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Testbiotech analysis of risk assessment strategies for genetically engineered plants used for food and feed in the EU

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Content

Summary

Within the first ten years of its activities, the work of the GMO panel of the EFSA can not be seen as being independent nor does it fulfil the requirements of EU regulations. In addition, the EU Commission fails to fulfil its task as risk manager, as it does not define sufficient risk assessment policies and neglects its duty to implement effective post marketing monitoring. Flaws of current risk assessment of the EFSA will be perpetuated by a planned new *Implementation Regulation* proposed by the EU Commission.

The recommendations for future risk analysis strategies include to drop the concept of comparative risk assessment and to apply a comprehensive risk assessment to each application of genetically engineered organisms.

1. Overview of market authorisations in the EU

By August 2012, 46 *events* of genetically engineered plants had been authorised for usage in food and feed within European Union. Most of them are for import and processing, two *events* are authorised for cultivation: Monsanto's Maize MON810 and the BASF potato "Amflora".

The 46 *events* include the following species: 26 maize, 8 cotton, 7 soybeans, 3 rapeseed, 1 potato, 1 sugar beet. The events can be divided into four groups of technical traits (one of which overlaps with two other groups):

- 8 *events* producing insecticidal toxins,
- 15 *events* tolerant to herbicides,
- 22 *events* a combination of insecticidal and herbicide tolerant plants (*stacked events*)
- others: 1 potato producing starch for industrial use, 1 rapeseed producing infertile pollen.

2. General requirements for risk assessment of genetically engineered plants in the EU

According to the regulations of the European Union (Regulation 178/2002, Regulation 1829/2003 and Directive 2001/18), the overarching goal of EU policy is to ensure a high level of environmental and consumer protection. In case of uncertainties the precautionary principle shall prevail.

Some quotes from the EU regulations:

>> Regulation 178/2002 "the Food Safety Regulation":
"Risk assessment shall be based on the available scientific evidence and undertaken in an independent, objective and transparent manner." (Art. 6, 2).

>> Regulation 1829/2003, „food and feed":
Products derived from genetically engineered plants "should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard." (Recital 9).

>> Directive 2001/18, „deliberate release":
The directive requires the examination of the "direct and indirect, the immediate and delayed effects" of the genetically engineered plant on human health or the environment (Annex II), "in accordance with the precautionary principle." (Article 1)

3. Risk assessment and the comparative approach

Since 2003, the European Food Safety Authority, EFSA, is conducting risk assessment on the basis of its own Guidance. The EFSA Guidance is built on the assumption that risks of genetically engineered plants are comparable to those of plants derived from conventional breeding. In consequence, a *comprehensive risk assessment* is not conducted and only a limited set of data is requested. The so-called *comparative safety assessment* is explained in the current EFSA Guidance (EFSA, 2011):

> *"The underlying assumption of this comparative approach is that traditionally cultivated crops have a history of safe use for consumers and/or domesticated animals. These traditionally cultivated crops can thus serve as comparators when assessing the safety of GM plants and derived food and feed."*

Consequently, current risk assessment is not comprehensive. For example, there are no requests for a detailed assessment of health risk in feeding trials and in long-term studies. The EFSA

assumes that risks that cannot be compared to those of conventional breeding will only occur in rare cases, and only in such rare cases will a comprehensive risk assessment need to be carried out. However, so far this has never happened (EFSA, 2011):

> *"Where no comparator can be identified, a comparative risk assessment cannot be made and a comprehensive safety and nutritional assessment of the GM plant and derived food and feed itself should be carried out."*

The EFSA Guidance for risk assessment of genetically engineered plants refers to international standards such as *Codex Alimentarius* and OECD, but, taking a closer look at those standards, it is evident that the *comparative approach* was mostly developed by industry. Here the *International Life Sciences Institute* (ILSI) plays a crucial role. The ILSI is funded by companies such as Monsanto, Dow AgroSciences, Bayer, DuPont and Bayer and it develops standards such as the *comparative safety assessment* on behalf of industry, and also plays an active role in introducing those standards to the Guidance of relevant state authorities.

