Statement

European Plant Science Organisation
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On the EC study on New Genomic Techniques (NGTs)

Brussels, 27.5.2020

Summary

The European Plant Science Organisation (EPSO) welcomes the ongoing European Commission (EC) study on new genomic techniques (NGTs). These are defined as techniques capable of changing the genetic material of an organism, which have emerged or have been developed since 2001. In this statement, EPSO refers specifically to genome editing leading via mutagenesis (point mutations or other modifications existing in nature) in plants and products obtained thereby.

EPSO members remarked that the implementation of **GMO legislation with regard to NGTs** did not cause any major technical obstacles, but represents a major administrative and financial burden, leads to increasing space constraints in GMO facilities, drastically reduces the number of field experiments, causes problems with the status of incoming germplasm, and has a negative impact on funding and on bringing products to the market.

Despite these constraints, fundamental and applied **research on NGTs** and **NGT products** is still blooming in Europe and concerns over 50 plant species. Although the ECJ ruling of 2018 led to widespread demotivation and reduced funding, efforts continue to increase the range of species and of genotypes in which NGTs can be applied, to further enrich the binding and/or cutting features of Cas9-like enzymes, and to generate the knowledge needed to improve traits by NGTs. A research gap exists in the comparison of NGTs to older techniques with a history of safe use.

NGTs and **NGT products** present numerous **benefits and opportunities** since they are a tool of choice to address major challenges to agriculture in Europe and worldwide, such as the overuse of pesticides and inputs, climate change, crop monocultures, and the desire for improved food and feed. NGTs can contribute to meeting and managing these challenges by enhancing genetic progress towards more diverse, better adapted, and yet high-yielding plant varieties.

EPSO did not note any specific **concerns on NGTs** or **NGT products** but identified obvious **challenges**. The detection of NGTs in foreign germplasm and products is not feasible, SMEs are not able to play a notable role due to the high cost of licence fees and of regulatory approval, and patents on NGTs and NGT traits raise questions on access to NGT technology and its coexistence with plant variety rights. **Safety concerns** should not differ from those relevant to plants obtained using methods with a history of safe use, because NGT mutations could also arise in nature or during conventional breeding programs. Off-target events can easily be reduced to a level similar to that of

spontaneous mutations occurring during natural plant reproduction in conventional breeding.

The real question on **ethical aspects** is not whether NGTs or NGT products as such are acceptable, but whether the use we make of them supports commonly accepted values and avoids harm to humans and the environment. It would be ethically problematic to reject NGTs having beneficial traits, provided they are not considered to pose a higher risk to humans or the environment than similar varieties developed by conventional methods.

With regard to **consumers' right for information** and **freedom of choice**, EPSO is opposed to obligatory labelling because it implies that NGT products as such are harmful or problematic, could not be enforced, and would lead to both labelling and non-labelling of identical products. Voluntary labelling has the advantage of giving voice to different types of values, maintaining information levels equal to all actors, and taking into account various lifestyle choices.

NGTs and NGT-products have a role to play in the European **Farm-to-Fork** strategy by ensuring sustainable food production and the shift to healthy, sustainable diets, for example through disease resistant crops, reducing pesticide use, and allergen-free food that promotes human health. They can also contribute to implement the European **Biodiversity** strategy by improving the performance and nutritional content of underutilised fruit, vegetable and cereal crops and thereby substantially increase diversity of cultivated crops.

Context

Upon request by the Council of the European Union, the European Commission (DG Health and Food Safety) is presently carrying out a study on new genomic techniques (NGTs), which will have to be delivered by 30 April 2021. This study regarding the status of NGTs (= techniques capable to change the genetic material of an organism and that have emerged or have been developed since 2001) under Union law will be crucial for the future of genome editing in Europe. It will have to (i) draw a picture of the status of NGTs after the Court of Justice's judgment in case C-528/16 and (ii) come up with a proposal, if appropriate in view of the outcomes of the study[1]. One of many possible outcomes would be a proposal to alleviate the present legislation on certain genome editing techniques.

In the framework of this study, the European Commission carried out targeted consultations with Member States and EU-level stakeholders (including EPSO) to gather information on different aspects of NGTs. The EPSO contribution[2] to the 7 themes has been submitted on 13 May 2020 and is summarized hereafter. In this statement, the terms NGTs and NGT-products are limited to plants and derived food and feed products obtained by genome editing leading to mutagenesis (point mutations or other modifications existing in nature) for agri-food and industrial applications and for research, unless otherwise specified.

1-Implementation and enforcement of the GMO legislation with regard to NGTs

Public European research is very active in the NGT field to (i) enhance the efficiency and specificity of NGTs and broaden their field of application, (ii) use NGT-plants in fundamental research to decipher biological processes and (iii) develop NGT-crops with improved agricultural performance or product quality.

Due to the longstanding experience with GMO legislation, its application to NGT-plants produced by European researchers did not present major technical obstacles. However, its implementation has several drawbacks that hinder full exploitation of NGTs. They include (i) the application of GMO regulation represents an extraordinary administrative and financial burden, (ii) the massive use of NGTs leads to increasing space constraints in facilities fulfilling GMO requirements, (iii) there is a strong reluctance to perform field trials despite a strong scientific interest to confirm results obtained in confinement under agricultural conditions, (iv) researchers used to work freely with EMS or transposon-induced mutants lack experience with GMO legislation and are bridled in their ambition and (v) in some countries the application of GMO legislation to NGT-plants had a negative impact on funding of public research in the NGT field.

