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REVIEWS

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Options to Reform the European Union Legislation on GMOs: Scope and Definitions

Dennis Eriksson,[1,@,*]
René Custers,[2]
Karin Edvardsson Björnberg,[3]
Sven Ove Hansson,[3,4]
Kai Purnhagen,[5,6] Matin Qaim,[7]
Jörg Romeis,[8]
Joachim Schiemann,[9]
Stephan Schleissing,[10]
Jale Tosun,[11,12]
and Richard G.F. Visser[13]

We discuss options to reform the EU genetically modified organisms (GMO) regulatory framework, make risk assessment and decision-making more consistent with scientific principles, and lay the groundwork for international coherence. The first in a three-part series, this article focuses on reform options related to the scope of the legislation and the GMO definition.

A wide range of stakeholders have recently called for reform of the legal framework for GMOs in the EU[i] [1–4]. One argument is that the implementation of the EU GMO law may lean too much towards precaution at the cost of stalling innovation [4,5]. There is also concern that the EU could forego potential benefits of technological innovations not only in transgenesis but also in gene editing; as a judgment of the Court of Justice of the European Union (CJEU) on the scope of the mutagenesis exemption in the GMO legislation (case C-528/16[ii]) implies, the products of targeted mutagenesis are also subject to the GMO legislative provisions [6,7]. The nondetectability of most products of gene editing has also made enforcement following the CJEU case C-528/16[ii] difficult, if not impossible[iii].

Molecular breeding technologies, such as transgenesis and targeted mutagenesis, have the potential to contribute to sustainable agriculture and food security by increasing agricultural yields, reducing pesticide use [8,9], and increasing the nutritional value of food and feed crops [10]. In Box 1, we present a number of potentially beneficial applications. The use of molecular tools results in products facing regulatory environments that differ by country, with procedures that are more demanding in some countries than in others. While some stakeholders recognize stringent regulatory procedures as a means to prevent harm, others emphasize that overly strict regulations may act as a disproportionate threshold with the potential to hinder innovation [11]. Regulatory procedures for the testing and commercial approval of GMOs are particularly lengthy and costly in the EU, as compared to the USA, Canada, and many other countries [12,13]. By contrast, authorization procedures provide a means to transfer information regarding the potential harm of these organisms from businesses to regulators, potentially closing the information gap between these two. If properly applied, the regulatory procedure is viewed as an enabler for more scientifically robust and socially acceptable public policies [14]. At the same time, applications for cultivation authorization of GM crops as well as funding for GMO research have been decreasing in the EU [15], which has been connected to a reduction in the overall level of innovation [16]. These facts provide a strong indication that the current regulatory framework is no longer fit for purpose.

With a focus on GM crops, we present details for a reform based on a rigorous application of a risk-based approach. In this article, which is the first in a series of three, we briefly describe the current EU regulatory framework and discuss reform options related to the scope of the legislation and the GMO definition (Figure 1). The subsequent two articles discuss reform options in terms of risk assessment and risk management as well as post-authorization requirements.

The Current EU GMO Legislation

The regulation of GMOs gained attention in the EU in the late 1980s. The first Council Directive 90/220/EEC covered their deliberate release into the environment and market introduction. Following a number of food crises and the requirement to realign with World Trade Organization law, several member states asked for a revision of the approval process and requirements for placing GMOs on the market by the end of the 1990s. In response to this, a new legal framework [inter alia Directive 2001/18/EC, Directive 2004/35/EC, Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1830/2003, and Recommendations for Coexistence] additionally introduced labelling and traceability requirements, a liability framework for adventitious presence, a centralized authorization procedure for GMOs, and coexistence recommendations. Risk assessment and risk management are largely harmonized at the EU level. However, in line with the requirements of the treaties governing the EU, a member state may provisionally restrict or prohibit the use and/or sale of a particular GMO under the safeguard clause of Directive 2001/18/EC if new findings indicating potential environmental or health risks of the organism appear. Since 2015, member states may additionally restrict or prohibit the cultivation of GM crops on their territory based on other than risk-related criteria. GMOs obtained by techniques listed in Annex 1B of Directive 2001/18/EC are exempt from the specific risk assessment, authorization, labelling, and traceability

