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Testbiotech comment on the EU Commission's draft for implementing regulation on applications for the authorisation of genetically modified food and feed

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Summary:
Testbiotech summarised its approach to the environmental risk assessment of genetically engineered plants in a report presented in 2011 (Then, 2001). Many of the points raised in this report are also relevant for the risk assessment of genetically engineered plants used in food and feed.

Some of Testbiotech's proposals are:

- Drop the concept of comparative risk assessment.
- Introduce cut off criteria for rejection.
- Introduce more mandatory testing.
- Develop a stepwise approach to risk analysis to include ethical and socio economic issues from the outset.
- Develop a comprehensive concept for post-market monitoring.

Some of the points presented by Testbiotech in 2011 were taken into account in the Commission's draft on implementing regulation (EU Commission, 2012).

Relevant points are:

- Mandatory testing of the entire genetically engineered plant material in feeding studies;
- basic scientific standards for the data presented by industry and
- more transparency concerning 'secretive' investigations carried out by industry but not presented with the application.

Taking a closer look, the overall concept of risk assessment as presented in the Commission´s draft is neither coherent nor comprehensive. This is shown in the following tabled overview.

Some relevant deficiencies are:

- Comparative risk assessment is still seen as the standard procedure rather than a more comprehensive risk assessment.
- The most relevant step in comparative risk assessment (the investigation of substantial equivalence) still is based on a concept that allows the introduction of flawed data.
- Interactions with the environment that can impact plant composition are not tested sufficiently.

- There is still no request for more recent technologies such as metabolic profiling.
- Testing for health risks is still not based on a stepwise concept that also takes into account mandatory *in vitro* investigations, targeted investigation of certain health risks and mandatory long term and multi generational studies. The need for further targeted investigations where there are uncertainties is not yet defined.
- Stacked events are still investigated less rigorously than single events.
- The necessary interplay with pesticide regulation is missing.
- Combinatorial effects will be taken into account, but the requirements for the investigation of synergistic, additive and accumulated effects are not yet defined.
- There is no mention of the need for fully evaluated methods to measure gene expression.
- No cut off criteria are foreseen.
- Post- marketing monitoring allowing identification of a negative effect on health and correlation with specific products is not yet defined.
- There is still no overall integrated concept that takes risk as well as ethical and socio-economic issues into account.
- Industry is not required to bear the costs of the authorisation process or to contribute to public funds for independent risk research.

Tabled overview: Comments on the new regulation for risk assessment of food and feed derived from genetically engineered plants as proposed by the Commission

Issue	Proposal by draft regulation	Comment
Molecular data (page 30-33)	Metabolic profiling is not requested	Metabolic data to identify unintended changes in plant gene activity and the emergence of unexpected compounds should be requested.
Expression data and genetic stability (page 34-35)	The impact of the environment on the gene expression of the plants is mentioned. But no coherent requirements arr defined on how to determine the impact factors and the actual range of variations in the expression of the newly introduced gene constructs (and other relevant elements such as ORF).	A stress test under defined conditions should be required to determine functional genetic stability and the possible range of variation in gene expression. In a stepwise procedure, field trials should be carried out over several years at each site. All geographic regions where these plants might be grown and subsequently imported into the European Union should be taken into account. Thus data from several sites over several years have to be presented.
	The need for information about the method used for expression analysis of the newly introduced	This is a slight improvement. But without fully validated methods, the data on the expression of the newly introduced gene constructs are not reliable. Validated methods also need to be established, for

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	gene is mentioned.	example, to measure the content of Bt toxins in the plants. So far, validated methods are only required for PCR detection methods.
Comparative assessment (Page 35 - 44	There are some wordings such as “natural variation” or “another test material in addition to the conventional counterpart“ that allow the introduction of flawed data into the process of comparison. As a result, unspecific and questionable 'historical' data unrelated to the actual field trials, e.g. the ILSI database, can still be used to claim substantial equivalence.	As long as historical data are acceptable in claiming substantial equivalence, the risk assessment will be undermined by flawed data and basic uncertainties. Where significant differences are found in the comparison of the genetically engineered plant and its closest comparator (isogenic line, conventional counterpart), there is a need for detailed investigation regarding environmental impacts and genetic background. New methods such as metabolic profiling have to be used in addition.
Agronomic and phenotypic characteristics (page 44-45)	The impact of environmental factors on plant composition is mentioned. But no coherent requirements are defined on how to determine the impact factors and the maximum range of possible variations.	There should be a requirement for a stress test under defined conditions to determine functional genetic stability and the possible range of variation in gene expression that can impact plant composition and phenotypic characteristics. In a stepwise procedure, there should be field trials over several years at each site. All geographic regions which might be used for the production of plants to be imported into the European Union should be taken into account. Thus, in each case, several sites are used over several years for field trials.
Toxicology (page 45-51)	90 days feeding arr required for each single event. But no long term studies are required. Further feeding trials with the stacked event are not mandatory in each case. (page 49)	The introduction of mandatory 90 day feeding trials is an improvement. But this requirement is only useful if the overall concept is sufficiently evolved. These subchronic feeding studies have to be integrated into a stepwise process that foresees mandatory *in vitro* examinations, more targeted investigations into specific health risks and long-term and multigenerational feeding studies. Mandatory follow- up investigations are required where there are uncertainties. Stacked events should be investigated even more carefully since combinatorial effects are to be expected.

