Systemic risks of genetically modified crops: the need for new approaches to risk assessment

Hartmut Meyer, ENSSER

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1 Genetic engineering in agriculture: impacts and restraints[1]

The first genetically modified organisms (GMO) deregulated and commercialised was the Flavr Savr tomato in 1994 in the USA, which did not prove to be commercially viable. US genetically modified (GM) agriculture actually started with Bt cotton planting in 1995, but it only was the introduction of Roundup Ready soybeans in 1996, being exported worldwide as basic ingredient for the feed and food industry that initiated the worldwide public debate on the use of GM crops. Meanwhile, James reports that 15 countries grow more than 50,000 ha of GM crops each with a sum of 133.9 million hectares [1]. According to FoEI - pointing to the fact that the data presented by James are mostly based on personal communic1ations by representatives of the biotechnology industry, which also funds his work - this area equates to 9.2% of the arable land worldwide [2].

Ninety-two percent of this area is located in five countries (USA, Brazil, Argentina, India, Canada). GM crop agriculture relies on five plant species (soybean, maize, canola, sugar beet and cotton) predominately producing animal feed, ethanol and fibres in high-input farming systems. Based on the data provided by James, it can be concluded that GM food products mainly comprise sugar, high-fructose corn syrup, soy protein, lecithin or different oils [1]. Some GM maize varieties can be used for direct consumption as, for example, in South Africa. In the USA, some GM papaya is marketed. The range of new properties used in GM crop agriculture is essentially limited to two features: resistance against the herbicides glyphosate and glufosinate and production of Bacillus thuringiensis (Bt) endotoxins that are used to kill specific lepidoptera and coleoptera larvae.

The main bottleneck for developing a higher variety of commercially viable products seems to be the limited potential of the technology itself. Complex characteristics of plants as drought or saline resistance are based on reactions of the plant organism at several, including but not only the genetic level. Many - still unknown - genes may play a role in the response to environmental condition. The application of genetic engineering alone might not lead to the improvement of such complex traits [3-5]. Only GM plants possessing genes - which are supposed to work in isolation from the plant's metabolism, as the herbicide resistance and Bt genes - are used commercially. Additionally, two GM plant types possessing pathogen-resistant genes which are supposed to interact with an invading organism could be developed into a commercial product: GM virus-resistant papaya and squash grown on 2,000 ha each in the USA [6].

Until the end of 2004 - which should leave enough time for the development of commercial seed until 2009 - the U.S. authorities approved 877 field trials with plants that were supposed to be virus resistant (988 until the end of 2009). Experiments with GM plants that were supposed to be resistant against fungi did not result in any commercial product yet, 622 field trials were approved in the USA until the end of 2004 (854 until the end of 2009). The main blocks to market fungi-resistant GM plants are the lack of deeper understanding of the molecular plant-fungi interactions and the unsatisfactory levels of resistance [7,8].

Stein and Rodríguez-Cerezo predict that a turning point has been reached in the limited commercialisation of GM traits [9]. The authors estimate that in 2015 the number of traits in farmers' fields might quadruple to 120, amongst them 17 soy traits (12 herbicide resistant, three altered oil composition, two pest resistant) or 15 rice traits (six insect resistant, four pest resistant, three herbicide resistant, two b-carotene). This development would mainly increase the number of traits mentioned above to 114. Only six traits aim at influencing more

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complex characteristics as drought resistance in maize while they still rely on single gene alterations.

2 Development of regulatory biosafety frameworks

2.1 Asilomar conference

It was U.S. scientists working in the fields of cancer research and molecular biology being concerned about the potential health risks of their work who started the scientific debate on the pros and cons of GMOs [10]. The participants of the 1973 Gordon Conference on Nucleic Acids drafted a resolution, which warned about the potential health risks of hybrid DNA molecules and called successfully upon the National Institutes for Health (NIH) to develop safety guidelines [11]. An international conference to support the development of safety standards was announced and even moratoria on certain types of experiments suggested [12]. In spring 1975, participants of the Asilomar Conference recognised that more than health problems might arise from the industrial, medical and agricultural application of genetic engineering, but they restricted their debates on this risk issue. While the conference concluded that mechanisms of self-control and voluntary guidelines should be the basis for the development of the technology, calls for a stricter and legally binding governmental oversight were launched during the emerging public debate in cities as Cambridge, Massachusetts, harbouring major research institutions [12,13]. Envisaging a growing unease of the public, prominent molecular biologists soon questioned the value of the early risk debate [14-16].

