Impulse Paper

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Genome Editing in plants: proposal for a pragmatic handling of the topic within the current legal framework

The development of molecular biology techniques has been advancing rapidly in recent years. New methods, such as TALEN, zinc finger nucleases, and CRISPR-Cas9[1], enable the genome of organisms to be modified in an accurate and very specific manner. These modifications can eventually be indistinguishable from naturally occurring genetic changes or those that were introduced by conventional methods. Nevertheless, the desired results are obtained significantly faster than by traditional selection methods.

In basic research these new methods have already enabled considerable novel insights into diverse bioscientific and biomedical topics. The potential applications of these techniques, such as their usage in disease treatment, cannot currently be fully assessable, but gives cause to hope.

Genome editing might also serve as a promising tool for plant breeders and could be used to improve specific features of crops. Whether a plant that has undergone genome editing should be considered a genetically modified organism (GMO) and thus has to be governed by the "Gentechnikrecht" (*Law on the regulation of genetic engineering*) has not yet been decided upon, provoking uncertainty among scientists and breeders.

The fast development of genome editing techniques challenges state actors regarding the establishment of necessary regulations. The advantages, disadvantages and risks of these novel methods need to be carefully assessed in order to enable a responsible application of genome editing in plant science. A number of scientific actors already delivered statements about the assessment of Genome Editing at European or national levels.[2]
We here propose a way that allows exploiting the benefits of genome editing within the current regulations in Germany (and the EU).

Genome editing in plant science and breeding

Traditional plant breeding relies on randomly occurring or intentionally introduced mutations whose genomic positions are unknown. Selection methods are subsequently used to tell

[1] TALEN, transcription activator-like effector nucleases; ODM, oligonucleotid-directed mutagenesis; CRISPR-Cas9, Clustered Regularly Interspaced Short Palindromic Repeats – CRISPR-associated protein 9. For a survey of methods see http://www.epsoweb.org/file/2181.

[2] E. g. Position of the European Plant Science Organisation (EPSO) (see http://www.epsoweb.org/file/2147) or the joint Position of Deutsche Forschungsgemeinschaft (DFG), national academy Leopoldina and national academy of sc ience and engeneering acatech (see *http://www.leopoldina.org/uploads/tx_leopublication/2015-03-26_Ad-Hoc-Stellungnahme_Gruene_Gentechnik.pdf)*

apart desired modifications from numerous unwanted genetic changes. By contrast, genome editing allows the introduction of distinct mutations by precisely targeting a genomic position where the DNA is then cut and one of the following modifications is introduced:[3]

1. Under normal conditions, cells will repair the DNA break, which introduces a mutation (point mutation, short deletion or insertion) at that specific position (this will be termed **genome editing 1, GE-1**). A recently developed CRISPR-Cas9-based method additionally enables to mutate single nucleotides without cutting the DNA[4]. So far, this new technique has not been used in plants but there are, in principle, no obstacles to its application in plant breeding. Point mutations can also be introduced without first cutting the plant DNA by the ODM method, which uses short strands of nucleic acid to mutate the DNA. These and other molecular biology techniques causing similar genetic modifications, such as specific point mutations, short deletions or insertions, or simply methylate DNA molecules without changing the DNA[5] sequence are generally referred to as GE-1 here.

2. In cases where a piece of DNA is introduced that is almost identical to the original sequence, but contains individual changes to the base sequence, the cell uses this fragment as a template to close the DNA break. As a result, the newly introduced DNA is stably integrated into the host genome (**GE-2**).

3. Upon the introduction of a piece of DNA that contains the original sequence next to a longer DNA fragment (more than 20 base pairs) or a complete gene from a different organism, the cell can integrate this piece of DNA at the site of the DNA break in the course of the repair process (**GE-3**).

Plants that are produced by GE-1 and GE-2 techniques cannot be differentiated from those that are produced by traditional mutagenesis methods or arise from natural mutations. The latter occur frequently and drive evolution. Only longer DNA fragments that are introduced by GE-3 techniques can easily be detected with molecular biology methods such as PCR.

Assessment

The question if the new breeding methods produce GMOs according to the "Gentechnikgesetz" and if the resulting products are thus to be governed by the current "Gentechnikgesetz" cannot be answered generally. It is not crucial that these techniques involve man-made changes of genetic material. It rather needs to be assessed if the changes introduced by those methods could have also arisen in a natural way- see §3 "Gentechnikgesetz" (*Genetic Engineering Act*). Most of the novel breeding techniques, including the CRISPR-Cas9 system, can produce a GMO as well as a non-GMO depending on their actual application (see above).

The critical factor, on which this proposal is based, is the presence or absence of DNA fragments longer than 20 bp, or of complete genes, from different organisms in the plants that are produced by genome editing. The proposed assessment of GE-1 and GE-2

[3] For further information see: Sprink, T., Eriksson, D., Schiemann, J., Hartung, F. (2016): Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts. Plant Cell Reports, 35:1493-1506.

[4] Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR (2016): Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature, 533: 420-424.

[5] This can bei done with RNA-directed DNA methylation (RdDM).

techniques assumes that the resulting plant lineages do not contain any transgenes, which also applies to cases where transgenes are temporarily introduced for technical reasons but are later on removed, for example by outcrossing.

Recommendation
Based on the current legal framework we are proposing the following approach in handling the issue of genome editing in plant research:

- Plants that are produced by GE-1 and GE-2 genome editing techniques do not fall into the category as defined by §3.3 of the current "Gentechnikgesetz" which only categorizes those organisms as genetically modified whose 'genetic material was modified in a way which would not have happened under natural circumstances by crossing or natural recombination'.
- Regarding the safety of users, products that were created by GE-1 and GE-2 techniques are to be treated equally to those that have been produced by conventional breeding. They should thus be governed by the same regulations. This means that they do not have to be inspected under the "Gentechnikgesetz", but implies that placing them on the market has to conform with the "Lebensmittelbasisverordnung" (EG) #178/2002 (*General Food Law Regulation 178/2002*). In analogy to this, plants produced by GE-1 and GE-2 techniques should be treated like plants produced by conventional breeding when used in scientific field studies.
- Plant lineages produced by GE-3 genome editing methods are to be governed by the "Gentechnikgesetz".

The German Life Science Association (Verband Biologie, Biowissenschaften und Biomedizin in Deutschland - VBIO e. V.) and its associated specialist societies have high expectations for the application of genome editing in plant science and breeding. The VBIO and its associated specialist societies would thus very much welcome if the respective ministries and agencies supported our proposal presented here.

We are hoping for a prompt and differentiated clarification of the legal issue by the European Commission and ask you to support this mission in front of the commission. Please do not hesitate to contact us for any assistance in scientific matters.

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