigation into whether such effects and their patterns are different in the plants derived from oligonucletid technology in comparison to those observed in plants derived from mutational breeding.

There are already some initial publications showing that the new technologies do indeed precipitate new risks. For example an investigation using human cells (Fu et al., 2013) shows that CRISPR which is used in a similar way to TALEN and oligonucleotid technology, can cause unintended mutations in many regions of the genome.

It also should be taken into account that oligonucletoid technology can also be used to change longer sequences of DNA if applied repeatedly as is, for example, the case in so- called "multiplex automated genome engineering" (MAGE, siehe z.B. Carr et al., 2012). This method can be compared to an assembly line that goes round in circles with many workers introducing small changes every time the cell passes around. The higher the number of cycles, the higher the degree of alteration. There are some protagonists who even want to use this method to transform one species into another, going step by step, inducing many single changes of the genome. According to George Church, this technology could be used to transform the genome of homo sapiens into the genome of a Neanderthal (Church & Regis, 2010):

"The same technique would work for the Neandertal, you would start with a stem cell genome from a human adult and gradually reverse-engineer it into the Neandertal genome or a reasonable close equivalent. … If society becomes comfortable with cloning and sees value in true human diversity, the whole Neandertal creature itself could be cloned by surrogate mother chimp - or by an extremely adventurous female human."

Similarly to Craig Venter, George Church is one of the most recognised experts in synthetic biology. His statement reveals which technological possibilities have emerged within recent years and how some protagonists of synthetic biology think about ethical boundaries.

In conclusion, synthetic genome technologies should not be excluded from regulation. If there is no regulation for such technology then livestock and other animals (such as insects) produced in this way would be exempt from regulation. Such animals could be released and used in farm and food production without being registered, subjected to risk assessment or food products thereof being labelled.

6. Plans for a new free trade agreement TTIP

In 2013, the US and EU decided to start negotiations on a new free trade agreement, the Transatlantic Trade and Investment Partnership, TTIP. One of the well-known obstacles for free trade between EU and the US is EU regulation for genetically engineered organisms. These regulations[30] request that

- the precautionary principle has to be observed in release or market authorisation of genetically engineered organisms,
- all genetic engineered organisms have to undergo risk assessment before they can be allowed for marketing,
- food and feed which are derived from genetically engineered organisms have to be labelled.

An important element in this regard is Regulation 178/2002, which states that the precautionary principle can be applied in cases where there is scientific uncertainty in order to provide a high level of protection for human health and the environment. As Article 7 reads:

"In specific circumstances where, following an assessment of available information, the possibility of harmful effects of health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment"

Also according Directive 2001/18, the precautionary principle is the basis of risk analysis prior to allowing deliberate release or a market authorisation of genetically engineered organisms (Article 1 of Dir. 2001/18). Thus, the precautionary principle is of particular relevance for uncertainties in risk assessment where there is no evidence of a hazard but there are remaining doubts about the safety of genetically engineered organisms (see Krämer, 2013).

30 EU Directive 2001/18, EU Regulation 1829/2003.

In the US these products are only assessed on a case by case basis. The difference is apparent in their treatment of stacked events: They do not have to undergo risk assessment in the US, if the single plants used for the combination of the stack have been assessed. Besides stacked events there are a number of genetically engineered plants and plants derived from synthetic genome technologies that have not been risk assessed (Ledford, 2013).

Amongst those are genetically engineered grasses which are known for their potential for persistence and invasiveness and therefore need to be regarded as plants with a high level of risk (see Bauer-Panskus & Then, 2013).The following table, taken from Ledford (2013) gives an overview of relevant products.

CROPPING OUT REGULATION

Since 2010, the US Department of Agriculture has told at least 10 groups that their genetically modified (GM) crops would not be regulated because a plant pest was not used to do the engineering.

