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Flaws in EFSA´s risk assessment: Examples from eight genetically engineered crops

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Already in July 2014, lobbyists from the biotech and feed industry such as COCERAL, FEDIOL und FEFAC[1] were pushing heavily to allow the import of eight genetically engineerd plants for food and feed, warning that a „huge disruption to feed grain trade and subsequent price hikes would follow if the EU regulator does not approve eight genetically modified (GM) crops before the summer recess“. The plants under discussion are:

- Soybean BPS-CV127-9 (BASF)
- Soybean DP 305423 (Dupont/Pioneer)
- Soybean MON87708 (Monsanto)
- Maize T25 (Bayer)
- Cotton T304-40 (Bayer)
- Maize MON87460 (Monsanto)
- Soybean MON87705 (Monsanto)
- Oliseed rape GT73 (Monsanto)

1 www.coceral.com/data/1405346370COCERAL_FEDIOL_FEFAC_joint_statement_urgent_EC_decision_food_feed_import.pdf

General requirements for the 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. The precautionary principle is intended to prevail in cases where there is uncertainty

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)

Some general deficiencies in EFSA GMO panel risk assessment and the current EU decision-making process

The comparative approach

EFSA guidance is built on the assumption that the risks of genetically engineered plants are comparable to those of plants derived from conventional breeding, and therefore only a limited set of data is required for risk assessment. There are, for example, no requests for feeding trials and long-term studies to make detailed assessments of risks to health. Why is the comparative approach problematic from a scientific point of view? From a technological and biological point of view conventional breeding and genetic engineering are fundamentally different. Unlike conventional

breeding, in genetic engineering, isolated, technically derived DNA constructs are inserted into the plants´ cell to force specific biological functions in the plants by overriding gene regulation and the barriers between species. Choosing the comparative approach increases the already high likelihood that risks associated with genetic engineering (such as disturbances of the gene regulation) will not be identified. If the comparative analysis does not reveal any relevant differences, EFSA does not request further detailed testing for toxicology, allergenicity or nutritional effects. The plants are generally regarded as safe as their conventional counterparts. In reality, the plants are only subjected to a quick inspection, but not to detailed empirical studies.

The process as performed by EFSA is nothing more than a system to avoid more detailed risk assessment, and although it might be in line with the interests of industry it contravenes the legal requirements.

Interaction between genetically engineered plants and the environment

Observable differences in plant components can indicate other changes affecting the level of anti-nutritional, hormonal or immunologically active substances in the plant. It is possible that any such relevant changes in plant characteristics may only be observed under specific environmental conditions. However, interactions with the environment that may impact the composition of plants are not systematically tested. 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 conventionally bred plants. 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.

Investigation of health effects

Testing for health risks is not based on a stepwise concept that includes 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 ongoing discussions and wide ranging opinions regarding the effects that genetically engineered plants have on health. There are already some reports about the negative impacts on the health of farm animals under practical conditions, and several scientific publications that indicate negative health impacts in laboratory animals. For example, there are a number of publications on effects on the immune system in mammals. For example, immune system reactions have been observed in fish, pigs, mice and rats. EFSA,

however, is still acting on the presumption that no effects on health have been observed and therefore there is no need for detailed investigations.

Measuring gene activity

There have been no requests from EFSA to use more recent technologies, such as metabolic profiling even though, as several investigations have shown, plant gene activity and metabolism are often unintentionally impacted by genetic engineering.

In contrast to 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 conventionally bred plants can be presumed to be a disturbance of gene regulation in genetically engineered plants. Methods such as metabolic profiling can help to identify causes, effects and potential hazards. This is especially relevant wherever technologies such as RNAi (RNA inference) come into play. These are used to interact with the gene regulation of the plants and are thought to produce biologically active substances that can pass through the food chain.

Investigation of residues from spraying

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 issue of residues from spraying cannot be left aside in the risk assessment of genetically engineered plants with herbicide resistance. Herbicide-resistant plants are meant to survive the application of the complementary herbicide while most other plants will die after a short time. Residues of glyphosate, its metabolites and the additives can accumulate in the herbicide-resistant plants and interact due to their additional genetic information. Furthermore, the complementary herbicides are likely to be sprayed several times during crop growth. This means that 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 spraying the glyphosate-resistant soybean plants with the complementary herbicide can change the composition of the soybeans. Consequently, the residues and their combinations are inevitable constituents of the plant's composition and will lead to

specific patterns of exposure in the food chain. Therefore, as constituents of the plant, they should be included in the risk assessment of genetically engineered plants.