In the case of the EFSA, Harry Kuiper who was the chair of the so-called GMO Panel from 2003-2012, not only played a decisive role in setting EFSA standards, but he was also a member of the ILSI task force which developed the concept of comparative safety assessment on behalf of the industry (ILSI, 2004; Then & Bauer-Panskus, 2010). The ILSI claims the introduction of the comparative assessment was a success:

> *"In 2004, the task force's work culminated in the publication of a report that included a series of recommendations for the nutritional and safety assessments of such foods and feeds. This document has gained global recognition from organizations such as the European Food Safety Agency and has been cited by Japan and Australia in 2005 in their comments to Codex Alimentarius. The substantial equivalence paradigm, called the comparative safety assessment process in the 2004 ILSI publication, is a basic principle in the document."* (ILSI, 2008)

As Kuiper explains in one of his publications the comparative assessment is nothing else than the principle of substantial equivalence:

> *„Although the Principle of Substantial Equivalence has received comments from all types of stakeholders (producers, regulators, consumers, evaluators, etc.), the basic idea behind the principle remains untouched. When evaluating a new or GM crop variety, comparison with available data on the nearest comparator, as well as with similar varieties on the market, should form the initial part of the assessment procedure."* (Kok&Kuiper, 2003)

What is the general problem with the comparative approach from a scientific point of view? Conventional breeding and genetic engineering can be seen as being fundamentally different from a technological point of view as well as from a biological perspective. Unlike conventional breeding, genetic engineering inserts technically derived DNA constructs to enforce specific biological functions in plants by disregarding the system of gene regulation and the barriers between species. Choosing the comparative approach implies a high likelihood that risks attributed to the method of genetic engineering (such as disturbances of the gene regulation) are not identified.

In the Guidance of the EFSA, the *comparative assessment* is the starting point in the overall process of risk assessment. The first step in this process is the identification of potential hazards, which need to be assessed during the later stages of the risk assessment. This starting point impacts all following steps of the risk assessment, and thus only a limited 'check up' takes place rather than a *comprehensive risk assessment*. As will be shown in the following section, the comparative approach is associated with flaws during other steps of the risk assessment conducted by the EFSA. And these flaws are also perpetuated by the *Implementation Regulation* of the EU Commission (EU Commission, 2012).

4. The initiative of the EU Commission

In 2012 the EU Commission published a *Commission Implementing Regulation (…) on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 (…)* (EU Commission, 2012). As soon as this regulation is adopted, it will become the basis for the work of the EFSA. However, compared with the current Guidance of the EFSA this regulation is not a real improvement. The most relevant change would be a mandatory feeding study of 90 days with rats to examine health effects. However this would apply to *stacked events*, inheriting several additional DNA constructs, derived from crossings of genetically plants. And more relevant tests such as multi generational studies are still not required.

In the following section, some points are listed to show some deficiencies of the proposed new regulation.

- *Comparative risk assessment* is still seen as the standard procedure. Instead of a comprehensive risk assessment there will only be a reduced 'check up' based on the assumption that risks from genetically engineered plants can be regarded as equivalent to those derived from conventional breeding (see above)

- The most relevant step in comparative risk assessment (the investigation of substantial equivalence) is still based on a concept that allows the introduction of flawed historical data. Especially database of the ILSI is widely used in current risk assessment by the EFSA despite the fact that even the members of GMO panel do not consider it as a reliable source. As Joe Perry, current Chair of the EFSA's GMO Panel explained in 2011[1]:

  "(…) at the present time we can't trust the ILSI database. There is not sufficient environmental information from where these trials were done and that's why we insist that the commercial reference variety should be planted simultaneously with the GM and the non-GM. Otherwise I think we are in an unsafe situation and I would worry that the limits would be too wide."

- Interactions with the environment that may impact the composition of plants are not tested sufficiently. No stress tests are applied to investigate the functional stability of the inserted DNA construct under defined conditions. There are several publications that show that genetically engineered plants do not react to environmental stress in the same way as plants derived from conventional breeding (see for example Meyer et al., 1992; Gertz et al., 1999; Matthews et al., 2005; Zeller et al., 2010). These interactions between genetically engineered plants and the environment can also engender new risks if, for example, the content of unhealthy compounds is increased or if the plants become more susceptible to plant pests.

- Testing for health risks is still not based on a stepwise concept that entails mandatory investigations such as toxicity tests on cell cultures, targeted investigation of relevant health risks and long term and multi-generational studies.