SOURCE: APHIS

Crop	Trait	Developer	Technique
Switchgrass	Easier conversion to biofuels	Ceres	Gene gun
Grapes	Red colour	University of Florida	Gene gun
Turf grasses	Herbicide tolerant	Scotts Miracle-Gro	Gene gun
Maize (corn)	Improved nutrition	Dow AgroSciences	Zinc-finger nuclease
Plums	Faster breeding	Appalachian Fruit Research Station	Non-transgenic offspring of GM parents
Tobacco	Faster breeding	North Carolina State University	Non-transgenic offspring of GM parents
Sorghum grass	Higher yields	University of Nebraska–Lincoln	Epigenetics
Not disclosed	Faster breeding	New Zealand Institute for Plant and Food Research	Non-transgenic offspring of GM parents
Ornamental plants	Not disclosed	BioGlow	Not disclosed
Not disclosed	Not disclosed	Cellectis	Meganuclease-targeted gene deletions

Table 4: Crops derived from genetic engineering and Synthetic Genome Technologies that did not undergo regulatory control in the US (source: Ledford, 2013)

The EASAC report

At the same time as the negotiations for a new free trade agreement began in June 2013, a report was published arguing the EU standards for risk assessment should be substantially lowered. Under the auspices of the European Academy Scientific Advisory Panels (EASAC, 2013), well-known proponents of agro-biotech such as Joachim Schiemann und Jörg Romeis[31] presented their own point of view. The bias of the EASAC report is shown for example in the prioritisation of new genetically engineered plants with herbicide resistance:

> *"Priorities include introducing insect-resistance and herbicide-tolerance into wheat, barley, oil seed rape, soybean, potato, vegetable brassicas and other horticultural crops."*

31 See www.testbiotech.org/node/785

The most troubling message in the EASAC report is that genetic engineering in plants should no longer be perceived as a risky technology and current regulations should be overhauled to that effect. The precautionary principle, in particular should no longer be the basis for risk analysis in the EU in its present form and current practice. EASAC experts argue that enough experience with genetically engineered plants has been gathered to agree that there would be no specific risks associated with their use in agriculture and food production:

> *"Even if stringent application of the precautionary principle had been justifiable in the early days of GM crop research and development when there were more uncertainties about impact, it is difficult to defend the merits of retaining a rigid, cautious, technology-specific regulation today when there is much less uncertainty."*

The precautionary principle as applied in the EU presupposes that market authorisation can be refused if there are substantial uncertainties regarding safety. This means that uncertainties and gaps in knowledge are very relevant for risk assessment[32]. This approach has evolved over more than a decade of discussions in the EU and it is a basic provision of EU regulations such as 178/2002 and Directive 2001/18. Contrary to existing EU regulations, the EASAC experts propose to reject market authorisations only in cases where there is already evidence of adverse effects. This would mean that measures might be taken too late. Further they are of the opinion that it would not be necessary to subject all genetically engineered organisms to risk assessment, but only specific products which are already known to have potential hazards. The effect would be a similar lack of regulatory oversight as shown by Ledford (2013). Further the authors claim evidence of benefits for agriculture:

> *"(...) in common with other sectors, the aim should be to regulate the trait and/or the product but not the technology in agriculture. The regulatory framework should be evidence-based. There is no validated evidence that GM crops have greater adverse impact on health and the environment than any other technology used in plant breeding. There is compelling evidence that GM crops can contribute to sustainable development goals with benefits to farmers, consumers, the environment and the economy. Action is needed to unify and harmonise the regulatory and innovation-enabling roles of the EU policymaking institutions and to ensure that regulation of the outputs of all the crop genetic improvement technologies has a firm foundation in sound science."*

However, it should be kept in mind that the so called "compelling evidence" of the benefits of the technology is just as controversial as the safety of the products (see Then 2013). If the opinion of EASAC´s experts is adopted in new regulations this would mean:

- replacing the precautionary principle with a system that will only accept evidence of adverse effects as a trigger for regulatory measures;
- abolishing regulations for centralised registration and risk assessment covering all genetically engineered organisms;
- abolishing comprehensive and mandatory labelling of genetically engineered organisms and products thereof and leading to less transparency and less choice for farmers and consumers.

32 As for example pointed out in EU Regulation 178/2002, which is also the founding regulation for EFSA.

EASAC experts also want to exclude new technologies in the context of synthetic genome technologies from any regulation:

> *"(…) here is need for urgent action to agree the status and regulation of New Breeding Techniques and, in particular, to confirm which products do not fall within the scope of legislation on genetically modified organisms."*

At the same time the EASAC experts are aware that new technologies will be available which will enable radical alterations in the genome:

> *"Further ahead, scientific discovery worldwide may enable much more radical options for GM crops, involving highly polygenic traits (…)."*

It seems highly contradictory to argue for lowering standards of risk assessment and excluding new technologies from regulation while at the same time new methods are being created that will generate many new uncertainties and risks.