Combinatorial effects

Several genetically engineered plants with tolerance to various herbicides have applications or market authorisations for the EU, making it necessary to devise a systematic approach to deal with new patterns of exposure, interactions between the substances and the accumulated impact on human and animal health. Potential interactions and accumulated effects between mixing of genetically engineered plants as well as the residues from spraying and other stressors such as insecticidal Bt toxins, toxic compounds, gut bacteria are not taken into account. There are currently no requirements to systematically assess synergistic, additive and accumulated effects.

Scientific standards

Most studies are performed by industry. Even peer reviewed published papers (if available at all) very often show involvement of industry. There are very few independent studies. Further, the scientific standards of the industry studies do not fulfil basic scientific standards (such as Good Laboratory Practise, independent controls, peer review).

Monitoring

EU Regulations require post-marketing monitoring because the risk assessment of genetically engineered plants involves a number of complex issues, and there will always be some remaining 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 targeted monitoring has been implemented within the EU to identify health risks associated with the consumption of food products derived from genetically engineered plants. Basically, the EU Commission is obliged to request such monitoring but the current practice of post market monitoring does not meet the requirements of existing EU regulations.

Tabled overview of deficiencies in the risk assessment of eight genetically engineered crops

Crop, name and company	Trait	Deficiencies in EFSA risk assessment
Soybean BPS-CV127-9 BASF	Herbicide resistance to imidazolinone	Only one field trial was conducted in the US, with an outcome showing large differences compared to those conducted in Brazil, indicating environmental x genome interaction. According to EFSA, seed weight and tocopherol content were different to those of the comparators. In consequence, EFSA should have requested much more data. The applicant carried out a 90-day subchronic study but this was not taken into account by EFSA because of several flaws. The GMO panel did not request a new 90-day study. Thus, there is no feeding study with the whole plants available to assess effects on health. The soybeans were tested with sera from small groups of individuals known to react to allergens from soybeans. Differences were observed but not deemed relevant. As the minutes of an internal EFSA meeting show, the experts have serious doubts about the reliability of the investigations with such a small number of patients conducted in this case. Therefore EFSA should have requested more detailed investigations taking into account possible changes in the content of relevant allergens known to occur in soybeans.
Soybean DP 305423 DuPont/Pioneer	Oil composition of the soybean is changed by RNA interference. Resistance to acetolactate synthase (ALS)-inhibiting herbicides.	Molecular characterisation revealed multiple rearrangements and several complete and truncated copies of gene constructs were detected. These truncated DNAs and rearrangements can interfere with gene regulation in the plants and may cause unintended effects. Metabolic and genomic screening would be required to investigate such effects whereby environmental stress factors would also need to be taken into account. There have been no such investigations. RNA interference (RNAi) is a complex process that might lead to biologically active substances that can be transmitted through the food chain and interact with humans or animals consuming those plants. For risk assessment of these plants it is necessary to measure levels of the various RNAs and assess its structure. But no such studies were conducted. The results of just one field trial (conducted in the US in 2011) were the basis for the comparative assessment. The field trial showed significant differences in several compounds between soybean 305423, its isogenic counterpart and several other soybean varieties. Much more field trials should have been conducted in different climatic regions to investigate interactions between the genome and the environment. No reliable data were presented to test health effects in humans or animals that are consuming these products.

