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Input to the EU Commission´s Consultation on Environmental Risk Assessment of Genetically Engineered Plants.

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

Christoph Then

Abstract:

Testbiotech has thus far published two reports on the risk assessment of genetically engineered crops in the EU (Then&Potthof, 2009; Then, 2010) and prepared several background papers. Here we have drawn up a short overview of the most relevant points for consultation on the environmental risk assessment of genetically engineered plants.

Testbiotech's proposals are:

1. Drop the concept of comparative risk assessment.
2. Introduce clear cut off criteria for rejection.
3. More mandatory testing.
4. Develop an integrated approach to risk analysis including ethical and socio economic issues from the outset.
5. Develop a comprehensive concept for post market monitoring.

1. Comparative risk assessment versus risk assessment per se: Choosing the right starting point

Methods used to introduce DNA into genetically engineered plants are not based on the mechanisms of common gene regulation and heredity. The newly introduced gene constructs have a specific potential unique to this particular technology for escaping and /or disturbing the normal process of gene regulation. Therefore, risk assessment should not be based on a comparative approach using conventional breeding. Instead, there should be an investigation into the specific technical properties of the specific genetically engineered plants.

Taking a comparative approach means that risk and hazard identification is based on a set of data that is too narrow, and specific risks such as unexpected interactivity between the genome and the environment might be overlooked. Comparison can be an important tool, but not a concept.

The first step of risk assessment should generate a broad range of non biased data to examine the specific properties of the genetically engineered plant. In this context, the genetic stability of the inserted gene sequences and the interactivity between plant´s genome and environment are crucial issues. Hypotheses for further investigations should be developed from measurement of gene activity, the transcriptom, the metabolom.

A stress test under defined environmental conditions should be introduced to obtain more information on the potential reactions of the plants to ongoing climate change and other environmental stressors.

If the plant produces specific compounds such as insecticides, the specific range of its content within all parts of the plant must be determined under various conditions. Methods for measurements need to be validated, published and made available.

A close interplay with the assessment of pesticides has to be established. In vitro systems should be used to test the protein, whole plant preparations and combinatorial effects in the first step of the investigation.

Overview of elements in the first step of risk assessment 'per se':

- molecular characterization – analysing the structure of the genome
- genetic stability and gene activity – analysing the dynamics of gene regulation using stress tests under defined conditions.
- compositional analysis - determining the range of variations of plant components using stress tests under defined conditions.
- toxicity (1): Determine the impact of new proteins / whole plant preparations on biological systems in vitro (such as cell cultures, test organisms).
- toxicity (2): Determine combinatorial effects between plant compounds, residues from spraying, abiotic and biotic factors on target and non-target systems in vitro (cell cultures, test organisms).

2. Define clear cut off criteria such as invasiveness and persistence for rejection of market applications

Companies as well as authorities can take responsibility for genetically engineered plants only as long as the plants that are released into the environment can be recalled at any time if necessary. There is a very basic need to have an option to control the abundance of relevant genetic material in terms of time and regional distribution. This need should be seen as an absolutely indispensable precondition of any release or commercial cultivation of the plants. So far, the lack of this basic precondition is not seen as a clear criterion for the rejection of market applications. In general, genetically engineered crops that show a potential for invasiveness and persistence should be excluded from release into the environment to prevent unintended effects during long-term evolutionary processes that cannot be predicted or controlled. Within the European ecosystems, for example, rapeseed and genetically engineered poplar show a high potential for invasiveness and persistence. In these cases, a general concept of prevention is necessary.

There is a clear requirement for further criteria relevant to the rejection of market applications; if certain crops are not compatible with sustainable agricultural practises (or other socioeconomic

criteria) they should not enter the market. For example, if it is known that herbicide use will increase or new pests triggered, then genetically engineered plants do not comply with the long-term goal of sustainable agriculture within the European Union and should be excluded from its market.

Clear criteria for rejection of market applications can help to save time and money, avoid animal testing and experimental field trials.

Overview of possible criteria leading to rejection of market applications at an early stage of risk assessment:

- genetic instability under stress conditions
- persistence and/or invasiveness
- signs of toxicity
- enhancement or introduction of unsustainable practice in agriculture
- coexistence is not possible

3. More mandatory testing

If the first step of risk assessment does not lead to the rejection of an application, more mandatory empirical investigations are necessary. There should be routine testing in each and every case. This could include, for instance, long-term multigenerational feeding to assess effects on health (including immunological and reproductive data). Genetically engineered plants are not only produced for use in food and feed, they may also be fed to wild animals such as birds and mammals. Mandatory feeding studies over the lifetime of relevant animals, including their offspring, are necessary. Detailed analyses of the fate of the gene construct and its passage into animal tissue need to be included.