The precautionary principle and evidence

The uncertainties regarding adverse effects of genetically engineered plants have, in fact, never been dealt with. Even where transgenic plants have been on the market for years, there are hardly reliable data on their long-term impact. The reason for the lack of data is that neither in the EU, nor in other regions, are these plants monitored for the effect they might have on health. There are, however, provisions for monitoring the impact on the environment although its implementation is a matter of ongoing controversy. The uncertainties in risk assessment and monitoring of genetically engineered plants are evident in statements made by many experts from Member States regarding the opinion making of EFSA.[33]

For instance, these uncertainties concern:

- unintended changes in the composition of the plants components
- interactions between plants and the environment
- combinatorial effects in stacked events
- risks for immune and reproductive system
- impact on non-target organisms and ecosystems
- results from feeding studies

In one positive move, a project financed by the EU examining the risks to the environment from genetically engineered plants was started by a group of experts, many of them known to be pro-biotech, to counter the precepts in the EASAC paper. The project known as BEETLE analysed more than 700 scientific publications from all over the world on genetically engineered plants and their potential effects on environment and biodiversity. Around 100 to 167 contributions were made to the online surveys from environmental experts representing a wide range of knowledge with special focus on the EU.

33 The comments from experts of EU Member States are published together with the opinions of EFSA see http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

The study identified many "great" or "important" uncertainties mostly related to long-term and cumulative effects. Some examples of relevant issues[34] were:

- increased fitness of the genetically engineered plants
- hybridisation between genetically engineered plants and wild species relatives and their persistence
- altered fecundity causing increasing seed (gene) flow
- development of resistance in pests
- effects on non-target organisms (NTO)
- effects on NTO due to accumulation of toxic compounds
- effects on rhizosphere microbiota
- effects on symbiotic NTO Changes on soil functions
- effects on biological control
- altered use of agrochemicals
- indirect changes in susceptibility of crops against plant pathogens
- adverse effects on agro-biodiversity
- indirect changes in fertiliser use
- potential changes in landscape structure
- increased mineral nutrient erosion and fertilizer leaching
- altered chemical attributes of soil fractions
- effects of stacked events
- regional aspects.

In the light of this evidence and current knowledge, the BEETLE project comes to the conclusion that particularly risk assessment will always include substantial uncertainties about the long-term effects of releasing genetically engineered organisms.

It should be further taken into account that genetically plants with pending authorisations raise new questions and uncertainties. Plants such as "SmartStax +" or "Syngenta Six" not only inherit single additional DNA sequences but produce six toxins at once and are resistant to several herbicides. At the same time, there have been hardly investigations into the combinatorial effects of plant components and residues from spraying. Stacking relevant DNA in the plants leads to an accumulation of uncertainties and risks. In addition, other plants with higher tolerance to drought, changed quality in oil or new resistances to herbicides or new insecticidal toxins raise new questions (see above). In the light of these findings, the precautionary principle should be given much more weight rather than be replaced by evidence-based regulation.

In future, genetically engineered animals or trees (not integrated in the report) and organisms such as algae engineered by synthetic genome technologies for energy production[35] will pose further risks.

34 See www.testbiotech.de/node/906

35 See http://www.testbiotech.org/node/412

As this report shows, current developments are leading away from the traditional systems of breeding and agriculture towards more and more complex technologies that are failure-prone and associated with more and more uncertainties regarding risks. If society wants to allow the use of some of these technologies and applications there is no alternative but to strengthen the precautionary principle in parallel. This is the only way to deal with the many uncertainties and factual limits of knowledge in a rational way.