Crop, name and company	Trait	Deficiencies in EFSA risk assessment
Soybean MON87708 Monsanto	Herbicide resistance to Dicamba	The outcome of the comparative analysis shows that several of the endpoints measured were significantly and consistently different but not investigated further. There was no assessment of interaction between plant components such as immunological or anti-nutritional, hormonal or immunologically active substances with the residues form spraying. These residues include substances such as formaldehyde. The outcome of the 90 days feeding study showed several changes in two of the four groups fed with genetically engineered plants. More detailed and long-term investigation of the health impact of the MON87708 soybeans should have been requested.
Maize T25 Bayer (renewal)	Herbicide resistance to glufosinate	Significant changes in the plants composition and the expression of the inserted genes seem to be dependent on interactions with the environment, but were not investigated further. Feeding study to investigate effects on health was rejected due to fundamental flaws in the design of the study.
Cotton T304-40 Bayer	Herbicide resistance to glufosinate. Produces an insecticidal Bt protein (Cry1Ab).	Plants composition is significantly different from its conventional comparator plant, but no further investigations were required. Feeding studies performed by Bayer were rejected due to flaws in the design of the studies. At the same time, EFSA did not ask for any new investigations.
Maize MON87460 Monsanto	Drought tolerance. Resistance to antibiotics	The plants contain a DNA sequence that confers resistance to antibiotics (npt II). Whereas it would have been possible in this case, the DNA was not removed from the plants. However, EU Directive 2001/18 requires the phasing out of this outdated technology as it may have adverse effects. How the DNA sequence conferring drought resistance actually works is not understood in detail. The plants produce an additional protein (CSPB) that is normally found in bacteria under stressful conditions such as cold shock. This new protein is continuously produced in all the plant's tissues throughout the period of vegetation. These effects in the plants are likely to be dependent on specific environmental conditions. Plants showed several unintended changes it is composition. To assess unintended effects and associated risks it is important to understand the mode of action of these proteins. However, EFSA is of the opinion that investigation of these details is not necessary as long as unintended effects in the plants are not proven. The maize was also tested in a 90 days feeding study which showed some effects such as reduction in the weight of some organs that

Crop, name and company	Trait	Deficiencies in EFSA risk assessment
		were considered non-relevant by EFSA. The study suffers from the fact that the feed of the control group was contaminated with genetically engineered maize. Although not mentioned it is also likely that genetically engineered soybeans were part of the diet. As a result, specific effects caused by maize MON87460 might be masked.
Soybean MON87705 Monsanto	Oil composition of the soybean is changed by RNA interference. Herbicide resistance to glyphosate	RNA interference (RNAi) is a complex process that might lead to biologically active substances that are transmitted through the food chain and interact with humans or animals consuming those plants. For risk assessment of these plants it is necessary to measure levels of the various RNAs and assess its structure. But no such studies were conducted. Several significant differences were observed in composition data, the data also show significant differences in agronomic performance. These differences have been declared irrelevant by EFSA through reference to historical data from the ILSI Database, which is known to be unreliable. The 90 days study was performed with defatted meal from soybean. Those characteristics of the beans that are changed by genetic engineering (composition of oil) were not tested by the 90 days study. Thus, no conclusion can be drawn on potential health effects of consuming the whole beans or oil derived from the beans. EFSA guidance on allergenicity speaks about the need for detailed investigations into risks for infants and individuals with impaired digestive functions. “The specific risk of potential allergenicity of GM products in infants as well as individuals with impaired digestive functions (e.g. elderly people, or individuals on antacid medications) should be considered, taking into account the different digestive physiology and sensitivity towards allergens in this subpopulation.” However, these risks were left aside during EFSA risk assessment.
Oilseed rape GT73 Monsanto (Renewal)	herbicide resistance to glyphosate (two different enzymes)	EFSA did not request a new investigation into GT73, but instead based its opinion mostly on studies that are 10-20 years old. In the light of the many significant findings in compositional analysis and feeding studies, much more investigation is needed before any conclusion can be drawn on the safety of this product. Further, EFSA did not take into account the true potential for persistence and invasiveness of the genetically engineered plants that will emerge from spillage. Residues from spraying with herbicides were not assessed.

Conclusion:

Risk assessment does not follow legal requirements and does not allow sufficiently reliable conclusions on the safety of these products. Therefore these applications should not be authorised.

Further Informations:

Soybean BPS-CV127-9 (BASF) www.testbiotech.org/node/1021

Soybean DP 305423 (Dupont/Pioneer) www.testbiotech.org/node/1013

Soybean MON87708 (Monsanto) www.testbiotech.org/node/950

Maize T25 (Bayer) www.testbiotech.org/node/949

Cotton T304-40 (Bayer) www.testbiotech.org/node/867

Maize MON87460 (Monsanto) www.testbiotech.org/node/754

Soybean MON87705 (Monsanto) www.testbiotech.org/node/745

Oliseed rape GT73 (Monsanto) www.testbiotech.org/node/321