

TESTBIOTECH Background 30 - 9 - 2020

Testbiotech comment on the Statement *„Towards a scientifically justified, differentiated regulation of genome edited plants in the EU“* published by the National Academy of Sciences (Leopoldina), German Research Foundation (DFG) and Union of the German Academies of Sciences and Humanities

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Biotechnology

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Summary

In 2019, the National Academy of Sciences (Leopoldina), the German Research Foundation (DFG) and the Union of the German Academies of Sciences and Humanities published a ‘Statement’ on genome editing, also known as new genomic techniques or new techniques of genetic engineering (New GE).

The authors of the ‘Statement’ claim that there are no specific risks associated with the application of genetic engineering in plant breeding and are demanding changes to EU GMO regulation. As a consequence, most genetically engineered organisms would no longer undergo mandatory risk assessment and approval process as requested by current EU regulation.

Institutions representing the highest scientific standards, such as Leopoldina and DFG, should carefully avoid any conflict of interest. However, several of the experts involved in the Statement have specific interests in patent applications in the field, and some also

have close affiliations with industry. The involvement of a substantial number of experts with vested interests in New GE applications undermines the credibility of the Statement. One gets the impression that highly regarded scientific institutions are at risk of being used as a platform for lobby groups.

Bias in composition of the experts group had a strong impact on the content of the Statement not being in accordance with the necessary scientific standards: instead of performing a detailed analysis of the differences between previous methods of GE and New GE, many assumptions are made which are not, or not sufficiently, based on science. In summary, the technical potentials and the risks of New GE are far more complex than presented in the Statement.

As shown in several more recent publications, the need for detailed risk assessment cannot be limited to organisms with additionally inserted gene sequences. Without strict regulation of New GE, the uncontrolled release of large numbers of organisms has to be expected with biological characteristics not developed gradually through evolution. This would result in the substantial likelihood of damage to ecosystems, agriculture, forestry and food production.

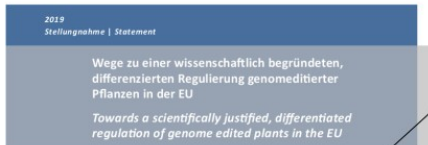
The Statement and the experts involved

In 2019, the National Academy of Sciences (Leopoldina), the German Research Foundation (DFG) and the Union of German Academies of Science and Humanities published a 'Statement' on genome editing, also known as new genomic technologies or new techniques of genetic engineering (New GE).

The Statement can be divided into two main parts: a short text on the technical characteristics of New GE processes and a longer text on political and regulatory aspects, including a call for the deregulation of most of the current New GE applications. These demands are very similar to those raised by industry and lobby groups active in this field.

Testbiotech has therefore looked at the list of experts involved (see Figure) in the Statement and found that experts on environmental risks are largely underrepresented. Furthermore, at least five of the experts in the working group have their own vested interests in applications of New GE. These experts are known for filing patent applications in the field and / or having close affiliations with industry: Ralph Bock (several patent applications, affiliated to the biotech company Plastomics), Bernd Müller-Röber (many patent applications, also in collaboration with Bayer), Holger Puchta (patent applications in collaboration with BASF), Detlef Weigel (many patent applications, consulting with industry, member of Scientific Board of Computomics, a company offering services to the seed industry) and Ernst-Ludwig Winnacker (long time affiliation with the Bayer corporation).

Members of the working group of Leopoldina: Experts for environmental risk assessment are underrepresented



Experts with patent applications in the field of genetic engineering and / or affiliations to companies such as Bayer and BASF

Mitglieder der Arbeitsgruppe

Prof. Dr. Regina Birner	Hans-Ruthenberg-Institut, Universität Hohenheim, Bioökonomierat
Prof. Dr. Ralph Bock	Max-Planck-Institut für Molekulare Pflanzenphysiologie, Potsdam-Golm, DFG-Senatskommission Grundsatzfragen der Genforschung
Prof. Dr. Hans-Georg Dederer	Juristische Fakultät, Universität Passau, DFG-Senatskommission Grundsatzfragen der Genforschung
Prof. Dr. Bärbel Friedrich	Nationale Akademie der Wissenschaften Leopoldina
Dr. Johannes Fritsch	Nationale Akademie der Wissenschaften Leopoldina
Prof. Dr. Bernd Müller-Röber	Lehrstuhl für Molekularbiologie, Universität Potsdam
Prof. Dr. Holger Puchta	Botanisches Institut, Karlsruher Institut für Technologie, Karlsruhe
Prof. Dr. Martin Qaim	Department für Agrarökonomie und Rurale Entwicklung, Georg-August-Universität Göttingen
Prof. Dr. Chris-Carolin Schön	Wissenschaftszentrum Weihenstephan für Ernährung, Landnutzung und Umwelt, Technische Universität München
Prof. Dr. Klaus Tanner	Theologische Fakultät, Universität Heidelberg
Prof. Dr. Jochem Taupitz	Juristische Fakultät, Universität Mannheim
Prof. Dr. Jörg Vogel	Institut für Molekulare Infektionsbiologie, Julius-Maximilians-Universität Würzburg
Prof. Dr. Detlef Weigel	Max-Planck-Institut für Entwicklungsbiologie, Tübingen
Dr. Ralf Wilhelm	Institut für die Sicherheit biotechnologischer Verfahren bei Pflanzen, Julius Kühn-Institut, Quedlinburg
Prof. Dr. Ernst-Ludwig Winnacker	Genzentrum der Ludwig-Maximilians-Universität München