There are several other ongoing lobby activities similar to those in the EASAC report. For example, in a joint letter sent in October 2013 to the EU Commission, companies such as Bayer, BASF, Dow Chemical, Dow AgroScience, Novartis and Syngenta AG demanded the introduction of a "Innovation Principle" as a counter balance to the precautionary principle[36]:

> *"Our concern is that the necessary balance of precaution and proportion is increasingly being replaced by a simple reliance on the precautionary principle and the avoidance of technological risk."*

These lobbying activities are accompanied by statements from various sides pretending that so far no evidence for damage caused by genetically engineered organisms has been produced and that "consensus" should exist that these products are safe. Anne Glover who was appointed as Chief Scientific Adviser to the President of the European Commission in 2011 is one of the most vocal protagonists amongst those denying specific risks[37]:

> *"There is no substantiated case of any adverse impact on human health, animal health or environmental health, so that's pretty robust evidence, and I would be confident in saying that there is no more risk in eating GMO food than eating conventionally farmed food,"*

It has to be assumed that the extremely biased position of Glover, who is Manuel Barroso's first ever Chief Scientific Adviser, mirrors the position of the majority of the EU Commission.

Such lobbying activities are showing initial results: The EU Commission unofficially announced that there will be an expert discussion on whether the precautionary principle should still be applied to genetically engineered plants. Furthermore, the Commission has already fixed a date for the re-evaluation of the regulations for risk assessment of genetically engineered plants. Currently, the Commission is waiting for the outcome of a project financed by EU that will be finished at the end of 2015[38]. The title of the project is **G**MO **R**isk **A**ssessment and **C**ommunication of **E**vidence (GRACE) and it is led by well-known proponents of agro-biotech such as Joachim Schiemann[39]. There are several possible scenarios after GRACE presents its conclusions. If the conclusion is that there is no evidence of risks to health from genetically engineered plants, the Commission could propose abandoning the precautionary principle. The standards for risk assessment could be lowered and precaution sacrificed in the interests of the TTIP. Some explicit wording might be written into the TTIP to avoid controversy. The Commission could make such a move just based on the outcome of GRACE while the TTIP itself would just refer to very general principles.

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36 http://corporateeurope.org/sites/default/files/corporation_letter_on_innovation_principle.pdf

37 www.euractiv.com/print/innovation-enterprise/commission-science-supremo-endor-news-514072

38 www.grace-fp7.eu/content/grace-brief

39 See for example www.testbiotech.org/node/785

7. Conclusions and recommendations

This report shows that genetically engineered organisms pose growing risks in light of current and future developments. Some of the most relevant reasons are:

- an increasing number of combinations of additional DNA sequences and relevant traits in so-called stacked events and related accumulation of uncertainties and risks;
- introduction of new herbicide resistance traits leading to an increase in residues in the plants from spraying with the complementary herbicides.
- insertion of new variants of insecticidal toxins by using synthetically derived DNA ;
- introduction of new traits such as higher tolerance to drought or new quality in oil which generate new uncertainties in risk assessment;
- environmental releases of genetically engineered organisms such as trees and insects which have a high potential to spread without control in the environment;
- increasing use of technologies in plants and animals that allow radical alteration of the genome ("Synthetic Genome Technologies") .

Against this background we make the following recommendations:

1. Enhancement of the precautionary principle

- Standards for risk assessment of genetically engineered organisms should be raised; combinatorial effects, long term impacts and residues from spraying should be taken into account. If doubts remain about safety, the burden of proof should be with the applicant. Post-marketing monitoring should be much more detailed and comprehensive.
- Genetically engineered organisms which cannot be controlled in their spatio-temporal dimension, should not be allowed for release. Precautionary measures only can be taken if a genetically engineered organism can be removed from the environment if this is urgently required[40].
- Regulate and label invasive methods of DNA alteration.

2. Definition of ethical boundaries

- New methods of making radical changes in the genome have become available which require the definition of ethical boundaries to protect genomic identity and the integrity of living organisms.

3. Implementation of a coherent agricultural policy

- The 'arms race' in the fields as observed in the context of crops such as SmartStax is not compatible with the aims of an environmentally friendly, multifunctional and sustainable agriculture. Targeted strategies are needed to minimise insecticides and herbicides in the fields and to enhance biodiversity in and around the fields. Decision-making in the EU on imports should also take into account the impact of cultivation of genetically engineered plants in other regions.
- The implementation of these recommendations should have priority above further releases and market authorisations.

