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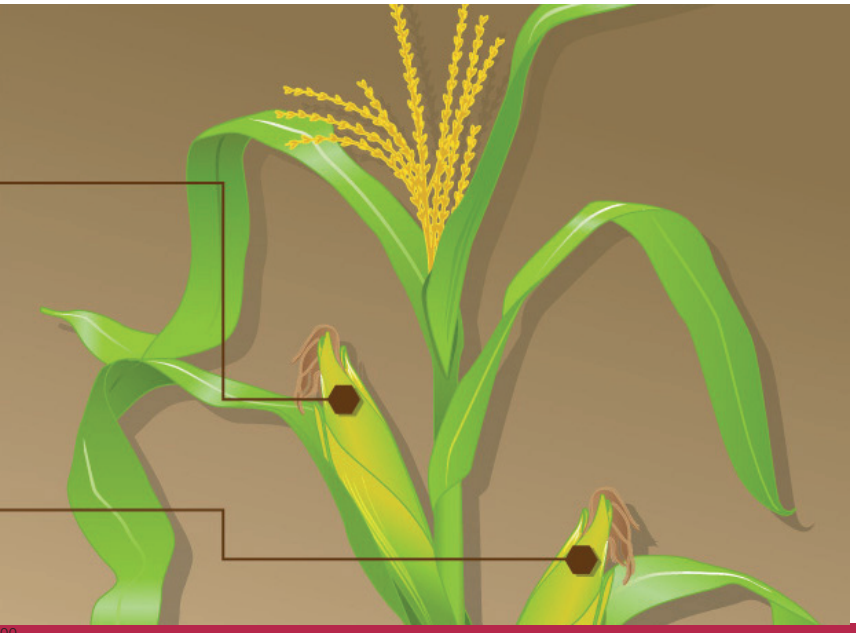

Agro-Biotechnology:

Testbiotech opinion on EFSA's draft guidance on the environmental risk assessment of genetically modified plants

A Testbiotech report for

The Greens | EFA
in the European Parliament

THINK BIO DIVERSITY

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Testbiotech opinion on EFSA's draft guidance on the environmental risk assessment of genetically modified plants

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Summary

The risk assessment of genetically engineered plants is a controversial issue in the European Union. Although its standards are discussed controversially by experts and stakeholders, the European Food Safety Authority (EFSA) has already published several favourable opinions on the cultivation and the use of genetically engineered food and feed. The EFSA has now drawn up new draft guidelines for ecological risk assessment as requested by the European Commission and several member states.

The new guidelines show similar problems as the existing guidelines for risk assessment of food and feed. These start with the comparison of conventional plants and genetically engineered plants. There is a disregard of the fact that the methods and results of genetic engineering are fundamentally different from conventional breeding and growing. In practise, this comparative assessment leads to an approach that is too narrow in hazard identification and risk characterisation. Accordingly, the genetically engineered plants are not seen as technically derived new organisms but similar (comparable) to conventionally bred plants. Starting from this premise, the EFSA does not require comprehensive investigations of the plants per se. Genetically engineered plants are known to have a broad range of unintended effects, some of them caused by the method of gene transfer that escapes the plants' own gene regulation. By mostly ignoring those unexpected non-linear effects the EFSA approach is likely to fail.

Further EFSA's standards are not mandatory even in crucial details. Empirical investigations are mostly replaced by considerations and assumptions. For example, plants with stacked events (combination of several additional gene constructs) need not be tested if the single gene constructs have already been assessed. Synergism and combinatorial effects that might emerge in those plants with stacked events are assessed mainly by very general considerations.

The procedure as proposed by EFSA does not address a step by step procedure as foreseen by European regulations which request a stepwise reduction of containment of genetically engineered plants. Deliberate release of genetically engineered plants has to be organised in a step by step procedure starting in the laboratory, going to the greenhouse, then to small field trials and after that to larger field trials. This process requires sufficient evidence from each step that the plants do not bear risks for the environment. Although EFSA is not directly involved in the authorisation of experimental field trials, it is necessary that EFSA defines requirements that must be met at certain steps in risk assessment before a company can apply for market authorisation.

The draft guidelines of EFSA do not mention any criteria for a rejection of applications. For example, commercial growing of plants that foster non-sustainable agricultural practises should be rejected. They should also reject any applications concerning genetically engineered plants likely to be invasive

or persistent and which therefore could not be removed from the environment after (large-scale) release.

Testbiotech proposes comprehensive testing of genetically engineered plants under defined environmental conditions before the plants are released. For example, genetic stability and genome-environment interactivity should be investigated by mandatory testing (called 'crash-tests'). Further, clear standards that safeguard sustainable practises in agriculture and the protection of biodiversity and its evolutionary integrity need to be integrated in any risk assessment of genetically engineered plants.

Introduction

In March 2010, EFSA published a new draft guidance document on the environmental risk assessment of genetically engineered plants. The document refers to a mandate given by EU Commission in March 2008, to develop criteria to assess the potential ecological effects of genetically engineered plants. These should include the selection of appropriate techniques to assess potential long-term effects of GM plants as well as recommendations for establishing baseline information.