See also: www.testbiotech.org/content/vertrauen-in-die-wissenschaft

These findings raise substantial questions in regard to the independence of the members of the working group. Whatever the case, the involvement of a substantial number of experts with vested interests in the application of New GE undermines the credibility of the Statement. Testbiotech believes that institutions representing the highest scientific standards, such as Leopoldina and DFG, should carefully avoid any conflict of interest. Otherwise, these highly acknowledged scientific institutions are at risk of being used as a platform for lobby groups.

Lack of rigorous scientific analysis

Taking a closer look at the published Statement, there is an evident lack of necessary due diligence in presenting the new technical potentials and risks of New GE. The Statement misses out sufficient explanation of the new technical potentials opened up by New GE, which go beyond conventional breeding and previous methods of genetic engineering.

These technical characteristics are highly relevant for the discussion on the risks of new GE organisms: In contrast to chemical or physical mutagens, tools such as CRISPR/Cas, can directly interact with the biological mechanisms on the level of the genome by circumventing natural mechanisms of gene regulation and genome organisation. Several

cytogenetic factors (mechanisms of gene regulation) are known to impact the mutation rates such as histone modifications, chromatin accessibility, distancing of coding sequences from mutational hotspots as well as specific repair mechanisms (see, for example, He et al., 2017; Belfield et al., 2019; Kawall 2019). These factors emerged during evolution and can, for example, protect specific genomic regions against too frequent mutations. The underlying mechanisms and processes will impact the outcome of physico-chemical mutagenesis as well as other method of traditional breeding. New GE is designed to circumvent these mechanisms. In particular, the nuclease CRISPR/Cas for the first time makes the whole genome available for technical interventions and alterations (Kawall 2019). Organisms generated by these methods can have profoundly changed genomes even if no additional genes are inserted.

New GE can enable changes in the biological characteristics of plants without introducing any additional DNA sequences. These changes can exceed the range of characteristics developed gradually through evolution or previous breeding methods. Therefore, the risks associated with the release or usage of the genetically engineered organisms for food production need to be examined thoroughly. For example, changes in the plant composition can also impact plant interactions with the environment (such as pollinators, wild life species and soil organisms). If, within short periods of time, a large number of these New GE organisms are released, they may become disruptive to ecosystems and severely endanger biological diversity (for overview see Testbiotech 2020).

There are further risks besides the intended new biological characteristics; a wide range of specific unintended effects has been observed in New GE experiments. These effects arise, for example, from the multi-step process of genetic intervention, which in many cases also implies the use of 'Old GE' methods. There are further causes of unintended effects such as the lack of precision of the CRISPR/Cas gene scissors. There have been reports of rearrangements of the genome, including the unintended insertion of additional genes. In many cases, the genome is unintentionally cut in regions which are similar to those of the target DNA, i.e. mistakenly cut by the gene scissors. These unintended effects can be significantly different from those arising from conventional breeding. Therefore, all the effects caused by the multi-step process of New GE have to be taken into account in risk assessment (for overview, see Kawall et al., 2020; Testbiotech 2020).

In summary, there are some major and very basic deficiencies in regard to the scientific standards of the Statement. To exemplify these deficiencies, Testbiotech has selected some passages from the summary of the Statement and commented in the Table below.