40 www.testbiotech.org/node/906

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Annex

Tabled overview on pending EU market applications till December 2013,
Sources: www.bfr.bund.de/cm/343/antraege-gvo-lm-fm-vo-1829.pdf
and http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?unit=GMO

Plant species/ name/ applicant	planned usage/ trait (complementary herbicide)	status of application
Rice LLRICE62 Bayer	Food and feed from herbicide resistant rice (glufosinate)	Examination finalised
Cotton MON531 x MON1445 Monsanto	Food and feed from insecticidal and herbicide resistant cotton (glyphosate)	Examination finalised
Maize 1507 x NK603 DuPont/Pioneer	Food and feed from insecticidal and herbicide resistant maize, including cultivation (glyphosate, glufosinate)	Application: 2005
Maize NK603 Monsanto	Food and feed from herbicide resistant maize, including cultivation (glyphosate)	Examination finalised
Maize 59122 DuPont/Pioneer	Food and feed from insecticidal and herbicide resistant maize, including cultivation (glufosinate)	Examination finalised
Soybeans GM 40-3-2 Monsanto	Food and feed from herbicide resistant soybeans, including cultivation (glyphosate)	Examination finalised
Maize 1507 x 59122 DuPont/Pioneer	Food and feed from insecticidal and herbicide resistant maize, including cultivation (glufosinate)	Application: 2005
Maize 59122 x 1507 x NK603 DuPont/Pioneer	Food and feed from insecticidal and herbicide resistant maize, including cultivation (glyphosate, glufosinate)	Application: 2005
Maize 3272 Syngenta	Food and feed from maize thermotolerant alpha-amylase	Examination finalised data inconclusive
Cotton MON88913 Monsanto	Food and feed from herbicide resistant cotton (glyphosate)	Examination finalised data inconclusive
Cotton MON88913 x MON15985 Monsanto	Food and feed from insecticidal and herbicide resistant cotton (glyphosate)	Application: 2007

Plant species/ name/ applicant	planned usage/ trait (complementary herbicide)	status of application
Soybeans 305423 DuPont/Pioneer	Food and feed from soybeans with increased oleic acid and herbicide resistance (ALS inhibitors)	Examination finalised
Soybeans 305423 x 40-3-2 DuPont/Pioneer	Food and feed from soybeans with increased oleic acid and herbicide resistance (glyphosate and ALS inhibitors)	Application: 2007
Maize 98140 DuPont/Pioneer	Food and feed from herbicide resistant maize (glyphosate, ALS inhibitors)	Examination finalised data inconclusive
Cotton MON15985 Monsanto	Food and feed from insecticidal cotton	Application: 2008
Cotton MON15985 x MON1445 Monsanto	Food and feed from insecticidal and herbicide resistant cotton (glyphosate)	Application: 2008
Maize GA21 Syngenta	Cultivation of herbicide resistant maize (glyphosate)	Examination finalised
Soybeans BPS-CV127-9 BASF	Food and feed from herbicide resistant soybeans (imidazolinone)	Application: 2009
Maize Bt11 x MIR162 x MIR604 x GA21 Syngenta	Food and feed from insecticidal and herbicide resistant maize (glyphosate, glufosinate)	Application: 2009
Cotton 281-24-236 x 3006-210-23 x MON88913 Dow AgroSciences	Food and feed from insecticidal and herbicide resistant cotton (glyphosate, glufosinate)	Application: 2009
Maize MON87460 Monsanto	Food and feed from maize with drought tolerance	Examination finalised
Soybeans MON87769 Monsanto	Food and feed from soybeans with stearidonic acid (SDA)	Application: 2009
Cotton GHB614xLLCotton25 Bayer	Food and feed from herbicide resistant cotton (glyphosate, glufosinate)	Application: 2010

Plant species/ name/ applicant	planned usage/ trait (complementary herbicide)	status of application
Soybeans MON87705 Monsanto	Food and feed from soybeans with increased oleic acid	Examination finalised
Maize NK603 x T25 Bayer	Food and feed from herbicide resistant maize (glyphosate, glufosinate)	Application: 2010
Maize MIR604 Syngenta	Cultivation of insecticidal maize	Application: 2010
Maize Bt11 x MIR604 x GA21 Syngenta	Cultivation of insecticidal and herbicide resistant maize (glyphosate, glufosinate)	Application: 2010
Soybeans MON87769 x MON89788 Monsanto	Food and feed from herbicide resistant soybeans with with stearidonic acid (SDA) (glyphosate)	Application: 2010
Maize Bt11 x MIR162 x 1507 x GA21 Syngenta	Food and feed from insecticidal and herbicide resistant maize (glyphosate, glufosinate)	Application: 2010
Maize DAS-40278-9 Dow AgroSciences	Food and feed from herbicide resistant maize (2,4-D and AOPP)	Application: 2010
Soybeans DAS-68416-4 Dow AgroSciences	Food and feed from herbicide resistant soybeans (2,4-D and glufosinate)	Application: 2011
Maize 1507 x 59122 x MON810 x NK603 Dow AgroSciences	Food and feed from insecticidal and herbicide resistant maize (glyphosate, glufosinate)	Application: 2011
Soybeans MON87708 Monsanto	Food and feed from herbicide resistant soybeans (dicamba)	Application: 2011
Cotton GHB614 x LLCotton25 x MON15985 Bayer	Food and feed from insecticidal and herbicide resistant cotton (glyphosate, glufosinate)	Application: 2011