This mandate was triggered by heavy criticism of EFSA's current practice of risk assessment. In 2006, the European Commission made a public statement calling for substantial amendments in the work of EFSA such as

"further steps to improve the scientific consistency and transparency for Decisions on Genetically Modified Organisms (GMOs). The measures proposed aim to bring about practical improvements which will reassure Member States, stakeholders and the general public that Community decisions are based on high quality scientific assessments which deliver a high level of protection of human health and the environment." [1]

The proposed guidelines follow a working process, taking into account *"problem formulation (including hazard identification), hazard characterisation, exposure characterisation, risk characterisation, risk management strategies and overall risk evaluation and conclusions"*. This approach is applied in the assessment of persistence and invasiveness, plant to micro-organisms gene transfer, interactions of the genetically engineered plant with target organisms and non target organisms, impacts on agricultural practises, effects on biochemical processes and effects on human and animal health.

Many details in the draft guidelines of the EFSA were widely commented on by various stakeholders.[2] The member states had a meeting with EFSA experts to discuss the draft guidelines, which were posted on the internet[3] A final version of the EFSA guidelines will be adopted in November 2010.

Testbiotech's opinion is centred on selected cross cutting issues and general strategies of the proposed guidelines. It is not a detailed analysis of all the proposed elements, but it tries to give a readable and rational account that allows interested public and decision-making bodies to enter into more general debate on the goals and strategies of risk assessment.

In order to understand the background of the new draft guidelines it is necessary to understand some of the problems with the current EFSA risk

1 http://europa.eu/rapid/pressReleasesAction.do?reference=IP/06/498&format=HTML&aged=1&language=EN&guiLanguage=en

2 See http://www.efsa.europa.eu/en/events/event/gmo100617.htm?WT.mc_id=EFSAHL01&emt=1

3 http://www.efsa.europa.eu/en/events/event/gmo100617.htm

assessment. In this opinion, we used the Dolezel et al. (2009) report to refer to the ongoing scientific debate on risk assessment within the EU.

The points raised in this report are also relevant for another process related to EFSA risk assessment in food and feed. The existing EFSA guidelines (EFSA 2006) might be adopted in large parts by the European Commission and then be the binding interpretation of Regulation 1829/2003 (EU Commission, 2010). These guidelines have similar basic deficiencies such as a lack of mandatory standards for empirical testing and a too narrow approach in hazard identification and risk hypothesizing (see Then & Potthof, 2009). These standards are not high enough to be accepted as sufficient by the EU risk manager. The EFSA standards for food and feed (EFSA 2006) should be re -discussed and further developed in a process parallel to the assessment of ecological risks.

1. The basic weakness of EFSA's concept

In its draft the EFSA proposes a step by step procedure organised in six steps: problem formulation, hazard characterisation, exposure characteristics, risk characterisation, risk management strategies, overall risk evaluation and conclusion.

This approach follows the basic assumption that hazards can be identified at an early stage in environmental risk assessment. Follow-on steps can then be developed in stages based on a hypothesis developed at the start of risk assessment. On page 14/15 the draft reads:

"Each risk assessment begins with a problem formulation in which the most important questions that merit detailed risk characterisation are identified. Problem formulation helps to make the risk assessment process transparent by explicitly stating the assumptions underlying the risk assessment.

In this document, problem formulation includes the identification of characteristics of the GM plant capable of causing potential adverse effects to the environment (hazards), of the nature of these effects, and of pathways of exposure through which the GM plant may adversely affect the environment (hazard identification). It also includes defining assessment endpoints and setting of specific hypotheses to guide the generation and evaluation of data in the next risk assessment steps (hazard and exposure characterisation). In this process, both existing scientific knowledge and knowledge gaps (such as scientific uncertainties) are considered.

Problem formulation starts with the identification of hazards through a comparative safety assessment. A comparison of the characteristics of the GM plant with those of its conventional counterpart enables the identification of differences in the GM plant that may lead to harm. These differences are theoretically assessed in the problem formulation process in order to identify the potential environmental consequences of these differences. While some differences may be deemed irrelevant to the assessment, others will need to be assessed for their potential to cause harm."

The following chapters discuss some of the basic weaknesses.

1.1 Broad scope versus narrow approach

From the field of toxicology we know that unexpected effects can emerge from a combination of stressors and toxins, which can synergise in a non-linear mode of action (see for example Kortenkamp et al., 2009). While in most cases, an approach of dose (concentration) addition can be applied, there are other cases where this approach will fail. As Kortenkamp et al. (2009) explain:

"Although dose (concentration) addition (and, to a limited extent, independent action) have proven surprisingly powerful in predicting and assessing

mixture toxicities, there are also clear cases of synergisms (i.e. higher than expected mixture toxicities). Such cases are very specific for certain mixtures (compound types, their concentrations and mixture ratios), particular organisms and endpoints. Hence they cannot be incorporated into a general risk assessment scheme, but must be treated on a case-by-case basis. Therefore, any regulatory strategy must include a certain element of flexibility that allows adequate provisions for such exceptional cases. When it comes to pinpointing the causes for synergisms or antagonisms, there are substantial knowledge gaps in our current scientific understanding. There is an urgent need to define the conditions that might lead to synergistic mixture toxicities, and to establish how large synergisms are likely to be."