Feeding studies must be performed in a way that avoids harming the animals. Several generations and different species of arthropods should be tested before vertebrates are included. Any test should be included within the framework of an integrated concept of risk analysis to reduce the use of animals as far as possible. If the risk manager comes to the conclusion that animal feeding studies cannot be justified for the marketing of certain crops then the products should not enter the market.

Experimental field trials in all relevant climatic / bio-geographical zones over several years are a further requirement. It is important to move step by step from small scale to larger scale and to avoid releases of plants that are persistent / and or invasive or cannot be managed in terms of coexistence. Clear cut off criteria for market rejection should help to avoid unnecessary releases. What is needed is a mandatory list of defined data generated step by step before any environmental release takes place, or before cultivation on larger scale can be allowed. This issue deserves stronger cooperation with national authorities since they are the ones to decide on first experimental releases. It is imperative to define a minimum set of necessary data to be generated before and during experimental field trials, and to make full use of these data in a transparent manner before cultivation on a large scale.

Further mandatory testing has to be established for plants that produce or tolerate biocides. Tests for synergistic effects must be conducted in target and non target organisms on all relevant levels of the food web and food chain. A much closer interplay with pesticide regulation has to be established.

Furthermore, existing agricultural practices and other potential stressors in the receiving environment have to be included. For example, combinatorial effects between insecticidal proteins (produced by the genetically engineered plants) and other factors such as agrochemicals must be investigated systematically, also taking into account several levels of the food web. In addition, the long-term accumulation of insecticidal proteins or complementary herbicides must be considered wherever different genetically engineered crops with a similar trait are cultivated in the same field in rotation. Assessment of traits with herbicide tolerance must take the residues and metabolites and their potential interactivities into account.

In exploring the risks for non-target organisms, risk assessment should follow a concept to 'expect the unexpected' rather than a concept such as a linear decision making tree or a 'tiered approach'. All levels of the food web should be taken into account, such as prey, predators, parasites, organisms below and above the ground, terrestrial as well as aquatic, including the whole range of organisms from micro-organisms to vertebrates. Indirect and delayed effects that emerge from specific processes within the ecosystem are likely to be overlooked if risk assessment is based on hypotheses that are derived at an early stage of risk assessment. The recipient environment with its specific fauna and flora has to be taken into account as well as existing regional agricultural practices and potential additional stressors such as the use of pesticides.

Stacked events must be considered as independent new applications. Their risk assessment cannot be reduced to a risk assessment of their individual compounds. Emerging combinatorial (even non-linear) effects can only be assessed by empirical investigations using all the plant material that incorporates the relevant combination of gene constructs.

Overview of some mandatory testing required for the second step of risk assessment

- perform multigenerational feeding studies
- perform step by step experimental release in all bio-geographical zones over several years
- in plants that produce or tolerate biocidals test for (synergistic) effects on all relevant levels in food web and food chain
- stacked events should be considered as independent new applications.

4. Developing an integrated approach to risk analysis including ethical and socio economic issues from the outset

An integrated concept is needed to deal with ethical and socioeconomic issues in an adequate manner. These issues should be included from the outset and accompany the whole process of risk analysis. Experts who can identify relevant ethical, social or socioeconomic issues should accompany the work of the GMO panel at EFSA.

If, for example, contaminations of other crops cannot be controlled or managed effectively this fact can become crucial for the final decision on a market application. In this case, the company should be given a clear signal at an early stage of the risk analysis process that their market application is very likely to be rejected in the end, no matter what the outcome of risk assessment might be. This integrated approach will help to reduce costs for the companies as well as help to avoid environmental releases and animal feeding studies that are not necessary. This issue deserves close cooperation between the risk assessor and the risk manager.

The overview (see table) shows the interplay between socioeconomic and ethical considerations and the EFSA risk assessment.

5. Develop a comprehensive concept for post market monitoring.

Risk assessment cannot end with market authorisation. In particular, combinatorial, cumulative and delayed effects may emerge during commercial use of genetically engineered plants. These effects cannot simply be observed through existing networks and farmers filling in questionnaires. Therefore, a scientifically sound monitoring plan must be developed.

In this context it is an important condition that any material released for commercial use (and its isogenic counterparts) must be freely available for independent scientific research and must not be restricted by consensus or contract with the intellectual property holder, as is the current practice.

Since there is a complete lack of effective systems for general surveillance of health effects market authorisation cannot proceed before this legally required instrument is implemented.