2.1 Emerging biosafety systems in the USA

When Cohen reported that his research enables scientists to cross the species barriers, suggesting the invention or creation of new species, U.S. politicians started, soon after, to draft regulations for the application of GMOs [17]. This in turn alerted those scientists that envisaged large economic potential based on their work and patents, and in 1977, a draft law for GMO regulation was stalled when Cohen convinced politicians that the results of the new technology could also have appeared in nature. Expecting a revolution in biology and an immense impact on business, genetic engineering was declared as equivalent to conventional breeding methods, meaning a GMO is not a new organism with unforeseeable risks and does not require specific regulation [18]. In 1976, the NIH adopted guidelines, which set up a system based on biological and physical containments.

Later, the U.S. National Research Council formalised the risk assessment approach [19]. When in 1983 the first GM bacteria and plants were released in field trials in California, the existing health protection guideline concept was applied to assess possible environmental risks [20]. The U.S. has opted using existing frameworks to set up a consultation system.[2] Nowadays, genes and proteins that render herbicide tolerance to GM plants are assessed and deregulated according to the rules for food additives; plants possessing Bt genes and proteins fall under the pesticide approval rules and growth hormone-producing fish has to be checked under the procedures for approval of animal drugs. Two recent U.S. law cases stated that the procedure agreed upon by the authorities and the applicant for deregulating herbicide-resistant golf lawn grass and alfalfa were faulty. A more rigid assessment under the norms of U.S. environmental laws had to be conducted. With these court decisions it seems

[2] Starting points for an overview about the U.S. biosafety regulations are:
http://www.aphis.usda.gov/biotechnology/index.shtml, http://www.fda.gov/Food/Biotechnology/default.htm
http://www.epa.gov/pesticides/biopesticides/pips/index.htm, http://usbiotechreg.nbii.gov/

that GM plants that can interact substantially with wild or domesticated genetic resources via pollen flow must undergo a more detailed risk assessment in the USA as, for example, GM soy or maize. It remains open until a final supreme court decision, if and how these court cases will influence the future GM crop regulation in the USA.

2.3 Biosafety frameworks at the European and UN level

In contrast to the situation in the USA, the debate in EU countries went beyond expert circles and involved more NGOs and citizen groups. It also lacked the strong focus on emerging commercial prospects of genetic engineering. While the model of the NIH guidelines was adopted by many European governments, the emerging public debate quickly reached the decision that an overarching, specific legal framework was necessary due to the novelty of GMOs [18,21]. The first biosafety laws were adopted in Denmark in 1986 and Germany in 1990, EU biosafety regulations followed in 1990.[3] Since that time, the concept of the European biosafety legislation is that the properties and behaviour of organisms which "genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination" cannot be predicted from the current experience with and knowledge about the parent organism. Although this socalled process-based system was developed under the umbrella of the community environmental law it did not adapt existing instruments for assessing environmental risks of technical and industrial activities, e.g. environmental impact assessment, but kept the GMO risk assessment approaches that had been developed in the context of the technology development.

In 1995, the negotiations of international binding biosafety rules under the framework of the CBD) started, which resulted in the Cartagena Protocol on Biosafety (CPB)[4] adopted in 2000 [22]. Comparable to the EU, the CPB adopted a process-based type of GMO regulation. As the Biosafety Clearing House of the CPB and other data banks show, legally binding specific biosafety legislation are currently in force or under development in 112 out of 200 countries:

- Seventy-nine states with legislation in force (amongst them 33 industrialised countries)
- Thirty-three states with legislation in development
- Fifty states with a national biosafety framework based on the CPB
- Eleven states having ratified the CPB Countries, which so far do not follow the process-based approach to biosafety legislation, are the USA and Canada.
- Twenty-five states have no biosafety system at all.

3 Conflicting concepts for assessing environmental risks of GMOs

3.1 The "ecotoxicological approach" versus the "environmental approach"

Ever since the first GMOs were released, it was discussed whether it is justifiable to apply methods developed for toxicology assessment of chemical substances to viable and reproducible organisms or if new methods had to be developed. The differences between the testing approaches were brought to a wider public when Hilbeck et al. and Losey et al. for the first time showed negative effects of Bt toxins and Bt maize pollen on ecologically relevant non-target organisms in laboratory experiments at a time when Bt crops where already deregulated and cultivated commercially in the USA [23-25]. The U.S. authorities did not require an ecologically oriented laboratory or even field test for the deregulation of Bt cotton in

[3] A starting point for an overview about the EU biosafety legislation is http://ec.europa.eu/food/food/biotechnology/evaluation/gmo_nutshell_en.htm

[4] The text of the CPB is available at http://www.cbd.int/biosafety/protocol.shtml

1995 [26]. The respective risk research and assessments were largely and still are based on ecotoxicological laboratory approaches. Standard protocols and organisms are used due to the good reproducibility of experiments, easy breeding of those organisms and low costs of the work. The two different concepts for GMO risk assessment were named “ecological approach” and “(eco)toxicological approach” [27,28]. According to EFSA, the current arguments and representatives are presented by Andow et al. and Romeis et al. [29-31].