In the context of genetically engineered plants (and biology) non-linear effects are even more common than in chemistry. There is a broad range of relevant issues such as cumulative effects and synergisms, genome-environment interactivity as well contaminations with viable material. Many examples of unintended effects of genetically engineered plants are known but these can hardly be detected at an early stage of risk assessment.

For example, non-linear effects can emerge from contamination of weedy relatives or hybridisation with closely related species that allow the technically introduced genes to persist in the environment. These crosses with wild relatives can produce plants with unexpected increase in fitness (Snow et al., 2003, Lu & Yang, 2009). The artificial gene constructs can also be reintroduced into the fields from the weedy relatives. Chinese scientists found that this re-crossing to the fields can cause unexpected risks of economic losses in rice (Lu & Yang, 2009). There may be similar effects with oilseed rape, since these crops can hybridise with other related species. Further unintended stacking of events occurs within the cultivated oilseed rape (Warwick 2005).

Other synergistic non-linear effects are known from Bt toxins. For example, Kramaz et al. (2007), found unexpected combined effects in non-target organisms (using snails as model organisms). Combinatorial effects of various stressors can be highly relevant for risk assessment of species such as honeybees, which are exposed to many adverse impacts of agronomic practise (see also Kaatz, 2005). Thus, risk assessment of Bt plants cannot just be reduced to hazard and exposure analyses, but has to take into account the recipient environment. Outside the laboratory, living organisms are not interfering with single stressors at set doses. In the real world, they face a combination of physical, chemical and biological environmental stressors that vary in space and time.

Non-linear effects can also be triggered by the stacking of events or by parallel cultivation of genetically engineered plants with different traits: It is known for example that interactivity between herbicide tolerant traits and Bt crops

can have an impact on the persistence and accumulation of residues in the soil (Accinelli et al., 2004).

Unexpected effects can also result from interactivity between pest insects being exposed to insect resistant plants, for example, pest replacement is known to occur in the US corn belt (Then, 2010). Another relevant issue in this context is an emerging cross-resistance in pest insects (Tabashnik et al., 1997).

Considerable attention must also be given to effects that only occur under certain environmental conditions such as climatic changes. Genetically engineered plants inherit technically derived features that are not controlled by the plant's gene regulation. Technical failures such as genetic instabilities and rise of undesired components can be triggered by specific environmental conditions. Relevant effects are known from genetically engineered soy (Gertz et al., 1999), cotton (Chen et al., 2005), maize (Then & Lorch, 2008) and potato (Matthews et al., 2005).

It is important to acknowledge that there are some broad uncertainties surrounding current scientific knowledge on how genetic engineering impacts on complex environments. Empirical data collection always depends on specific time and/or spatial scales under investigation, and is performed within particular ecological or management contexts. The absence of observable effects should not be interpreted as an evidence for the safety of any particular effect.

The draft concept of the EFSA (see for example lines 332-348) shows that the there is a high chance that only those risks identified at early stage will be assessed properly during the process. If risk identification and hypothesising is fixed at an early stage of the process then often remaining uncertainties will only be acknowledged if they are related to the hypotheses as assumed.

Risks or hazards which emerge in more complex interactions between genome and environment might not be hypothesised at the beginning of risk assessment. Modern molecular biology shows that the function of a gene, the processes of gene regulation and the interaction between gene and environment are not organised in a linear cause-effect relationship, but often follow non-linear patterns while emerging. Thus the risks of genetically engineered plants cannot be sufficiently assessed by a linear hypothesis driven approach as suggested by the EFSA. These risks or hazards might only be identified by a concept that follows a different principle of ‚expect the unexpected' on each level of the process. The basic dilemma is also described by Dolezel et al. (2009) as a problem in current risk assessment (page 180):

"In its first steps problem formulation and hazard assessment, the current ERA (Environmental Risk Assessment, CT) model narrowly defines potentially adverse effects. This leads in many instances to an exclusion of for the ERA relevant issues. It is therefore strongly suggested to broaden the scope of the

assessment to be compliant with the provisions of Directive 2001/18/EC and the guidance notes for risk assessment (EC 2002).“

To escape these problems, ERA should start as comprehensively and inclusively as possible and be based on a broad generation of empirical data not already confined to certain hypotheses. In general, risk assessment in plants has to be organised in a way that challenges the hypotheses and findings from earlier steps on each level of the process. Besides risks and potential hazard that can be hypothesized, one of the main challenges for ERA is the emergence of unexpected effects that cannot be predicted. Thus risk assessment has to be based on a broad range of empirical data and mandatory investigations that can cast a ‚wide but finely meshed net' on each level of risk assessment, and not be organised in the linear model of a decision-making tree.