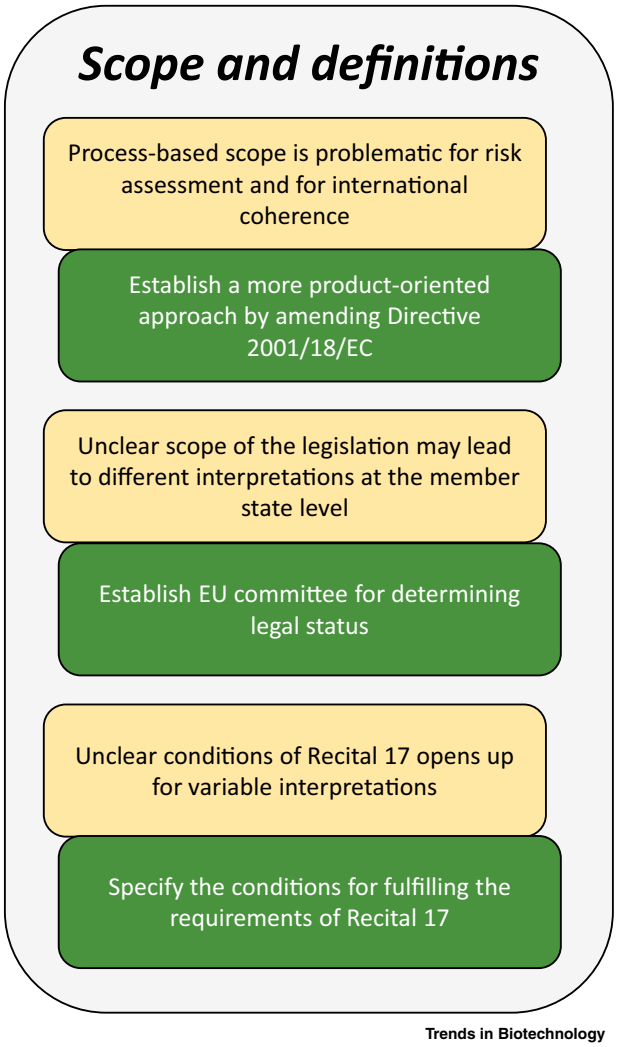

Figure 1. Reform Options of the Legislative Framework for Genetically Modified Organisms in the European Union, Concerning the Scope and Definitions. Problematic issues with the regulatory framework are identified in the yellow boxes; suggested potential solutions are identified in the green boxes.

procedures. This includes mutagenesis techniques that were in use before the Directive entered into force in 2001 but not newer forms of mutagenesis, according to the CJEU decision in case C-528/16[ii].

Reforming the Scope and Definitions

Assessment by Product, Not Process

Three decades of research on GMOs have shown that potential risks associated with a new variety are related to the phenotypic traits of the plant and its derived products and not the technique that was used for breeding [17]. This is in stark contrast to the emphasis on process as a trigger for the applicability of the GMO legislation in the EU. We propose to amend this framework to move away from process-based triggers for regulatory oversight and put a stronger emphasis on the product. One measure could be to establish a definition of GMO that is more in line with the definition of a Living Modified Organism (LMO) in the Cartagena Protocol on Biosafety (CPB) to the Convention on Biological Diversity, which stipulates that an LMO is 'any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.' This is in line with the view expressed by some EU member states before the CJEU judgment on the mutagenesis exemption [18]. Another alternative would be to amend Annex 1B of Directive 2001/18/EC, as proposed by the Dutch government[iv], by which the exemption from the provisions of the Directive would apply to organisms not containing sequences foreign to the organisms' gene pool and/or recombinant nucleic acids. This would imply that products harboring only point mutations and no foreign DNA would be exempt from harmonized regulation [1]. The CJEU ruling in Case C-528/16[ii], however, also stipulated that exempted products of mutagenesis can be regulated at a national level, so this approach would carry the risk of further fragmentation of the EU internal market. Another possibility would be to introduce a stratified approach similar to that proposed by the Norwegian Biotechnology Advisory Board, according to which, regulatory requirements are adjusted based on the type of genetic change [2]. More generally, we propose that products that are identical to those that can be developed using any conventional breeding technique, and/or may (to a reasonable degree of probability) occur without human intervention, should not be subject to the provisions of the EU GMO legislation as they currently stand. We believe it is reasonable from a risk perspective that identical products are subject to similar regulatory procedures. This would also be in line with the regulatory approach taken

Box 1. Transgenesis and Gene Editing in Plant Research and Breeding

Plant breeders depend on genetic variation for the development of new desirable traits in agricultural crops. To increase genetic variability in a particular species, breeders have for a long time used wide crosses, hybridization, randomly-induced mutagenesis, and other techniques. Transgenesis and gene editing has opened up new horizons as the genetic variation available for breeding has become much larger.

The use of the CRISPR–Cas systems and other gene editing techniques to develop crops with new desirable traits is a very dynamic field of research. According to a recent review, around 100 market-relevant applications of gene editing in 28 different crop species have already been documented in scientific publications [20], and this number is increasing rapidly. Many of the applications involve resistance against fungal, bacterial, and viral diseases in crops, such as rice, wheat, maize, banana, and cassava. Disease resistance is a valuable trait to reduce crop losses and chemical pesticide sprays. Further, crops more tolerant to soil salinity, drought, and other climate stresses have been developed. Market-relevant applications also include crops with improved food and feed quality traits, such as wheat with reduced gluten content, vegetables with increased vitamin levels, and oil crops with improved oil composition and decrease of antinutritional compounds [10]. Many other gene editing applications are in the research pipeline and could help to make agriculture more sustainable and climate smart [21]. Under the current GMO legislation, such applications can hardly be developed and field tested in the EU, let alone commercially used.

in many jurisdictions on the American continents and elsewhere [19].