Table: Selected findings and assumptions from the Statement (see ‘summary and recommendations’) and Testbiotech comments

Assumptions made in the Statement	Testbiotech comment
<p><i>In contrast to traditional breeding methods, genome editing methods enable directed, cost and time-saving modifications (mutations) of the genome of crops which are often indistinguishable from naturally occurring mutations.</i></p>	<p>(1) We agree that the method of genome editing differs from traditional breeding methods. However, these differences are not explored in the Statement. This is a major deficiency, e.g. as shown by Kawall et al. (2020); these differences are highly relevant for the risk assessment of the resulting organisms.</p> <p>(2) To check this claim, we examined the list of New GE organisms published in the USDA’s Animal and Plant Health Inspection Service (APHIS)¹. We were unable to find any indication that these organisms would not be distinguishable. On the contrary, e.g. Duensing et al. (2019) point out that in most cases, plants derived from New GE can be distinguished by their genotype. Furthermore, Chhalliyil et al. (2020) showed that even minor changes in the genome can be used to identify the relevant products.</p>
<p><i>The blanket legal classification as a GMO therefore fails to consider the type of genetic modification present in the genome edited organism, and whether this modification could have occurred accidentally or through traditional breeding methods.</i></p>	<p>The Statement mixes up facts (such as the processes used to produce New GE organisms) with speculation (such as accidental occurrence of specific organisms). Such speculation would severely undermine the scientific basis for risk assessment in the EU. From a scientific point of view, there is no alternative to starting with the technical process in order to enable sufficiently reliable risk assessment of GE organisms.</p>
<p><i>It also disregards whether the origin of the genetic modification can be identified and attributed to a particular breeding method.</i></p>	<p>The Statement confuses the relevant regulatory details. EU regulation requests a method of identification of specific products (such as those presented by Chhalliyil et al., 2020). However, these methods do not always allow the identification of the process used to develop the organism. Therefore, the method used to produce the GE organism has to be described in the dossier filed for approval.</p>
<p><i>Potential risks can only emanate from the modified traits of the organism as a product of the breeding process, and not from the process itself.</i></p>	<p>This claim is factually wrong. No matter whether transgenesis or New GE is applied, the process used for generating the organism is highly relevant for risk assessment (see, for example, Kawall et al., 2020; Eckerstorfer et al., 2019).</p>
<p><i>The products of random mutagenesis breeding using high-energy radiation or mutagenic chemicals have been classified by the European legislator as ‘safe’ GMOs for decades and are therefore exempt from GMO regulation. This is in line with the consistent</i></p>	<p>The Statement fails to explain the fundamental differences between breeding and genetic engineering:</p> <p>(1) methods using physico-chemical mutagens</p>

¹ [www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated Article Letters of Inquiry](http://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated%20Article%20Letters%20of%20Inquiry)

<p><i>application of the precautionary principle, under due consideration of opportunities as well as risks. Likewise, even after almost 30 years of worldwide utilisation of transgenic crops produced using conventional genetic engineering in agriculture, no risks inherent to the technology could be detected for humans, nature or the environment.</i></p>	<p>(which are often summarised as ‘random mutagenesis’) are fundamentally different from biotechnological methods (using biological mutagens such as CRISPR/Cas): New GE can directly introduce new traits into plants and organisms by circumventing the mechanisms and processes which naturally shape the pattern of mutations in plants and animals. Several cytogenetic factors, e.g. histone modifications, chromatin accessibility, distancing of coding sequences from mutational hotspots and certain repair mechanisms are all known to impact the mutation rates. These mechanisms of gene regulation will impact the outcome of physico-chemical mutagenesis as well as of any other method of traditional breeding (see, for example, He et al., 2017; Belfield et al., 2019; Kawall 2019). However, New GE makes the whole genome accessible for genetic changes (Kawall, 2019), generating organisms with biological characteristics and risks that go beyond methods used in conventional breeding (Testbiotech 2020). Therefore, organisms derived from New GE always have to undergo mandatory risk assessment.</p> <p>(2) It is factually wrong that no risks inherent to the GE technology have been detected for people, nature or the environment. Indeed, many risks are known to be inherent in the method of genetic engineering and are routinely assessed by the European Food Safety Authority (EFSA). These risks concern the molecular level as well as plant composition and phenotype.</p>
<p><i>For example, the GMO definition or the associated exemptions should be revised in order to exclude genome edited organisms from the scope of application of genetic engineering law if they do not contain foreign genetic information and/or if they contain a combination of genetic information which may also arise naturally or through traditional breeding methods.</i></p>	<p>Organisms generated through New GE may contain pervasive changes in their genomes, including in cases where no additional genes are inserted. Therefore, the need for detailed risk assessment cannot be limited to organisms with additionally inserted gene sequences.</p> <p>Deregulation as proposed in the Statement is likely to result in the uncontrolled release of large numbers of organisms with biological characteristics that have not adapted through evolution. Consequently, there is a high likelihood of damage to ecosystems, agriculture, forestry and food production.</p>

Consequences of insufficient regulation

If the recommendations presented in the Statement were to be turned into political decision-making, this would lead to the emergence of problems similar to those known from the US: already around 80 New GE organisms have been exempted from regulation by the US FDA.² At the same time, there is no access to detailed data about the process and target of the genetic intervention used in those cases. The necessary information for monitoring, control and independent risk assessment are not available.