1.2 Choice of the comparator

The starting point proposed by EFSA is a comparison of the genetically engineered plant with its conventional counterparts. This approach is based on the concept of substantial equivalence and familiarity as described in the current EFSA guidelines (EFSA 2006). It is based on the assumption that genetically engineered plants are just like conventional plants with some additional genes added.

As modern molecular biology shows, this approach will fail. It is known that the insertion of a single gene by invasive genetic engineering can cause changes in the activation of several thousands other gene function in the plant. Genetically engineered plants have to be seen as being technically derived organisms with technically derived features (and potential technical failures) which cannot be compared to plants derived by conventional breeding.

Basic differences between breeding and genetic engineering can be deduced from the role and function of genome regulation. While the changes in genetic activities can in conventional breeding (even by inducing mutations) be seen as an normal adaptation within the system of gene regulation, changes occurring in the context of genetic engineering have to interpreted with much more caution.

As Batista et al. (2008) for example show, genetic engineering as well as mutation breeding can affect the activity of thousands of plant genes and many of these changes can even be traced to following generations. But while mutation breeding can (at least to some extent) be seen as using the biological potential of plants as trained by evolutionary mechanisms, genetic engineering is not based on evolutionary mechanisms. As defined in Directive 2001/18 (Art 1):

"Genetically modified organism (GMO) means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."

Genetic engineering is an invasive method to enforce new metabolic pathways to the plants that cannot be controlled by its normal gene regulation. As Diehn et al. (1996) for example show, it is necessary to overcome the normal genetic regulation in plants to allow technical gene constructs to be expressed in the plants. Thus changes in gene activity of plant genes induced by genetic engineering should be interpreted much more as a symptom of a disturbed system than as a process within normal gene regulation.

Given these observations, genetically engineered plants should be treated as being basically different and not substantially equivalent or ‚similar' to their conventional counterparts. Comparisons with plants derived from conventional breeding are essential to refine risk assessment at certain stages, but cannot be the decisive starting point for developing hazard identification and crucial hypothesis, which guide the whole process of risk assessment.

EFSA generally presumes that risks can be deduced from the analysis of newly introduced genes and their products. This approach is also integrated in the new draft guidelines and is applied in current risk assessment of transgenic plants. The authority argues for example that, in the case of herbicide tolerance or insect resistance, the introduction of additional genes would change the plants only in relation to certain characteristics (EFSA 2007):

"The current generation of GM plants cultivated for commercial purposes has been modified through the introduction of one or a few genes coding for herbicide tolerance, insect resistance or a combination of these traits. In these plants the genetic insert leads to the production of a gene product, which does not interfere with the overall metabolism of the plant cell, and does not alter the composition of the GM plant except for the introduced trait."

For example, Prescott et al. (2005) (also see Valenta & Spök, 2008) indeed show that genetically engineered plants should not be considered as just being conventional plants with some additional genetic function added. The immunological effects observed in genetically engineered peas did not only concern the specific protein as transferred from beans but also other proteins occurring naturally within the peas. Thus, genetically engineered plants can inherit emerging risks for human health that cannot be predicted from parts and pieces that have been technically added. Similar conclusions regarding environmental risks have to be drawn from Snow et al. (2003), which revealed unexpected fitness-related effects derived from genetically engineered sunflowers. Unpredictable effects emerging from interactivity within the metabolism of the plants can also be expected from crops producing Bt toxins. Combinatorial or synergistic effects of recombinant proteins acting as

adjuvants to immunostimulatory effects, for example, or as potential allergens, have been discussed with regard to Cry1Ac (Moreno-Fierros et al., 2003, Rojas-Hernandez et al., 2004).

To start with, genetically engineered plants should not be seen as being comparable to plants derived from conventional breeding, but as technical products that require a comprehensive risk assessment per se. Otherwise unintended effects resulting from the transformation process, or from interactions of the novel substance or the environment might be overlooked and omitted. It is not sufficient to focus only on certain defined features that have been inserted into the plant by genetic engineering. As Dolezel et al., 2009 explain:

"In the current risk assessment practice of GMO notifications notifiers generally do not specify hazards but define them on a general level, such as 'the expression of the transgene' or 'the presence of GM trait'. The fundamental flaw is thus the delineation of the transgene or the introduced trait from the GMP thus ignoring the whole GMP as a stressor."

1.3 Cumulative risks in stacked events

According to EFSA's general approach as described in lines 1127-1131 (page 34), risk assessment of stacked events starts with the risk assessment of single events:

"In the context of this GD, the term ‚stacked event' will refer to a GM plant derived from conventional crossing of assessed single events. Where all single events have been fully risk assessed for their potential risks due to cultivation, the risk assessment of stacked events should mainly focus on issues related to a) stability of the inserts, b) expression of the events and c) potential synergistic or antagonistic effects resulting from the combination of the events."