There are numerous discussions and wide ranges of opinions with regards to the health effects that might be imposed by the consumption of genetically engineered plants. There are some reports about negative impacts on the health of farm animals under practical conditions. There are several scientific publications that point to health impacts and disturbances of organs in laboratory animals (for example: Even & Pusztai, 1999; Malatesta et al.; 2002, 2003; Spiroux et al., 2009;

1 The EFSA's consultative workshop on its draft guidance for the selection of Genetically Modified (GM) plant comparators, held in Brussels on 31 March 2011, http://www.efsa.europa.eu/en/events/event/gmo110331.htm

Gallagher, 2010) which require further investigations. There is evidence that genetically engineered plants can provoke reactions by the immune system. Reactions by the immune system are observed in fishes, (Sagstad et al., 2007, Frøystad-Saugen, 2008), pigs (Walsh et al., 2011) mice (Finamore et al., 2008, Adel-Patient et al., 2011) and rats (Kroghsbo et al., 2008).

- There is no request to apply more recent technologies, such as metabolic profiling. As several investigations have shown (Batista et al., 2008, Jiao et al., 2010), the plant's gene activity and its metabolism are often unintentionally impacted by the method of genetic engineering.

In contrast with methods based on mutagenesis, crossing and selection, genetic engineering uses invasive methods and technical means to enforce specific biological functions in the plants. This implies that the newly introduced gene sequences escape the plant's normal gene regulation, and new metabolic pathways are introduced into the plants, rather than being adopted naturally. Thus the observed changes in gene activity of genetically engineered plants have other causes and can result in different effects than those observed in plants derived from conventional breeding. What is regarded as a normal reaction in plants derived from conventional breeding, can be presumed to be a disturbance of gene regulation in the case of genetically engineered plants. Methods such as metabolic profiling can help to identify causes, effects and potential hazards.

- The necessary interplay with pesticide regulation is missing. In general, the GMO Panel of the EFSA leaves all questions concerning the risk assessment of residues from spraying to the EFSA Pesticide Panel.

There are, however, several reasons why the risk assessment of genetically engineered plants with herbicide tolerance cannot leave aside the issue of residues from spraying: Herbicide tolerant plants are meant to survive the application of the complementary herbicide while most other plants will be killed after a short time. Thus, residues of glyphosate, its metabolites and the additives can accumulate and interact in the plants that survive due to their additional genetic information. Furthermore, the complementary herbicides are likely to be sprayed several times during crop growth.,Thus the pattern of usage and the level of residues can be significantly higher compared with non-resistant crop plants. Finally, there are many studies that show that for example spraying the glyphosate tolerant soybean with the complementary herbicide can change the composition of the soybeans (a list of publications can be found at Testbiotech, 2012). Consequently the residues and their combinations are inevitable constituents of the plant's composition leading to specific patterns of exposure in the food chain and should be seen as constituents of the plant that should be included in the risk assessment of genetically engineered plants.

- Bt toxins are not assessed according to pesticide regulation. The mode of action of Bt toxins is not fully understood; it is even a matter of controversial debate (Pigott & Ellar, 2007). Strict selectivity of the Bt toxins is not shown by empirical evidence but deduced from its mode of action as described previously. Soberon et al., (2009) show that there are mechanisms that might cause toxicity in other species and even in mammals. Hilbeck et al (2012) show that expectations in strict selectivity in Cry1Ab are failing in regard to non-target organisms. Mesnage et al. (2012) show that Cry1Ab toxins used in genetically engineered plants can impact human cells.

Furthermore, there are several important differences between the Cry toxin as produced in plants and its usage in traditional mixtures (for general overview on these issues see Hilbeck & Schmid, 2006; Szecaks & Darvas, 2012). So far Bt toxin was only used in traditional mixtures and in its crystallized (inactivated) form. But in the plants the Cry toxins are solubilised (activated). Further, it is applied throughout the whole period of vegetation, while the traditional sprays are used in a much more targeted way. To be effective, it has also to be exposed in a higher concentration than traditional mixtures: In mixtures, additive and synergistic effects require only a low level of the

single compound. Further, some details of the DNA sequence are changed during the process of transferring the DNA into the plants´ genome. These changes in DNA can render changes in the toxicity of the proteins. As Pardo Lopez et al. (2009) and Pigott et al. (2008) show, synthetically derived and modified Bt toxins can show much higher toxicity than native proteins. Even small changes in the structure of the proteins can cause huge changes in toxicity. Thus, risks for human health cannot be excluded by assumption or considerations but only through empirical testing before market authorisation. All in all, without full authorisation of the Cry toxins (as produced in plants) under pesticide Regulation, the placing of genetically engineered plants on the market establishes double standards for the safety of pesticides within the EU: Under GMO regulation a much lower standard is applied than under pesticide regulation.

