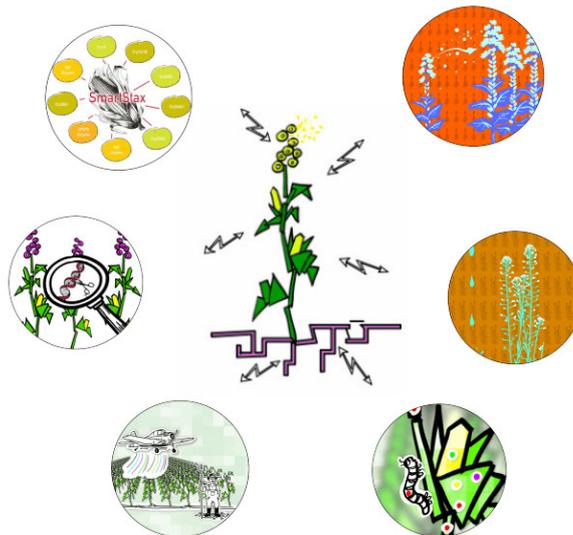


Overview: The RAGES Project

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The EU Parliament has in recent years adopted around 40 resolutions against further approvals for the import of genetically engineered (GE) plants. One of the main criticisms was a lack of adequate and sufficient risk assessment. Experts from several member states raised similar criticisms. Nevertheless, the EU Commission gave the green light to all these imports. The results of the international research project RAGES now show that the concerns of EU Parliament are fully justified: There is a substantial contradiction between the legally required safety standards and the reality of the EU approval process.

What is and who is RAGES?

The RAGES project (Risk Assessment of Genetically Engineered Organisms in the EU and Switzerland) was carried out between 2016 and 2019. Its purpose was to critically evaluate risk assessment of genetically engineered (GE) food plants as performed by the European Food Safety Authority (EFSA) and its Swiss counterpart. RAGES focused on the risks of transgenic plants intended for food production, and also took some new methods of genetic engineering (genome editing) into account. The European Network of Scientists for Social and Environmental Responsibility (ENSSER), its Swiss branch CSS (Critical Scientists Switzerland), GeneWatch UK and Testbiotech all participated in the project. The project was funded by the Mercator Foundation, Switzerland, and was completely independent of the interests of the biotechnology industry.

Genetically engineered organisms are a controversial issue throughout society, especially if they are to be released into the environment or used in food production. In this context, the identification and determination of risks, potential hazards and the likelihood of adverse effects are of utmost importance. However, current discussions on the risks are largely dominated by the perspective of the agbiotech-industry. These companies fund and control most research projects on transgenic plants as well as generate the data for the approval processes. Moreover, they also exert considerable influence on regulatory authorities. At the same time, they are trying to create the impression that all the risks of GE organisms are strictly manageable and controllable, and that the safety of their marketed products has been demonstrated. Consequently, there is a substantial probability that risks are disregarded and relevant research findings overlooked by the current regulatory system. Against this backdrop, RAGES provides an urgently needed critical counter-perspective, giving priority to the protection of health and the environment.

Legal framework

In the EU, EFSA is responsible for the risk assessment of GE organisms. EFSA, and in particular its GMO panel, assesses applications for approval of GE organisms for import (for the production of food and feed) and for domestic cultivation. The most relevant legal frameworks for risk assessment in the EU are EU Directive 2001/18/EC and EU Regulation (EC) No 1829/2003. In addition, the Commission Implementing Regulation (EU) No 503/2013 defines standards for health risk assessment of food and feed products derived from GE plants.

In Switzerland, several different authorities evaluate the filed applications, but as a rule they follow EFSA decisions. Even though in Switzerland there has been a moratorium on the cultivation of GE plants since 2005, several applications for the import of GE plants were approved based on the same data set used by the EU in its decisions to approve imports. The way in which the EU deals with the risks of genetic engineering technologies will in future continue to be crucial to further

developments in Switzerland in regard to import and cultivation prohibitions.

The legislation under which the EU regulates risk assessment of GE organisms stipulates a high level of protection for health and the environment. Article 4 (and Article 16) of Regulation (EC) No 1829/2003 requests that food and feed products derived from GE organisms are “adequately and sufficiently demonstrated” and

“must not: have adverse effects on human health, animal health or the environment”.