Further empirical data concerning the wholesome plant that inherits the combination of gene constructs are not required necessarily. The risks from plants with stacked events might be simply deduced from theoretical scientific considerations (see lines 1134-1138):

"A risk assessment of the single events is a pre-requisite for the assessment of stacked events. The assessment of GM plant containing more than two transformation events combined by conventional crossing shall cover all sub-combinations of these events. In such a case, the applicant shall either provide a scientific rationale justifying that there is no need for experimental data obtained for the concerned sub-combinations or provide the experimental data." (page 35)

This approach is exemplified by EFSA in the context of persistence and invasiveness, interaction with target and non target organisms – none of these levels of risk assessment will require mandatory experimental testing. The following is suggested in 1153-1155, for example, concerning persistence and invasiveness:

"In GM plants with more than a single transgene (e.g. stacked GM plant events), the applicant should consider whether the combination of transgenes may lead to enhanced persistence or invasiveness that is more than the expected from the simple product of the single traits. "

Thus consideration can replace empirical investigation and scientific data. Based on a similar concept (EFSA 2007) the EU has already authorised several stacked events for import (such as NK603 x MON810 and MON863 x MON810). With a positive opinion on Bt11 and 1507 maize the EFSA favours the cultivation of transgenic maize in the EU combining insect resistance and herbicide tolerance.

EFSA largely ignores the fact that it is known that cumulative unexpected effects can result from the combination of traits such as insect resistance and herbicide tolerance. Synergies can emerge between different Bt toxins (Schnepf et al., 1998, Then, 2009), for example: Then (2009) reviewed several publications that show certain factors and synergisms that impact the toxicity of Bt toxins. These extrinsic factors are various and include other Bt toxins or parts from the spore of Bacillus thuringiensis as well as certain enzymes, environmental stress, non-pathogenic microorganisms, and infectious diseases. These effects are relevant for risk assessment in honeybees: The investigation of Kaatz (2005), which so far is not available in peer reviewed publication, showed honeybee colonies to be susceptible to Cry1Ab if certain parasitic gut organisms (Nosema apis) were apparent. Thus, this organism is likely to act as additional stress factor, which enables toxicity of Cry1Ab in this non-target species.

Interference between Bt producing plants and the use of chemicals (herbicides, pesticides) has been demonstrated as well. It has been published that the additional use of insecticides impacts the concentration of Bt toxins in the plants (Griffiths et al., 2006). Furthermore, if Bt toxins are used in combination with herbicides such as glyphosate and glufosinate, the herbicidal residues in the soil will decrease slower (Accinelli et al., 2004). These findings show that EFSA's approach is not sufficient for testing for unintended, delayed and cumulative effects in stacked events as required (see requirements of Annex II of Dir 2001/18).

As has been shown, the new proposed EFSA guidelines for the risk assessment of stacked events also do not foresee mandatory specific empirical investigations. The EFSA assumes that in most cases the assessment of each

of the single constructs will be sufficient. This is not in accordance with EU regulations. Annex II of the 2001 Directive explicitly mentions interactions between genetic engineered plants and cumulative effects. Cumulative effects and potential interactions have to be taken into account as well in the parallel cultivation and imports of different genetically engineered plants and in the case of stacked events in single transgenic plants.

According to a report by the EU Joint Research Centre (JRC, 2009) it can be expected that more than 100 different events might be introduced into markets in the next few years until 2015, and that several hundreds or even thousands of possibilities will be created by combining these events in stacked plants. It is of major concern that, according to the standards proposed by EFSA, detailed analyses of potential interactions or cumulative effects will only be performed in some rare cases.

2. Defining a step by step procedure

The step by step procedure as proposed by EFSA might be a way to organise the work flow of the authority (of its GMO panel) but it is not the step by step procedure as foreseen by the EU regulation. As Recital 24 of EU Dir 2001/18 says:

"The introduction of GMOs into the environment should be carried out according to the step by step principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken."

The step by step process as foreseen under Dir. 2001/18 does not talk about steps to simply organise work flow with regard to risk assessment. Rather, it foresees the reduction of containment, dependent on the availability of sufficient scientific data. A step by step process as intended by European legislation would follow for example the steps of desk-based studies, laboratory investigations, greenhouse work, and semi-environment, small scale and large scale releases.

This very basic concept is not integrated in EFSA's proposal. It is only vaguely addressed (see page 29 of the draft proposal). Thus, EFSA fails to address the essential requirement of a step by step procedure necessary for safeguarding the environment and human health by having earlier steps evaluated (with high levels of containment) before moving to the environment. When combined with the highly questionable concepts of early hazard identification, endpoint definition (that can even be chosen by the applicant – see line 409-411) and the use of comparators from conventional breeding, the approach as proposed by EFSA does not fulfil the requirements of EU legislation. The need for safeguarding a proper step by step procedure is also expressed by Dolezel et al., (2009):

"Since it must be evident that GMPs do not cause an adverse effect on the environment, one or several testing steps with the GMP in question may be required at different levels of confinement: laboratory, greenhouse, and field. Especially, if significant uncertainties remain at one level, it is necessary to proceed to the next level of (lesser) confinement with caution. Precaution is operationalized by lifting the level of confinement successively and not moving in one step from the laboratory straight to the field." (page 193)

Applying a proper step by step procedure means gathering technical data in the laboratory and the greenhouse as much as possible before the plants are released into the environment. A next step requires the systematic use of small scale experimental trials so as to generate as much data as possible before any large scale release can be allowed.