Issue	Proposal by draft regulation	Comment
	No *in vitro* testing (such as usage of human cell cultures) is required. Some methods for toxicity testing are listed (page 58-60) but none are mandatory.	There are many in vitro systems that can be used to assess relevant risks such as toxicity or carcinogenicity. These in vitro systems should be mandatory in a stepwise procedure before feeding trials are conducted. For example, testing Bt toxins alone and in combination with each other as well as in combination with other external factors should be requested.
	Structural and functional equivalence of proteins produced *in planta* with those produced by bacteria has to be shown (page 47).	The actual toxicity of newly introduced proteins produced by the plants can be different from the one from native sources or the one produced by bacteria. For example, it is known that Bt proteins with identical structure but stemming from different batches can show highly differing toxicity. Therefore, in vitro investigations need requirements to compare and determine the toxicity of proteins used for risk assessment.
Reproductive and developmental testing (page 49)	Only required in particular cases.	Long-term and multigenerational studies should be requested for each application.
Immunotoxicity (page 48)	Only required in particular cases.	Immunotoxicity should be examined in each case.
Stacked events (page 49)	Are tested less rigorous than single events.	Stacked events should be tested even more rigorously than single events since combinatorial effects are likely to occur.
Testing of new constituents other than proteins (page 48)	The interplay with pesticide regulation is missing.	Residues from complementary herbicides have to be considered during the risk assessment of genetically engineered plants. They are an inevitable element of plant constituents to which the food and feed chain will be exposed. Data on the actual load of residues in the plants resulting from varying agricultural practices have to be made available by the applicant. The data on residues are also relevant for the assessment of combinatorial effects.
Combinatorial effects	Should be taken into account	This requirement is not defined sufficiently. Combinatorial effects have to be tested on a broad range of living material including microorganisms from the gut as well as cell cultures from human sources. Testing has to include mixtures of GMOs in food and feed, residues from the spraying of complementary pesticides and native plant ingredients.

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Allergenicity page 51-55	The methods required do not exclude the rise of new allergens. They inherit major uncertainties regarding immune reactions.	No products should be placed on the market without testing its impact on the immune system. Since significant uncertainties cannot be ruled out before market application, case specific monitoring has to be required in each case if products are introduced.
Scientific standards (Article 4)	GLP and OECD standards are necessary for the data presented by the applicant.	This is an improvement. But independent investigations and peer reviewed publications are still necessary and cannot be replaced by investigations performed by industry. It should also be stated that EFSA has to take account of publications that do not fulfil these standards if they indicate risks to health or the environment.
Transitional provisions (Article 9)	Data from the applicant already being forwarded to EFSA but do not fulfil necessary standards do not have to be replaced by new investigations.	All existing applications and authorisations have to be checked to determine whether they comply with the necessary scientific standards. New dossiers have to be presented to replace those that do not comply with the standards.
Transparency (Article 6)	A list of all studies related to the toxicological, allergenic or nutritional characteristics of the genetically modified food and feed must be presented even if they arr not required for the risk assessment.	This is an improvement. All data relevant to risk assessment and owned by the applicants should be made available.
Antibiotic resistance marker genes (page 5)	ARMG genes should be avoided.	Plants inheriting ARMG should be rejected by the authorities. The recommendation in the draft regulation is too weak.
General surveillance (page 27)	Requirements are not defined	If no case specific monitoring is requested, surveillance has to be performed in a way that identifies negative effects on health and allows correlation to specific products.
Cut off criteria	Cut off criteria are not defined	Cut off criteria requiring the rejection of an application should be defined. These cut off criteria will help to save time and money if they can help to stop applications that do not have sufficient expectation of being accepted at an early stage.

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Costs	Financial contribution is requested from the applicant in cases where a full validation procedure of a method of detection and identification for a single GMO event is required. (page 12)	If no fully validated methods are made available by the applicant to measure the expression of the newly introduced gene constructs, these methods should be developed by JRC and paid for by the applicant. The applicant should also be obliged to fund independent risk research and general costs incurred by the authorisation process.

References:

EU Commission, 2012, COMMISSION IMPLEMENTING REGULATION (EU) No …/.of XXX on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Regulations (EC) No 641/2004 and (EC) No 1981/2006

Then, C., (2011), TESTBIOTECH Background 8 4 2011 Input to the EU Commission´s Consultation on Environmental Risk Assessment of Genetically Engineered Plants, http://www.testbiotech.org/node/462/