This includes ensuring that:

“...genetically modified food and feed should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard, to be undertaken under the responsibility of the European Food Safety Authority (Authority), of any risks which they present for human and animal health and, as the case may be, for the environment.”

Similarly, EU Directive 2001/18/EC demands high standards in environmental risk assessment (e.r.a.) and requests e.g. in section A of Annex II that:

“The objective of an e.r.a. is, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct and indirect, immediate or delayed, on human health and the environment which the deliberate release or the placing on the market of GMOs may have.”

What did RAGES examine?

The analyses carried out in the RAGES project are based on case studies regarding published EFSA opinions, peer reviewed scientific publications and other scientific data/expertise. RAGES compiled six reports on specific topics that were identified as particularly important in this context. These topics are:

- health risks associated with the consumption of products derived from herbicide tolerant GE plants;
- the assessment of environmental risks associated with the cultivation of insecticidal Bt crops;
- health risks associated with the consumption of products derived from GE plants with altered nutritional composition;
- health risks associated with the consumption of products derived from GE plants with a combination of traits (‘stacked events’);
- environmental risks due to persistence, self-propagation and uncontrolled spread of GE plants; and
- risk assessment of GE organisms derived from new genetic engineering technologies.

Which GE plants are allowed in the EU?

There is ongoing controversy over whether or not EFSA risk assessments are adequate to comply with the above mentioned legal requirements. For example, the EU Parliament has in recent years adopted around 40 resolutions against further EU approvals, whereby substantial concerns about scientific standards at EFSA were voiced. Some scientific authorities in member states have also objected to EFSA risk assessment opinions approving GE organisms. Nevertheless, based on EFSA opinions, around 80 GE events¹ currently have approval for import into the EU. In addition, the insecticide-producing maize MON810 is grown in a few EU member states, mainly Spain. The

¹ An “event” is characterised by the gene construct and its place of insertion in the plants genome

number of GE plants authorised in Switzerland is much lower than in the EU.

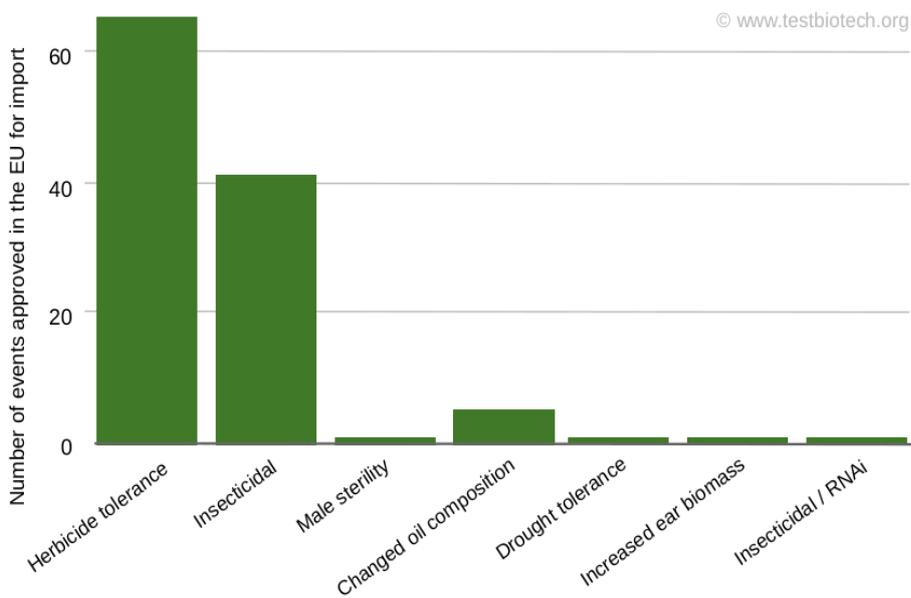
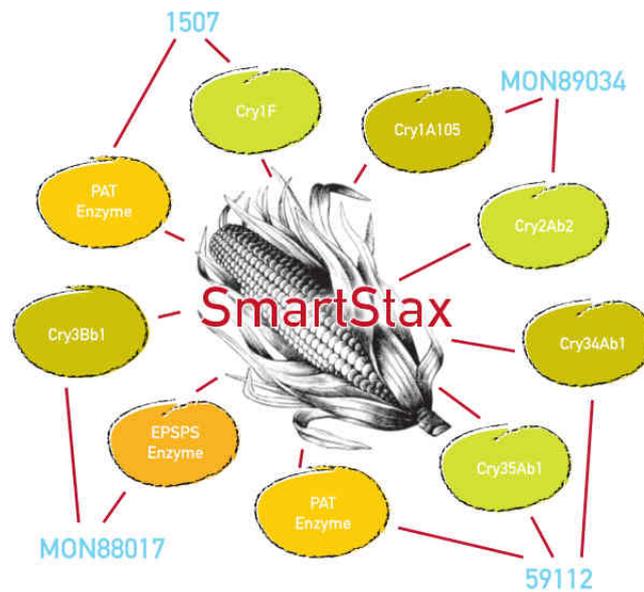