These basic aspects of a step by step procedure were ignored in the draft guidelines. Thus an indispensable prerequisite for risk assessment is missing.

It is likely that the existing problems will be perpetuated. In most data from experimental field trials, for example, there is hardly any scientific evidence on risk related aspects (Dolezel et al., 2009). The field trials are often driven by an approach in which mainly agronomic parameters are assessed, thus ignoring the purpose of a step by step procedure as foreseen by EU regulation. Although EFSA is not directly involved in authorisation of experimental field trials, it is necessary that EFSA defines requirements that have to be met at certain steps of risk assessment before a company can apply for market authorisation.

For example at the level of laboratory and greenhouse work, the proposed guidelines by EFSA do not require systematic generation of empirical data before any release can take place. Then & Potthof (2009) propose a system they call ‚crash test', the aim of which is to systematically investigate genetic and metabolic stability of the genetically engineered plant before any large scale release is made. This concept was triggered by the observation that so far not even very basic data such as the level of the expression of the Bt protein in the plants have not been investigated sufficiently. Appropriate test protocols in ring testing have not been evaluated, and systematic explorations under changing environmental conditions have not been published (Then & Lorch, 2008).

In general it is known that genetically engineered plants react to environmental conditions such as climate (Chen et al., 2005), soil (Bruns, 2007) and stress (Matthews et al., 2005). These reactions can and should be measured under controlled conditions, such as laboratory or greenhouse conditions, before plants are released in any large scale cultivation.

Other very basic data that should be compiled under laboratory and greenhouse conditions concern external factors (co-factors) that might interfere with the transgenic traits or transgenic plants. It is known for example that Bt toxins are likely to interact with a broad range of external factors (for overview see: Then, 2009). So far, even there, the mode of action of Bt toxin has not been investigated thoroughly (Pigott & Ellar, 2007, Broderick et al., 2006 and 2009).

Interactions caused by combinations of herbicide tolerant crops with their complementary herbicide should also be taken into account as a matter of routine. Basic data have to be generated in the laboratory and the greenhouse, to generate sufficient empirical data about metabolites of the herbicide in the plant and possible interference with plant components.

A basic tool that is not foreseen by EFSA but should be used as a matter of routine is the systematic investigation of changes in gene regulation or metabolic profiles in genetically engineered plants. As Batista et al. (2008) and Zolla et al. (2008) demonstrate, for example, the method of invasive genetic engineering provokes much more change within the plants than so far had been thought. Thus advanced scientific tools need to be integrated at an early stage of the risk assessment, and combined with precise information regarding

intended or unintended insertions, open reading frames and resulting metabolites.

3. Sufficient mandatory testing

Several levels of the risk assessment as foreseen by EFSA lack a comprehensive mandatory testing regime. This can be shown for example in requirements for assessing the impact on non target organisms, the evaluation of stacked events and interaction between genomes and the environment.

As the EFSA describes their concept (page 22):

"The ERA should be carried out on a case-by-case basis, meaning that the required information may vary depending on the type of the GM plants and trait(s) concerned, their intended use(s), the potential receiving environment(s). There may be a broad range of environmental characteristics (regional-specific) to be taken into account. To support a case-by-case assessment, it may be useful to classify regional data reflecting aspects of the receiving environment(s) relevant to the GM plant (e.g. botanical data on the occurrence of wild relatives of GM plants in different agricultural or (semi) natural habitats of Europe, effects of production systems on the interactions between the GM plant and the environment)." (underlining by Testbiotech)

Testbiotech is of the opinion, that much more extensive mandatory empirical testing of genetically engineered plants is required than is set out in the current draft. While it is true that risk assessment always has to be flexible enough so that additional points can be included when it is made, a basic set for mandatory testing has to defined. By choosing an approach with early hazard identification in combination with a highly flexible system of testing, risk assessment can be easily narrowed down and thus become flawed through using selective data. To organise a sufficiently broad process a set of mandatory testing needs to be defined without the possibility of escaping the testing through superficial or wrong hypothesising.

As Dolezel et al. (2009) describe, the lack of sufficiently clear standards and insufficient compliance are major deficiencies in current risk assessment:

"The requirements specified in the EFSA guidance document on risk assessment (EFSA 2006a) currently leave too much room for interpretation of the proposed standards by the notifiers (...). This leads also to substantial heterogeneity in the data basis provided in the different notifications on which conclusions are based. (...) This, in turn, supports the need for both, specification of requirements and development of further guidance in order to eliminate the existing room for interpretation as much as possible. In addition, a more stringent compliance by the notifiers to scientific standards and existing guidance will be a prerequisite for the improvement of risk assessment (...)".

Since EFSA uses expressions like ‚may', ‚should' or ‚could' in nearly every passage of its draft guidelines it is likely that these guidelines will not evade the problem as observed. The guidelines as proposed open the gates for a pick and choose approach by companies in preparing their data, and give EFSA too

much flexibility in preparing their opinions. Some of the elements foreseen in the draft guidelines could produce higher standards of risk assessment than are the case so far. These potential advantages threaten to be lost as a result of the lack of clearly defined mandatory testing.