- The requirements for investigation of synergistic, additive and accumulated effects are not sufficiently defined. Instead, stacked events are still investigated less rigorously than single events. The need for more detailed investigations can be exemplified by synergistic mode of action of Bt toxins: Some plant enzymes that diminish the digestion of proteins (protease inhibitors) can strongly enhance the toxicity of Bt toxins (Pardo Lopez et al., 2009). Even the presence of very low levels of protease inhibitors can multiply the insecticidal activity of some Cry toxins. It is known that maize and especially soybeans produce such inhibitors. Interactivity between toxins or in combination with environmental toxins, bacteria, plant enzymes or pesticides can cause unexpected higher toxicity and lower selectivity (Then, 2010). These effects can impact human health as well as ecosystems.

The case of *SmartStax* (a genetically engineered maize developed by Monsanto and Dow AgroSciences) gives evidence on failures of the current risk assessment that will be perpetuated by the proposed Commission Regulation (EU Commission, 2012): *SmartStax* inherits DNA constructs that are derived from more than seven species. It produces six modified bacterial toxins (one of them synthetic) and is made tolerant against two herbicides. But synergistic effects in the food chain were not investigated. Also the draft Implementation Regulation of the Commission does not require a more comprehensive investigation of combinatorial effects.

- The need to establish fully evaluated methods to measure the expression of the newly introduced DNA constructs is not mentioned. One of the prerequisites of risk assessment is to have sufficient data on the expression of the newly expressed proteins. But for example in the case of Bt toxins, standardised protocols to measure the content of Bt toxins in a way that the results can be reproduced by other laboratories are missing (Székács et al., 2011). Further, data are not requested to show how these plants and the expression rate of the newly introduced proteins will be influenced by extreme weather conditions such as drought. Several investigations show that genetically engineered plants can exhibit unexpected reactions under stress conditions. This can also impact the Bt content in plants (Then& Lorch, 2008).

- The proposal of the Commission is missing sufficiently clear quality standards for investigations conducted by industry. The Commission claims that one of the main improvements of its planned Regulation is to require quality assurance for studies (Good Laboratory Practice, GLP or ISO). Indeed these could be seen as an improvement. However the GLP standards are only required for new applications. Existing market authorisations and pending applications are not included. The exemption of these products is a violation of current EU law which requires scientific evaluation of the highest possible standard in each and every case (Regulation 1829/2003).

- Post-marketing monitoring to allow identification of negative health effects is not required. EU Regulations require post-marketing monitoring because the risk assessment of genetically engineered plants involves a number of complex issues and there will always

remain some uncertainties. There are two categories of monitoring: Case-specific monitoring (targeting specific risks) and general surveillance. Post-marketing monitoring is meant to trace and identify direct or indirect, immediate, delayed or unforeseen effects on human health or the environment of genetically engineered plants after they have been placed on the market (Dir. 2001/18).

But no monitoring is implemented within the EU to identify health risks of consumption of food products derived from genetically engineered plants. The potential health impacts of these food products cannot be *traced* and *identified* as required (Recital 43 of Directive 2001/18). There is no way to perform *"observation, in a systematic manner"* (Annex VII of Directive 2001/18). This is a well-known problem. As the European Commission stated in 2005 (European Communities, 2005):

> *"(...) 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."*

In conclusion, the current practice of post market monitoring does not meet the requirements of existing EU regulations. This is also underlined by a legal dossier compiled on behalf of Testbiotech (Kraemer, 2012).

Also current obligations imposed for the monitoring of environmental risks are insufficient. Industry is handing out questionnaires to farmers and uses existing environmental observation networks that were not developed for this specific purpose. These measures are not adequate to meet the requirements of a sufficient monitoring for environmental risks.

5. Some conclusions and recommendations

Within the first ten years of its activities the work of the GMO panel of the EFSA can not be seen as being independent nor does it fulfil the requirements of EU regulations. Further, the EU Commission fails to fulfil its task as risk manager. It does not define sufficient risk assessment policies and it neglects its duty to implement effective post marketing monitoring. Ethical questions and socio-economic consequences are not included in the process of risk analysis.

Some recommendations for future risk analysis strategies:

- Drop the concept of comparative risk assessment; do not presume safety, equivalence, similarity or familiarity; use comparison as a tool and not as a concept;
- Always require a comprehensive risk assessment in the case of genetically engineered organisms;
- Establish clear cut-off criteria for rejection of applications;
- Reassess EU market authorisations;
- Promote independent risk research;
- Set higher standards for independency of the EFSA.

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