Figure 1: Number of events approved in the EU for import, categorised in traits; the overall number of events authorised at the end of 2019 was around 80. (Many events inherit a combination of traits, therefore, the number of traits is higher compared to the number of events).

Currently, most of the plants have several genetically engineered trait e.g., SmartStax maize, developed and marketed by Monsanto (Bayer) and DowDupont (Corteva).

Figure 2: SmartStax maize, jointly developed by Monsanto and Dow AgroSciences, combines the traits of four genetically plants (MON88017, MON89034, 59122, 1507): it produces six insecticidal Bt toxins (Cry-Toxins from different strains of *Bacillus thuringiensis*, of which one, Cry1A105, does not have a natural template) and is tolerant to two herbicides.



Why do the risks of genetic engineering technology need detailed risk assessment?

Existing gene combinations and biological characteristics of living organisms have evolved over three to four billion years. At the same time, people have, for thousands of years, used selection and crossing based on existing biodiversity to breed plants and animals for food production. In more recent history, techniques such as mutagenesis have been used to create genetic diversity within shorter periods of time for breeding. These methods of conventional breeding are all based on natural diversity and evolutionary mechanisms. They are profoundly different from the technology used in genetic engineering. In short, the methods and mechanisms used in what is known as 'conventional' breeding are characterised by:

- using genetic diversity as a starting point;
- application to the whole cell or organisms;
- not inserting genetic information using direct technical interventions;
- not deleting genetic information using direct technical interventions.

Ultimately, mutagenesis breeding creates greater genetic diversity even though the desired traits are not brought about by direct technical interventions. It is only through crossing and selection of plants and animals exhibiting the desired traits that a new variety can emerge. This process is time-consuming and requires careful choice and repeated testing by breeders. Nevertheless, some organisms resulting from conventional breeding might also require risk assessment in regard to health and the environment.

On the other hand, genetic engineering directly intervenes at the level of the genome, i.e. inserting material that was prepared outside of the cells to achieve targeted changes in the genome or epigenome (for further interpretation see the wording of Directive 2001/18/EC, Annex I A). These techniques and processes:

- are not based on the potential of natural biodiversity and do not use a large pool of genetic diversity. Rather, the goals of the technical intervention are to achieve quite distinct changes in the genome which, in most cases cause specific new gene combinations;
- enable by-passing mechanisms of natural heredity and gene regulation;
- enable traits to be established that do not occur naturally e.g., plants producing insecticidal proteins derived from *Bacillus thuringiensis*, or plants with specific patterns of change in their genome (as is often the case with so-called 'genome editing' which uses nucleases);
- make it possible to insert additional genes not found in nature: for example, in the case of plants that produce Bt toxins, the DNA sequences are modified in the laboratory giving rise to truncated or chimeric Bt proteins that do not exist in nature.

In summary, experience gained from conventional plant breeding cannot simply be extrapolated to the risk assessment of GE plants. Due to the methods used in genetic engineering, the resulting patterns of genetic change, the resulting gene combinations as well as biological characteristics and associated risks can be very different compared to those derived from conventional breeding. Therefore, according to EU law (Directive 2001/18/EC), all organisms derived from processes of genetic engineering require specific, case-by-case risk assessment before they are released into the environment or allowed for use in food products.