Designated EU Authority for Determination of GMO Status

The recent CJEU ruling in case C-528/16[ii] provides an indication as to how the scope of Directive 2001/18/EC should be interpreted in relation to mutagenesis. However, many questions regarding what exactly is covered by the EU GMO laws remain, in particular, for techniques that are not a form of mutagenesis. In order to cope with the fast-moving pace of innovation, societal developments, and the need for predictability of legal systems, a designated expert committee could be entrusted with a mandate to issue nonbinding recommendations on the various legal terminologies and to decide whether specific genetically altered organisms should be within the scope. This approach would be similar to the 'Am I regulated?' approach of the United States Department of Agriculture[v], which has offered nonbinding advice to applicants since 2011. The organization and mandate of such a designated expert committee needs to be designed in accordance with the requirements of EU law for the establishment of such bodies (as witnessed, e.g., by the *Meroni* doctrine) and has to make certain that the institutional balance within the EU is maintained. The composition of this expert group should be framed by EU law to ensure that the correct legal and scientific expertise is present and EU law is observed.

Conditions of Recital 17 of Directive 2001/18/EC

Recital 17 of Directive 2001/18/EC stipulates that: 'This Directive should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record.' The exemption currently applies to conventional, randomly-induced mutagenesis, however, it is not specified exactly what the requirement of a long safety record entails. The inclusion of Recital 17 demonstrates an early intention to shape a GMO regulatory framework that would evolve and take experience into account. We suggest implementation of a product-oriented approach when interpreting the requirement of a long safety record in Recital 17. This would resemble the practice of safety assessments, as safety assessments measure product-related features. It is not the mutagenesis technique itself that has a long safety record; it is the products that were introduced to the market or released into the environment after additional breeding and variety registration. Article 7 of Directive 2001/18/EC provides the possibility for differentiated (simplified) procedures for risk assessment and management whenever sufficient experience with a particular GMO has been gained [3]. However, to date, Article 7 has never been used, which underlines that the original intention of an evolving regulatory practice is not being followed and that Directive 2001/18 is interpreted in a static way. This makes a reform of the Directive particularly important.

In the next article, we continue discussing various details that may be reformed within the risk assessment and risk management procedures.

Author Contributions

D.E. took the initiative and prepared the first draft manuscript. All other coauthors contributed a section each to the manuscript and shared in the finalizing of the manuscript.

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Resources

[i]https://publications.europa.eu/en/publication-detail/-/publication/a9100d3c-4930-11e9-a8ed-01aa75ed71a1/language-en/format-PDF/source-94584603

[ii]http://curia.europa.eu/juris/documents.jsf?num=c-528/16

[iii]www.infogm.org/IMG/pdf/comeur_note-detection-nveaux-ogm_nov2018.pdf

[iv]http://rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2017/09/13/proposal-for-discussion/proposal-for-discussion.pdf

[v]www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated

[1]Department of Plant Breeding, Swedish University of Agricultural Sciences, 23053 Alnarp, Sweden

[2]Vlaams Instituut voor Biotechnologie, Ghent BE-9052, Belgium

[3]Division of Philosophy, KTH Royal Institute of Technology, 100 44 Stockholm, Sweden

[4]Department of Crop Production Ecology, Swedish University of Agricultural Sciences, Uppsala, Sweden

[5]Law Group, Department of Social Sciences, Wageningen University, 6706 KN Wageningen, The Netherlands

[6]Rotterdam Institute of Law and Economics, Law School, Erasmus University of Rotterdam, 3062 PA Rotterdam, The Netherlands

[7]Department of Agricultural Economics and Rural Development, University of Goettingen, 37073 Goettingen, Germany

[8]Research Division Agroecology and Environment, Agroscope, Reckenholzstrasse 191, 8046 Zurich, Switzerland

[9]Institute for Biosafety in Plant Biotechnology, Julius Kühn-Institut (JKI), 06484 Quedlinburg, Germany

[10]Institute of Technology–Theology–Natural Sciences at the Ludwig-Maximilians-Universität München, 80539 München, Germany

[11]Institute of Political Science, Heidelberg University, 69115 Heidelberg, Germany

[12]Heidelberg Center for the Environment, Heidelberg University, 69120 Heidelberg, Germany

[13]Plant Breeding, Wageningen University & Research, 6700AJ Wageningen, The Netherlands

@Twitter: @cultivision

*Correspondence:
dennis.eriksson@slu.se

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Stacked Bt Proteins Pose No New Risks to Nontarget Arthropods

Jörg Romeis[1,*] and Michael Meissle[1]

Concerns have been raised that multiple insecticidal proteins produced by genetically engineered (GE) crops may interact unexpectedly and pose new threats to biodiversity and nontarget organisms. We reviewed the literature to assess whether this concern is justified and whether the current regulatory framework needs to be adapted to address this concern.

GE crops producing insecticidal proteins from *Bacillus thuringiensis* (Bt) have been grown on millions of hectares worldwide for more than 20 years. Before the cultivation of any new GE plant, potential adverse effects on valued nontarget organisms are assessed. This nontarget risk assessment follows a tiered approach in which testing begins with laboratory studies under highly controlled conditions. High concentrations of the purified insecticidal proteins or GE plant tissue are fed to representative test species with the aim of creating worst-case exposure conditions. If adverse effects are detected or if unacceptable