Plant species/ name/ applicant	planned usage/ trait (complementary herbicide)	status of application
Maize 5307 Syngenta	Food and feed from insecticidal maize	Application: 2011
Cotton GHB119 Bayer	Food and feed from herbicide resistant cotton (glufosinate)	Application: 2011
Cotton T304-40 Bayer	Food and feed from insecticidal and herbicide resistant cotton (glufosinate)	Examination finalised
Soybeans FG72 Bayer	Food and feed from herbicide resistant soybeans (glyphosate und isoxaflutole)	Application: 2011
Maize Bt11 x 59122 x MIR604 x 1507 x GA21 Syngenta	Food and feed from insecticidal and herbicide resistant maize (glyphosate, glufosinate)	Application: 2011
Soybeans MON87705 x MON89788 Monsanto	Food and feed from herbicide resistant soybeans with increased oleic acid (glyphosate)	Application: 2011
Oilseed rape MON88302 Monsanto	Food and feed from herbicide resistant oilseed rape (glyphosate)	Application: 2011
Maize Bt11 x MIR162 x MIR604 x 1507 x 5307 x GA21 Syngenta	Food and feed from insecticidal and herbicide resistant maize (glyphosate, glufosinate)	Application: 2012
Cotton GHB614 Bayer	Cultivation of herbicide resistant cotton (glyphosate)	Application: 2012
Maize 3272 x Bt11 x MIR604 x GA21 Syngenta	Food and feed from insecticidal and herbicide resistant maize thermotolerant alpha-amylase (glyphosate, glufosinate)	Application: 2012
Soybeans DAS-44406-6 Dow AgroSciences	Food and feed from herbicide resistant soybeans (glufosinate and 2,4-D)	Application: 2012

Plant species/ name/ applicant	planned usage/ trait (complementary herbicide)	status of application
Soybeans MON87708 x MON89788 Monsanto	Food and feed from herbicide resistant soybeans (glyphosate, dicamba)	Application: 2012
Oilseed rape 73496 DuPont/Pioneer	Food and feed from herbicide resistant oilseed rape (glyphosate)	Application: 2012
Maize MON87427 Monsanto	Food and feed from herbicide resistant maize (glyphosate)	Application: 2012
Soybeans SYHT0H2 Syngenta	Food and feed from herbicide resistant soybeans (glufosinate und mesotrione)	Application: 2012
Maize MON89034 x 1507 x NK603 x DAS-40278-9 Dow AgroSciences	Food and feed from insecticidal and herbicide resistant maize (glufosinate, glyphosate, 2,4-D, AOPP)	Application: 2013
Maize MON89034 x 1507x MON88017 x 59122 x DAS-40278-9 Dow AgroSciences	Food and feed from insecticidal and herbicide resistant maize (glufosinate, glyphosate, 2,4-D, AOPP)	Application: 2013
Cotton MON88701 Monsanto	Food and feed from herbicide resistant cotton (dicamba)	Application: 2013
Soybeans DAS-68416-4 x MON89788-1 Dow AgroSciences	Food and feed from herbicide resistant soybeans (glyphosate, glufosinate and 2,4-D)	Application: 2013
Soybeans DAS-81419-2 s Dow AgroSciences	Food and feed from insecticidal and herbicide resistant soybeans (glufosinate)	Application: 2013
Maize MON87427 x MON89034 x NK603 Monsanto	Food and feed from insecticidal and herbicide resistant maize (glyphosate)	Application: 2013