Results

Many biotech stakeholders, company representatives and academics are trying to create the impression that current risk assessment methods have been sufficient to identify and control the risks. They claim that so far no major or acute damage has been observed and argue that therefore all plants that have been approved and cultivated thus far are safe. However, such statements are misleading and not scientifically verifiable. We are aware that in previous years the EU Commission has repeatedly issued several ‘populist’ statements claiming there are no specific risks associated with genetically engineered plants e.g.:

“The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research, and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than e.g. conventional plant breeding technologies.”

This statement is however not based on robust scientific evidence. It is taken from a report titled “A decade of EU-funded GMO research (2001 – 2010)” (EU Commission 2010) and is frequently quoted by stakeholders interested in the development and marketing of GE organisms. The EU Commission report mostly provides technical details relating to the development of GE-organisms and their potential applications. However, it does not deal with risk assessment in regard to health and the environment as discussed and elaborated in the RAGES project.

Moreover, the report was published in 2010 and is mostly outdated. It does not deal with current agricultural practices, ‘stacked events’ or more recent publications and new issues that have arisen over the last ten years; these were the issues discussed and considered in the RAGES project.

The RAGES project results show that risk assessors in the EU and Switzerland are actually failing to deal with the real and more recent problems. In many cases, they follow a ‘*don’t look, don’t find*’ approach, which does not take the limits of knowledge into account or identify crucially important uncertainties and knowledge gaps. Substantial gaps in EFSA risk assessments are set out in the detailed RAGES reports.

EFSA focuses on issues than can be examined most easily, but fails to assess a number of highly relevant risks:

- risk assessment of HT GE crops largely ignores the specific pattern of residues from herbicide spraying and their effects on the overall safety of food and feed;
- risk assessments of HT GE crops do not take into account the application of high dosages and repeated spraying of the complementary herbicides, which is the current practice in commercial cultivation. Therefore, the GE plants tested in field trials do not represent the GE plants as approved for import;
- risk assessment of Bt crops ignores the complexities (and uncertainties) of the modes of action of the toxins and their interactions with co-factors and other stressors;
- risk assessments of Bt crops also largely ignore the fact that the selectivity and efficacy of Bt toxins can be modified by changes in their structure that occur when they are produced in the GE plants;
- if traits are combined in GE crops, such as tolerance to various herbicides and/or the production of several Bt proteins (so-called ‘stacked events’), EFSA fails to require the whole food and/or feed and its mixed toxicity to be tested and assessed;
- if several GE plants are mixed in a diet, the cumulative and combined effects and their mixed toxicity are not investigated;

- metabolic pathways are often multifunctional and complex and can affect plant growth or nutritional composition. Even if a pathway is directly affected by the genetic intervention, EFSA does not require more detailed assessment of the overall effects;
- only a relatively small fraction of the biologically active compounds naturally produced in the plants and their composition are considered in EFSA risk assessments;
- large parts of relevant health effects, e.g. reproductive and immune system effects, as well as the impact on the gut microbiome, are neglected in current EFSA risk assessments;
- even though environmental stressors can influence the expression of the inserted gene constructs, such processes and their impacts are not systematically assessed by EFSA;
- only a small selection of relevant geo-climatic conditions and regions representing the countries of cultivation are taken into account in the field trials required by EFSA;
- EFSA assessments of impacts on ecosystems and food webs suffer from major gaps in the selection of relevant organisms, and also from neglect of relevant pathways of exposure;
- if GE plants can persist, propagate and spread via uncontrolled gene flow, data on the next generation effects are not required and so are not assessed by EFSA.

Consequently, current standards of risk assessment are not sufficient to fulfill the legal requirements to determine that the safety of genetically engineered organisms and food and feed derived thereof is “adequately and sufficiently demonstrated” by applying “highest possible standard” of “any risks which they present”.

An example: herbicide-tolerant GE crops

One of the problems identified by RAGES is that herbicide-tolerant GE crops are currently assessed independently of the residues of herbicides to which they are resistant. This is completely absurd because the plants are always marketed and cultivated in combination with the ‘complementary’ herbicides. This means there will always be residues of the respective herbicides present in the harvest. The division in risk assessment results in major problems:

One consequence: the herbicide amounts applied in most field trials are much lower compared to the real agricultural conditions in which these crops will be cultivated. Therefore, the plant material assessed by EFSA is not equivalent to the plant material that will actually be imported. This means that the results of risk assessment are not reliable and is likely to underestimate the risks.