Hilbeck et al. questioned whether the design of these ecotoxicological tests would contribute to assessing the ecological risks of Bt crops [32]. For example, the water flea Daphnia magna was exposed to Bt maize pollen and the measurement of “no effects” was judged as “no risk” although the Bt toxin contained in the pollen will not dissolve in the water and Daphnia cannot eat pollen.

Similarly “no effect” results with the earthworm Eisenia fetida were accepted although there was no proof that the worms actually had taken up the toxin in the feeding trials. Apart from questionable test designs, it is known that, for example, the widely used earthworm Eisenia fetida does not live in agricultural ecosystems [33]. The criticism on using environmentally irrelevant organisms and ill-designed tests added to the existing uncertainty on how to measure “indirect effects”, e.g. the effects of the herbicides used together with herbicide tolerant crops, as demanded by the legal framework, how to deal with the foreseeable EU-wide use of antibiotic marker genes in foodstuff made out of GM crops containing these transgenes and how to evaluate the research work pointing to considerable gene flow in GM canola [34]. It was against this background that the EU environmental council[5] declared the stop of all pending GMO application procedures in 1999 until the EU biosafety regulations had been revised.

4 Different reactions on the new EU biosafety framework

This scientific dispute in combination with societal and economic impacts influenced the revision of the EU GMO regulations [35]. The new EU biosafety Directive 2001/18/EC supports the ecological approach and prescribes a more detailed environmental risk assessment (ERA), establishes the precautionary principle as baseline for decision making and also serves as ERA reference for the regulation (EC) 1829/2003 on GM food and feed market approval.[6] The five steps of current risk analysis procedures (hazard identification, exposure assessment, consequences assessment, risk characterization, mitigation options) were accepted as valid for GMOs, but methodologies and interpretations should be adapted to meet the specific features of living organisms and their interactions with the receiving environment [36-39].

Although Directive 2001/18/EC establishes a new framework for ERA prescribing the testing of the GMO as such (not only of the new genes and proteins) or the consideration of the receiving environment (not only some field trial locations as basis for an EU-wide approval), a review of the soil ecotoxicological tests presented in GMO dossiers concluded that they do not reflect the new legal requirements [40]. These authors, in line with Andow and Hilbeck and Snow et al., emphasise that it is crucial not to rely on standard test species only but to choose test species representative of the agro-ecological environments in which the GM plants will be grown [41,42]. A recent EFSA Scientific Opinion elaborates extensively on the

[5] http://register.consilium.europa.eu/pdf/en/99/st09/st09433-re01.en99.pdf
http://register.consilium.europa.eu/pdf/en/99/st09/st09433-ad01.en99.pdf
http://register.consilium.europa.eu/pdf/en/99/st09/st09433.en99.pdf
[6] http://ec.europa.eu/food/food/biotechnology/gmo_intro_en.htm

issue of species selection that should take into account the “ecological relevance of the species, susceptibility to known or potential stressors, anthropocentric value, testability, exposure pathways” of non-target organisms [29]. Furthermore, experiments with the actual GM crops at different levels of complexity have to be performed as basis for a sound risk assessment [43].

The stated deficits in the GMO dossiers and a series of publications that argue against a wider application of the ecological approach in ERA show that the implications of the new legal framework are seen critical by developers of GM crops and scientists advocating their use. A scientist of Syngenta states that “environmental risk assessment research has often attempted to describe the multitude of potential interactions between transgenic plants and the environment, rather than to test hypotheses that the cultivation of transgenic plants will cause no harm.” [28]. The ecological approach obviously supports decision makers against approving GM crops, and ecologists advocate even more research into complex ecological interactions. Raybould addresses not only the methodology of ERA but also the central normative problem in the relationship between risk research and risk assessment: who determines what kind of hypothesis has to be tested, which level of scientific knowledge and certainty is needed before making decisions, and where is the border between “need to know and nice to know”.

Developers of GM crops suggest different approaches on how to accelerate the GM crop approval under the new EU system. One basic suggestion of Raybould is that “ecologists must avoid the temptation to test null hypotheses [of no difference between a transgenic plant and a non-transgenic comparator]” but test risk hypotheses on adverse effects of GM crops on environmental goods and processes that need to be protected [28].