For example, Bauer-Panskus & Then (2010) found a significant lack of empirical data when EFSA (EFSA 2005, 2008) assessed maize 1507 and Cry 1F. Many data were simply derived in analogy to Cry1Ab. Cry1Ab showing some significant differences in toxicity in lepidoptera (butterflies) larvae. Nevertheless no specific data were requested concerning protected butterflies abundant in Europe. This basic flaw in risk assessment by EFSA was clearly due to inadequate standards for mandatory testing. It cannot be denied that a pick and choose approach will still be possible to a large extent during risk assessment as outlined by the current draft of EFSA.

The lack of mandatory testing and empirical data also has severe implications for monitoring and surveillance at a later stage. To fulfil requirements monitoring must be able to identify relevant risks correctly. In many cases, the specifications for monitoring will only mirror those risks that have been identified already and not aim to examine unexpected effects in detail. Thus, those risks that are not identified during risk assessment also have a higher chance of escaping monitoring and general surveillance. To avoid this situation, comprehensive testing is required to assess risks and monitoring must be organised in a way that allows systematic investigation of remaining uncertainties.

4. Safeguarding sustainable agriculture and biodiversity

Large scale cultivation of genetically engineered plants in some regions of the world have revealed a broad range of adverse impacts on the future of sustainable agriculture, such as increased weed resistance (Service, 2007), increasing use of pesticides (Benbrook, 2009), pest resistance (Tabashnik, 2009) and pest replacement (Then, 2010).

Concerns have been raised that the ecosystem is destabilised by suppressing certain insects at the same time that the door is opened to pest replacement or pest resistance in major pest insects. Other aspects include the eradication of certain flora and insects by the permanent application of herbicides and continuous exposure to insecticides. It has to be acknowledged that EFSA refers to some complex and unpredictable long term impacts of large scale cultivation of genetically engineered plants (see for example lines 3606-3626):

"Primary (simple) and secondary (complex) effects can be envisaged. Sustained, intensive cropping (which GM herbicide tolerant break crops might exacerbate), will cause the primary effect – a gradual decline in the seedbank, eventually after several decades, to the point of zero ecological function. Effects on the flora are likely to be found in the year of cultivation, and might be carried over to the subsequent one or two years for some variables. They might then disappear until the next time the GM herbicide tolerant plant is grown. Over several cultivation sequences, the effects are likely to accumulate. (...) The primary effect will lead to secondary effects through loss of habitat and food for the invertebrates and vertebrates dependent on the plants. Such secondary effects on distributed food web organisms are spatially complex and cannot be determined in small experimental plots, however. Depletion of function might occur gradually at first, but there may come a point when the function ceases, for example if food plants become so low in abundance that the dependent animal populations decline and finally collapse. In this case, the loss of function might not be readily reversible. If the decline occur over a wide area of the landscape, recolonisation might be very slow. "

But in reading the conclusions regarding possible impacts in agricultural practices and the cultivation of specific genetically engineered crops (line 2484-2488), no suggestion is made that unsustainable methods of agricultural practises (that lead to higher exposure of insecticides, herbicides and a reduction in biological diversity) might not be favoured by a positive opinion. The identified effects shall only be ‚mitigated' – which means that commercial cultivation is still likely to be allowed.

"Where specific risks associated with the cultivation of the GM plant are identified during the ERA, risk management strategies should be proposed to mitigate these risks and applicants should indicate how these measures will be introduced and enforced. Furthermore, monitoring is required either to

confirm any assumptions regarding the occurrence of adverse effects or the efficacy of mitigation measures."

EFSA presents a long list of environmental protection goals to be striven for on a legal basis in the EU (Table 1, line 420). But what is broadly missing in its approach is any interconnection between risk assessment, the precautionary principle and the safeguarding of a sustainable agriculture and promoting biodiversity.

For example, Then (2010) shows (by referring to publications of Dorhout & Rice, 2010), that pest replacement in the US corn belt is caused by large-scale cultivation of certain types of genetically engineered maize. It has been argued that a permanent exposure of pest insects to insecticidal toxins produced by genetically engineered crops is not sustainable. Pest replacement and pest resistance can be seen as an inevitable consequence of any strategy that continuously tries to suppress or eliminate pest organisms. This is especially true in the case of Bt crops, since the release of the toxin is not targeted and time limited, but implies permanent exposure throughout the whole period of cultivation. Effects are not only observed in Bt maize, but also in Bt cotton (Lu et al., 2010). EFSA has failed to define any criteria that could be seen as being preventive in respect to such unsustainable agricultural practises.