6. Further general requirements for risk assessment:

It should be compulsory for applicants to reveal any data already available from studies that have been carried out on an event. Applicants must also provide an informative list of all studies performed or commissioned by them on an event including all data collected. This will put risk assessors in the position to decide independently which studies and results are relevant for risk assessment. Further peer reviewed publication of the results and independent quality controls so far are largely missing in current risk assessment.

Overview of further general requirements for risk assessment

- identify uncertainties
- involve independent research institutions
- apply independent quality control
- publish results in peer review process
- give access to all raw data (including genomic data)
- give access to research material

Table: Some elements for stepwise risk analysis of genetically engineered plants based on a "risk assessment per se"

<table>
<tr><th colspan="3">Starting point / First step/ technical characterization / first hypothesis on risks and hazards</th></tr>
<tr><td colspan="2">Assessing unbiased data from lab and glasshouse
genomic data
reaction to defined conditions / stress test
metabolic profiling, measuring gene activities
compositional analysis (comparison) of material exposed to varying conditions
lab data on risks for potential non target species and the food chain/ human health
Investigate combinatorial effects</td><td>ethical and socioeconomic considerations</td></tr>
<tr><td colspan="2">Initial risk and hazard identification
developing first hypothesis for later steps

stop authorization process and field trials for crops that prove persistent or invasive, show technical deficiencies such as genetic instability or show signs of toxicity.</td><td>Initial ethical and socioeconomic conclusions
developing questions for further considerations

stop authorization process and field trials for crops that require non-sustainable cultivation methods, do not meet criteria for coexistence or do not render significant improvements.</td></tr>
<tr><th colspan="3">Following steps (if cut off criteria do not apply)</th></tr>
<tr><td colspan="3">Full publication of all data, call for comments on risk findings and ethical and socioeconomic issues</td></tr>
<tr><td>Mandatory investigations

>multigenerational feeding studies including immunological and reproductive data[1]

>experimental release in all relevant climatic / biogeographical zones over several years going step by step from small scale to larger scale[2]

>stacked events deserve complete risk assessment, assessment of single events is not enough.</td><td>Further investigations according to results from step 1 (case by case)

>Mandatory for all HT plants: close interplay with pesticide assessment / change in agricultural practices / residues in food and feed.

>Mandatory for all IR plants: Tests for synergistic effects in non target organisms. Tests to determine effects at all relevant levels of the food web and food chain.</td><td>Generating specific data about impact on agriculture / coexistence/ sustainability</td></tr>
<tr><th colspan="3">First opinion on risk assessment including uncertainties and necessary reiterative investigations</th></tr>
<tr><td colspan="3">Full publication of all data, call for public comments on all preliminary findings</td></tr>
<tr><th colspan="3">Final risk assessment</th></tr>
<tr><th colspan="3">Risk analysis</th></tr>
<tr><td colspan="3">Check for effective systems for monitoring/ surveillance, also for coexistence. Identify uncertainties.</td></tr>
<tr><th colspan="3">Decision of the risk manager</th></tr>
<tr><td colspan="3">including socio- economic and ethical findings</td></tr>
</table>

[1] Necessary from scientific point of view (to assess risks for humans, livestock and wildlife), but controversial from ethical perspective

[2] Necessary from scientific point of view but controversial because of environmental risks created by experimental releases

For more information:

Then, C. & Potthof, C., 2009, Risk Reloaded – risk analysis of genetically engineered plants within the European Union, Testbiotech report, http://www.testbiotech.de/sites/default/files/risk-reloaded_engl_sc_0_0.pdf

Then, C., 2010 Testbiotech opinion on EFSA's draft guidance on the environmental risk assessment of genetically modified plants, Testbiotech report, http://www.testbiotech.de/sites/default/files/Opinion%20Testbiotech%20EFSA%20GMO%20draft%20guidance_2_1.pdf

TESTBIOTECH Background, 9-2010: Ten crucial elements in the environmental risk assessment of genetically engineered plants, http://www.testbiotech.de/sites/default/files/Ten_crucial_elements_in_%20ERA_Testbiotech_0.pdf

TESTBIOTECH Background 21-12-2010: Testbiotech analysis of EFSA Guidance on the environmental risk assessment of genetically modified plants; EFSA´s standards for environmental risk assessment not sufficient, http://www.efsa.europa.eu/en/scdocs/doc/1879.pdf

TESTBIOTECH Background 15-1-2011: Testbiotech comment on Selection of Comparators for risk assessment, http://www.testbiotech.de/sites/default/files/Testbiotech%20comment_Comparator.pdf

Contact:

Testbiotech e.V.
Institute for Independent Impact Assessment in Biotechnology
Frohschammerstr. 14,
80807 München
info@testbiotech.org
www.testbiotech.org