With regard to the EU political and legal background, it seems questionable if this approach will lead to the desired outcome. First, the necessary decisions on protection aims have not yet been taken in the EU. Furthermore, the suggestion does not reflect the concept of the EU biosafety legislation saying that the application of gene technologies might lead to new risks and that, therefore, the first requirement of risk assessment is to test the above-noted null hypothesis on unforeseen differences between the GMO and its parents.

The second suggestion of private sector representatives of the ecotoxicological approach is that field tests should not be a prerequisite for GMO approvals, but should only be demanded when literature studies or ecotoxicological experiments show significant negative effects [44]. A scientist of Monsanto suggests that this model should also be applied to his company’s droughtresistant GM maize, a trait that until now was seen as model case for more complex, ecologically oriented risk research and assessment [45]. This approach enabling a more expedient approval of GM crops was supported by U.S. and EU governmental risk assessors and public scientists in a joint publication on risk assessment of non-target effects of Bt crops and accordingly shaped the draft guidance on GM crop risk assessment presented by the European Food Safety Authority [31,46].

5 Normative dimensions of risk assessment

In those discussions, it became apparent that ERA steps 1 and 5 as described by Hill are not restricted to the application of scientific methodology but must also be based on substantial normative and thus value-loaded decisions [37]. Many authors state that step 1 indeed needs to be broadened and developed into a “Problem Formulation”. Scientists advocating the ecological approach developed the problem formulation and option assessment (PFOA) tool, based on stock-taking exercises, stakeholder consultation and broader public participation

procedures [47]. The PFOA was tested in developing countries not only to improve the ERA but as a technology assessment tool following the suggestion of OECD [48-51]: “Analyses leading to risk management decisions must pay explicit attention to the range of standpoints, in particular in situations with a high potential for controversy. This is often best done by involving the spectrum of participants in every step of the decision-making process, starting with the very formulation of the problem to be analysed. Introducing more public participation into both risk assessment and risk decision-making would make the process more democratic, improve the relevance and quality of technical analysis, and increase the legitimacy and public acceptance of the resulting decisions.” When Raybould reflected on the UK farm scale evaluation of GM herbicide tolerant (GMHT) crops, he illustrated clearly that the problem formulation (step 1) strongly depends on the respective stakeholder interests [52].[7] From a herbicide-producing company’s perspective, the preservation of arable weeds presents no value and the aim of any GMHT crop system is to reduce their abundance; from a nature conservation perspective, however, arable weeds are a valuable part of biodiversity that should not be eradicated in agro-ecosystems.

While this attitude of a scientist from the private sector is not very surprising, it can be observed that public scientists in application-oriented fields as plant biotechnology tend to adopt comparable attitudes [53]. Kvakkestad et al. interviewed 62 Scandinavian scientists on their perspectives with regard to the deliberate release of GM crops against their professional and funding backgrounds [54]. Two perspectives prevail: perspective 1 is held by many publicly funded scientists who emphasised that the environmental effects from GM crop are unpredictable, and perspective 2 is held mainly by scientists from the biotechnology industry who emphasise that GM crops present no unique risks. No ecologist associated himself with perspective 2. Publicly funded scientists that do not hold above perspective 1 but promote biosafety systems that establish enabling environments for the adoption of GM crops are meanwhile organised in lobby groups as the Public Research and Regulation Initiative, funded by a former Syngenta manager [55].

Also, step 5 and the activities leading to the final decision involve much more than pure science. Millstone et al. stated that the attitude of authorities to deal “asymmetrically” with research that showed negative effects compared to research that could not show negative effects is interpreted by the public as support of the authorities for the developers of GMOs [56]. The Cartagena Protocol on Biosafety explicitly refers in its Risk Assessment Annex to this common attitude when it obliges its member states to consider that “lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk”. This formulation was agreed upon by the negotiators as a way on how to implement the precautionary principle in GMO risk assessment and decision making [57]. To address these normative issues in a democratic and socially acceptable way, new processes are needed, which must secure that the point of view of every stakeholder can have its influence on problem formulation in risk assessment and the final decision-making [58,59,51,60].

[7] “In the UK Farm Scale Evaluations of GM herbicide tolerant (GMHT) crops, an assessment endpoint was the sustainability of populations of arable weeds in fields. The observed reductions in arable weed populations in some GMHT crops were considered detrimental effects, because weeds were considered to be valuable biodiversity.”

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