5. Safeguarding evolutionary integrity

EFSA does not foresee any clear criteria for not allowing market authorisation in certain cases. Given the technical quality of genetically engineered plants and the emergent nature of risks, any release into the environment has to be confined to levels that allow the control of duration and location. For example it is known that the persistence, spread and outcross of genetically engineered oil seed rape cannot be controlled if commercial large scale releases take place, as summarised for example in Dolezel et al., 2009:

"Oilseed rape is known to occur as a volunteer in crop rotations and GM oilseed rape has frequently been shown to occur in regions with extensive GM oilseed rape cultivations beginning to constitute major agronomic problems to farmers with the occurrence of multiple herbicide traits derived from different spontaneous hybridisation events. Additionally, persistence of oilseed rape volunteers, including GM oilseed rape in agricultural environments over several years has been observed even without selection pressure. Feral oilseed rape is also known to build up stable and self-dispersing populations outside cultivated fields which persist for at least several years or even longer. When sexually compatible wild relatives are present and grow next to the crop, hybridization may lead to the creation of crop-wild hybrids. While the hybridization between oilseed rape and its wild relatives as well as the fertility of the resulting hybrids and their occurrence in the wild is relatively well known, the behaviour of such crop-wild hybrids is currently largely unpredictable, especially as it depends not only on the plant but also on the recipient habitat where the plant is likely to survive. As crop-wild hybrids are not restricted to a controlled area (i.e. the cultivated field) the ecological consequences of such a scenario is currently difficult to predict."

Crops that show a high level of persistence and invasiveness, and are able to exchange genetic information with surrounding biodiversity, have to be generally excluded from large scale releases and commercial cultivation. Faced with very limited chances of predicting their behaviour and long term impact on biodiversity, they must be prevented from being released if the future of biodiversity and ecosystems is to be safeguarded. If no clear criteria for eliminating large scale releases are defined, artificial gene constructs might accumulate and interfere with evolution in an uncontrollable way, putting future biodiversity at risk. It is not only up to the risk manager to take decisions as necessary, the risk assessor also has to include some clearly defined criteria that will lead to crops being barred. These criteria are also important for the industry so as to enable it to take decisions at early stages of investment.

The safeguarding of evolutionary integrity (in other words the ability to control abundance of genetically engineered plants with respect to time and location) is one of the basic prerequisites for fulfilling long term protection as foreseen by many EU regulations that aim to safeguard natural habitats, endangered

wild fauna and flora and biodiversity in general. As Breckling (2009) points out:

"The use and application of GMO follow intended purposes which are spatially and temporally limited. The feasibility of risk assessment and management as far as it bases on direct empirical investigations is also limited and operates on time scales of a few years. It is methodologically impossible to exhaust the combinatory potential of a transgene in a new genomic environment. Unexplored combinations that could become self-amplifying, pose a risk that is specific for GMO as living entities. The safety of transgenes cannot be assessed exhaustively but only in incomplete approximation with regard to a self-organising evolutionary context. Thus, it is desirable, that the integrity of the evolutionary processes is not overlaid with genomic introductions that could not have occurred by means of natural processes. "

But EFSA does not acknowledge any general limitations in regard to the invasiveness and persistence of genetically engineered plants. These risks are seen not as being prohibitive for a favourable opinion, but much more as an issue that can in any case be mitigated by risk management measures, as is explained in its conclusions in lines 1533-1539.

"The risk assessment should conclude on i) the extent to which the GM plant and/or hybridising relatives are more persistent or invasive in different environments, including agricultural and other production systems and semi-natural habitats; ii) whether any changes in fitness may result in changes in population size; iii) the extent to which changes in population size may result in environmental damage, including the consequences for biodiversity (and functional biodiversity) and impact on any other biota in different receiving environments; iv) why any anticipated harm may be considered acceptable; v) what risk management measures may be required to mitigate any harm. "

By failing to define sufficient criteria to allow effective prevention of persistence of genetic material stemming from genetically engineered crops in the environment, EFSA is failing in its task in one of the most crucial aspects in ecological risk assessment.

6. Conclusions and Recommendations

- A concept of early hazard identification and linear decision making cannot be used to assess biological effects that very often emerge in a non-linear manner. You always have to expect the unexpected.
- Risk assessment in genetically engineered plants has to start from the assumption that its methods and outcomes must be suited to genetically engineered plants which are fundamentally different to conventionally bred plants. Therefore a broad set of empirical data is required to assess their technical properties and genetic stability (including metabolic profiles), their reaction to environmental conditions and their interactivity with the environment. A kind of ‚crash-test' to expose the genetically engineered plants to defined stressors has to be developed.
- Special attention must be paid to synergistic and cumulative effects. Stacked events must be subjected to their own risk assessment.
- Clear mandatory criteria must be defined for each step of risk assessment (laboratory, glasshouse, small-scale experiments etc.).
- The recipient environment, climatic and regional conditions as well as interference with other biotic or abiotic stressors must be fully taken into account and (as far as possible) have been investigated under controlled conditions before genetically engineered plants are released.
- Monitoring has to take into account that the absence of observable effects cannot be interpreted as evidence for the safety of the plants. Systematic investigations of any uncertainties must be fully integrated.
- Criteria for the rejection of applications must be integrated into the overall concept. At an early stage it must be made sufficiently clear to applicants that plants that are invasive and/or persistent will be rejected as will plants that foster unsustainable agricultural practises.

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Testbiotech opinion on EFSA's draft guidance on the environmental risk assessment of genetically modified plants

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