Another consequence: the pesticide experts at EFSA repeatedly and explicitly stated that they do not have enough data to assess safety of the residues in the GE plants.

A third consequence: most GE crops are not resistant to just one herbicide, quite often they are resistant to several herbicides, and also produce insecticides. However, the combined toxicity / combined effects of all these components are not tested.

Instead of attempting to solve these problems, the EU Commission has taken a defensive stance on the obvious gaps in risk assessment. It claims that the missing data need not be taken into consideration for the approval process because the approval process for GE plants is regulated independently of pesticide regulation. This means that the biotech industry receives approvals even if crucial data are missing. Consumers are then exposed to an increasing risk because more and more herbicides are used in GE plant cultivation; this is not dealt with or assessed under the separate pesticide regulation.

The results of RAGES concerning insufficient risk assessment of GE herbicide tolerant plants were also published in a peer reviewed international Journal (Miyazaki et al., 2019).

The demands

The findings of the RAGES project show that the precautionary principle needs to be applied far more consistently and comprehensively. While each sub-report presents a list of specific recommendations, there are several overarching implications of the findings:

- More risk research needs to be carried out independently of stakeholders interested in the development and marketing of GE organisms.
- Risk assessment policies need to be developed to address gaps in current knowledge and inadequacies in prevailing approaches to assessing risks. Policies also need to be developed and implemented to engage with new findings in biology, as well as to develop new investigative methodologies and improve guidance for risk assessments.
- Spatio-temporal control is key for the implementation of precaution. Without such possibilities of control, effective measures cannot be implemented in the event adverse effects and damage to the environment occurring. No releases of GE organisms can be allowed if they cannot be prevented from persisting and propagating in the environment. Applications with inadequate spatio-temporal control include gene drive organisms.
- Field trials have to be conducted under conditions which represent the real agronomic practices under which the plants are expected to be grown commercially.
- The responses of the plants to changes in environmental conditions e.g., climate change, have to be taken into account.
- Wild/natural populations should be strictly protected against gene flow from GE organisms.
- Much more attention must be paid to the assessment of combinatorial effects and their possible impact. This is applicable both to GE plants that have been genetically engineered multiple times and when several different GE plants are mixed into feed.
- Combinatorial and accumulated effects also have to be assessed if plants with more than one trait are cultivated, or where several events are grown in the same region.
- New mechanisms for monitoring post-release impacts need to be developed to close gaps in current knowledge. Research is needed to provide more information on the more subtle long-term effects, even in cases where these were not already identified as manifestly adverse during the process of risk assessment.
- Organisms resulting from processes of ‘genome editing’ must undergo an approval process and labelling in accordance with EU GMO regulation, whereby specific guidance needs to be developed in regard to risk assessment.

The results of RAGES project were presented at workshops in Brussels and Neuchatel (Switzerland) in 2018 and 2019. The EU Commission, EFSA and Swiss authorities all participated; this was very much appreciated although there was no consensus on many findings. The findings of RAGES were updated to correspond with the results from the workshops. The reports as published provide an important and unique source of material regarding the risks of GE organisms and the EU approval process. Some of the results will be forwarded for further review in scientific journals. A first peer reviewed publication was accomplished in December 2019 (Miyazaki et al., 2019). Another peer reviewed publication on the risks of glyphosate resulted from the wider context of the project (Bohn & Millstone, 2019).

The RAGES reports: www.testbiotech.org/projekt_rages

First peer reviewed publication on results from the project:

Miyazaki, J., Bauer-Pankus A., Bøhn T., Reichenbecher W., Then C. (2019) Insufficient risk assessment of herbicide tolerant genetically engineered soybeans intended for import into the EU, Environ Sci Eur., <https://doi.org/10.1186/s12302-019-0274-1>

Further publication derived from the wider context of the project:

Bøhn, T. & Millstone, E. (2019) The Introduction of Thousands of Tonnes of Glyphosate in the food Chain - An Evaluation of Glyphosate Tolerant Soybeans, Foods 2019, 8, 669, doi:10.3390/foods8120669