It has to be kept in mind that without sufficient regulation of New GE

- severe damage to biological diversity is likely;
- risks to food production may be introduced and accumulate unnoticed;
- access to data needed for risk assessment by independent experts will not be made available;
- no measures can be taken against the uncontrolled spread of the organisms in the environment;
- no data will be available to track and trace the New GE organisms and products derived thereof;
- agriculture and food production relying on GE free sources can no longer be protected.

Conclusion

Organisms generated by New GE may contain pervasive changes to their genomes even if no additional genes are inserted. Therefore, the need for detailed risk assessment cannot be limited to organisms with additionally inserted gene sequences. As a result, detailed examination of all organisms derived from New GE has to be mandatory and has to start with the specific process used to generate the organisms.

Without strict regulation of New GE, the uncontrolled release of large numbers of organisms with biological characteristics not arising from evolution can be expected. This would result in the substantial likelihood of damage to ecosystems, agriculture, forestry and food production.

² [www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated Article Letters of Inquiry](http://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated%20Article%20Letters%20of%20Inquiry)

References

- Belfield, E.J., Ding, Z.J., Jamieson, F.J.C., Visscher, A.M., Zheng, S.J., Mithani, A., Harberd, N.P. (2018) DNA mismatch repair preferentially protects genes from mutation. *Genome Research*, 28(1): 66-74. <https://genome.cshlp.org/content/28/1/66.short>
- Chhalliyil, P., Ilves, H., Kazakov, S.A., Howard, S.J., Johnston, B.H., Fagan, J. (2020) A real-time quantitative PCR method specific for detection and quantification of the first commercialized genome-edited plant. *Foods*, 9(9): 1245. <https://doi.org/10.3390/foods9091245>
- Duensing, N., Sprink, T., Parrott, W.A., Fedorova, M., Lema, M.A., Wolt, J.D., Bartsch, D. (2018) Novel features and Considerations for ERA and Regulation of Crops Produced by Genome Editing. *Frontiers in Bioengineering and Biotechnology*, 6: 79. <https://doi.org/10.3389/fbioe.2018.00079>
- Eckerstorfer, M.F., Dolezel, M., Heissenberger, A., Miklau, M., Reichenbecher, W., Steinbrecher, R.A., Wassmann, F. (2019) An EU perspective on biosafety considerations for plants developed by genome editing and other new genetic modification techniques (nGMs). *Frontiers in Bioengineering and Biotechnology*, 7: 31. <https://doi.org/10.3389/fbioe.2019.00031>
- He, Y., Wang M., Dukowic-Schulze, S., Zhou A., Tiang, C.L. Shilo, S., Sidhu, G.K., Eichten, S., Bradbury, P., Springer, N.M., Buckler, E.S., Levy, A.A., Sun, Q., Pillardy, J., Kianian, P.M.A. Kianian, S.F., Chen, C., Pawlowski, W.P. (2017) Genomic features shaping the landscape of meiotic double-strand-break hotspots in maize. *PNAS*, 114(46): 12231-12236. www.pnas.org/cgi/doi/10.1073/pnas.1713225114
- Kawall, K. (2019) New possibilities on the horizon: genome editing makes the whole genome accessible for changes. *Frontiers in Plant Science*, 10: 525. <https://doi.org/10.3389/fpls.2019.00525>
- Kawall, K., Cotter, J., Then, C. (2020) Broadening the GMO risk assessment in the EU for genome editing technologies in agriculture. *Environmental Sciences Europe*, 32(1): 1-24. <https://doi.org/10.1186/s12302-020-00361-2>
- Nationale Akademie der Wissenschaften Leopoldina, Deutsche Forschungsgemeinschaft und Union der deutschen Akademien der Wissenschaften (2019) Wege zu einer wissenschaftlich begründeten, differenzierten Regulierung genomeditierter Pflanzen in der EU / Towards a scientifically justified, differentiated regulation of genome edited plants in the EU. Halle (Saale). www.leopoldina.org/publikationen/detailansicht/publication/wege-zu-einer-wissenschaftlich-begruendeten-differenzierten-regulierung-genomeditierter-pflanzen-in/
- Testbiotech (2020) Overview of genome editing applications using SDN-1 and SDN-2 in regard to EU regulatory issues. www.testbiotech.org/node/2569