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Gene-editing and plants & animals used in food production: some technical, socio-economic and legal aspects

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There has been much debate for several years now on new methods of genetic engineering that can be collectively termed “gene-editing”, and used for plants and animals in food production. As two recently published legal dossiers show, these techniques are definitely covered by EU Directive 2001/18. If the new techniques were to be exempted from regulation, all plants and animals derived from them could enter the market without risk assessment and labelling, thus undermining the protection goals of EU regulation.

Legal assessment

In a legal dossier published in September 2015[1], Professor Dr Ludwig Kraemer argues that gene-editing techniques, such as Oligonucleotide-Directed Mutagenesis (ODM) and CRISPR/Cas fall within the ambit of EU regulation, even if no additional DNA is inserted into the genome. According to the legal dossier, there are two basic categories of processes that are used to produce 'GMOs'. The first category includes those processes already in use and regarded as having a long and safe history of use when the EU Directive 2001/18 came into force - and which are, therefore, exempt. And the second category, which includes processes that were introduced at a later stage and are, therefore, regulated under the EU Directive. Thus, according to EU Directive 2001/18, random mutagenesis is regarded as resulting in a GMO that is exempt from the regulation, while applications of oligonucleotides and nucleases result in GMOs that are subject to regulation.

A second legal opinion published by the German Federal Agency for Nature Conservation (BfN), drawn up by Professor Dr. Tade Matthias Spranger, comes to a similar conclusion.[2] According to this analysis, gene-editing techniques are included in the non-exhaustive list of technologies that fall within the ambit of the Directive (Annex I A Part 1). In this regard, it does not matter if mutation occurs naturally. The relevant question is by which techniques the genetic changes were introduced. In this context, the list of exemptions (Annex I B) has to be interpreted narrowly. According to Spranger, the precautionary principle and the process-orientated approach to risk assessment as established under EU law can only be implemented if the new methods are covered by the Directive.

[1] www.testbiotech.org/node/1342
[2] http://bfn.de/fileadmin/BfN/agrogentechnik/Dokumente/Legal_analysis_of_genome_editing_technologies.pdf

In a document published in November 2015, the German Federal Office of Consumer Protection and Food Safety (BVL), considered the opinions of Krämer and Spranger. The German authority opines that it is both the process and product of genetic engineering that need to be considered in order to decide whether Directive 2001/18 applies.[3] This reflects the view expressed by some experts that a change in EU regulations is needed with regard to what they call the new plant breeding technologies (NPBTs):[4]

> " (…) it may be suggested that plants modified by crop genetic improvement technologies, including genetic modification, NPBTs or other future techniques, should be evaluated according to the new trait and the resulting end product rather than the technique used to create the new plant variety."

However, current legislation does not follow a product-based approach but instead applies a process-based approach to GMO regulation, which is fully justified in the light of the associated unintended and unpredictable effects, risks and uncertainties resulting from application of the new techniques.

Why gene-editing techniques have to be assessed

When applying genome-editing techniques, it is not necessary for DNA derived from another species to be inserted into the cells. Rather, the genome can be 'rewritten' directly in the cells. It is well known that this 'editing' can still lead to a wide range of off-target effects. These unintended effects might in some cases be the cause of risks and hazards. Therefore, there has to be case specific risk assessment. In this context, it is not decisive whether the new DNA is inserted into the cells or not. For example, parts of the DNA can also be removed (*knock-out*) or the activity of the natural genes can be changed by epigenetic effects intentionally or unintentionally. Thus, the application of gene-editing can lead to a wide range of uncertainties and risks that need to be assessed.

Further, with regard to regulatory aspects, it also has to be taken into account that the single steps meant to induce small changes can be applied several times in same organism. This can lead to much more extensive changes in the genome. Moreover, plants and animals showing single or several genetic changes can be crossed with each other. In addition, all the different techniques could possibly be used in combination. So, if the single steps are exempt from EU regulation then how can the final varieties of the modified organisms be assessed? These plants or animals might completely escape the scrutiny of the regulatory bodies.

To assess the actual risks it is necessary to know which techniques were applied for which purposes. The relevant data have to be collected systematically and assessed independently. If these techniques are exempted from regulation, the relevant data will be kept as confidential business information. In this case, independent scientists as well as the authorities will not be able to access the data in a way that will enable them to obtain a sufficient overview of the specific techniques, the relevant traits and the associated risks.

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[3] http://www.bvl.bund.de/SharedDocs/Downloads/06_Gentechnik/gentechnikrechtlichen%20Einordnung%20von%20neuen%20Pflanzen%C3%BCchtungstechniken.pdf;jsessionid=3612825C11C7DA181259CA35745C8EAE.2_cid332?__blob=publicationFile&v=5

[4] http://onlinelibrary.wiley.com/doi/10.1111/tpj.12413/full

What products can be expected and who is working on them?
Companies such as Dow AgroSciences, Bayer, BASF, Dupont/ Pioneer and Monsanto have all been active in filing patents in this field for some years. For example, Dow AgroSciences and Bayer are especially focussing on nucleases or 'gene scissors' (such as zincfinger, meganucleases, TALENS and CRISPR). Each of these companies has already filed one to two dozen patents, some of them jointly with specialised partners such as Sangamo or Cellectis.

As regards the patents, many applications concern the introduction of traits such as herbicide resistance, insecticide production and changes in oil quality, which are similar to those in genetically engineered plants already on the market. Several patent applications not only describe what can be inserted into the DNA, but also what parts of the DNA can be removed. For example, an application by Dow Agro Sciences aims to make plants more susceptible to herbicides.[5] This is not likely to be applied to crops in the field, but rather to native weed populations.[6] If such plants were to be genetically engineered this would create a whole new dimension of environmental risk.

There are applications being discussed for animals with the aim of producing a higher proportion of muscle in livestock or horn-free cattle[7]. This even includes genetically engineered insects to be used in agriculture that can introduce completely new DNA into native populations via gene drives[8].

Socio-economic impacts
Patent research shows that the big corporates will dominate the market for these new technologies, which will be protected by patents. These companies are expecting to gain far reaching control of food production through patented technology. Conversely, because the development is largely driven by patents it is unlikely that small and medium-sized enterprises (SMEs) in the breeding sector will benefit much since they mostly rely on the plant variety protection system, and cannot afford costly patents[9]. Indeed, it has to be expected that the new technology will simply promote further market concentration in this sector. It is also unlikely that under these conditions, the costs of the regulatory system will be a decisive limiting factor. In any case, these costs are currently unknown. It is likely that there will be specific guidance for the risk assessment of each technique.

Some conclusions
- Legal analysis shows that organisms derived from gene-editing must undergo risk assessment and labelling as required by EU regulation.
- There is a wide range of risks and uncertainties attached to these new techniques that justify case by case risk assessment.
- The application of the regulatory system is unlikely to hamper plant breeding or SMEs in this field which is driven by patents.

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[5]WO2009042164
[6] See also: http://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf
[7]See for example Tan, W., Carlson D.F., Lancto, C. A., Garbed, J.R., Webster, D.A., Hackett, P.B. (2013) Efficient nonmeiotic allele introgression in livestock using custom endonucleases, www.pnas.org/cgi/doi/10.1073/pnas.1310478110
[8]Gantz, V.M., & Bier E. (2015). The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. Science, 348(6233), 442-444. www.sciencemag.org/content/348/6233/442.short
[9]Louwaars N., Dons H., Overwalle G., Raven H., Arundel A., Eaton D., Nelis, A., 2009, Breeding Business, the future of plant breeding in the light of developments in patent rights and plant breeder's rights, University of Wageningen, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1720088