With regard to incoming NGT-plants or NGT-products, GMO legislation can readily be applied if the genome modifications are known, which is the case, for example, in international scientific collaborations. However, in the absence of prior knowledge on the potential genome alterations their detection and identification does not seem to be feasible by PCR-based detection methods[3]. Often suggested as the ultimate tool, whole genome DNA sequencing actually allows under certain conditions the near-exhaustive detection of unknown DNA modifications in a plant genome. However, the detection of a sequence alteration does not permit the identification of the process that generated it and to decide whether GMO legislation needs to be applied or not[4]. Indeed, identical DNA alteration may be obtained by NGTs or by conventional breeding or random mutagenesis techniques, which are exempted from GMO legislation.

GMO legislation has a strong negative impact on the number of field trials involving NGT-plants carried out in Europe. The number of 5 past or present trials and 3 foreseen projects is approximately 50-fold lower than the number of research projects in confined environments. There is also a more than 10-fold difference between Europe and the rest of the world, China and the USA carrying out the vast majority of field trials[5]. This is fundamentally different from research with mutants obtained by techniques with a safe history of use, which are frequently analysed under field conditions, or research in conventional breeding, which is essentially carried out under field conditions.

2-Research on NGTs/NGT-products

Among NGTs, genome editing techniques leading to mutagenesis (point mutations or other modifications existing in nature) are the almost exclusive focus of research efforts. Since its development in the last 10-15 years, genome editing spread very quickly in all fields of plant research and is nowadays a routinely used tool in 45 plant genera belonging to 24 botanical families for plant researchers worldwide[6]. (Shan et al., 2020). In particular, CRISPR/Cas9 based applications in plant science grew exponentially since their discovery in 2012, representing 78% of the 1328 studies reported in 555 publications reviewed in 2019[7]. Among the 51 genome-edited plant species, more studies were devoted to the model species rice (35.0%), Arabidopsis (16.4%) and tobacco (8.1%) than to crops such as tomato (6.3%), maize (5.8%), wheat (4.7%) or soybean (4.0%). This reflects both the intense daily use of genome editing in fundamental research and a growing effort in applied research.

European research is still competitive with 15% of the published studies[7] and a recent survey in France documented active research on 38 species of microalgae and higher plants. Two European research programs have been funded by EU H2020 grants to apply genome editing to chicory (CHIC, 7.3 M€) and tobacco (NEWCOTIANA, 7.2 M€) for health benefits and industrial uses. In addition, there have been several major national funding initiatives providing support for research not only on models and major crops but also on minor crops with local or regional importance such as olive, apple, cherry, strawberry, basil, eggplant, artichoke or rose. The goals of the applied research programs concern (i) agronomic value characteristics such as biomass, architecture, flowering time or fruit shape, (ii) disease resistance to fungi, bacteria and viruses, (iii) resilience to abiotic stresses such as drought, high/low temperature or heavy metals and (iv) food and feed quality, for example balanced oil composition, low allergen content or enhanced vitamin content.

The 2018 ECJ ruling had a major negative impact on this flourishing research. A substantial number of European public researchers reported overall demotivation and a direct or indirect effect on the funding of research involving NGTs or NGT-products. An example for direct effects are 5 international consortia that were declared ineligible for the SusCrop ERA-Net Cofund Action under H2020 because of planned confined NGT work. European researchers now tend to avoid participation in big collaborative applied projects that would require the intentional release of NGT-plants for proof of concept in the field. Indirect funding restrictions are caused by demotivation of industrial partners who are not interested to invest in projects without the later possibility to use the product in the EU. Even fundamental research is concerned, since research grant applications are not only judged for their scientific excellence but also their socio-economic impact, which certain reviewers now consider as not credible. Altogether, in particular applied research using NGTs is clearly handicapped in the EU compared to other countries in Asia and South- and North-America that handle NGTs more flexibly.

A number of needs and gaps were identified regarding NGT-related research. An urgent need is to increase the efficiency of transformation and regeneration to increase the range of species and of genotypes within species in which NGTs can be applied[8 9]. In addition, the number and type of addressable target sequences in a given genome needs to be enhanced, for example by further enrichment of the family of Cas9-like enzymes that possess different binding and/or cutting features (i.e. different PAM sequences)[10]. Most importantly, there is a continued need to generate the upfront knowledge necessary to improve traits by NGTs. There is also a large need to improve research/society interactions, so that research can take on board society's expectations and fears, both from technical and ethical point of views. In addition to these research needs, an identified research gap is the comparison of NGTs to older techniques with a history of safe use (e.g. chemical mutagenesis, in vitro propagation, conventional breeding) with regard to large deletions, inversions and other genome modifications. Such a comparison would undoubtedly help to put an end to current suppositions and to assess the safety of NGTs on a scientific basis.

3-Potential benefits and opportunities of NGTs/NGT-products:

NGTs are a lever to address challenges to agriculture in Europe and worldwide, such as the overuse of pesticides and inputs, climate change, crop monocultures or the desire for improved human food. NGTs can contribute to meeting and managing these challenges by enhancing genetic progress towards more diverse, better adapted and yet high yielding plant varieties[7,11,12].

To reduce pesticide use, novel disease resistance traits can be introduced into crop varieties by inactivation of susceptibility genes, activation of silent resistance genes by promoter editing or copying active alleles. To mitigate climate change impact, NGTs allow to adapt the length of the life cycle by mutations in flowering genes or to improve stress tolerance to drought, high temperature, cold, salinity, flooding by acting on transport or hormone genes[13]. To contribute to global food security, higher yields can be achieved by knocking out genes with negative effects on grain number, size, weight, panicle size or tiller number[14]. To increase cultured biodiversity the domestication of forgotten crops or wild relatives can be accelerated by the simultaneous modification of known domestication genes[15,16]. In addition to such contributions to a sustainable and yet productive agriculture, NGTs can be used to satisfy consumers' demands by alleviating health problems through knockout of allergen genes or increased contents in vitamins or other health promoting compounds[17,18]. Finally, NGT can ease the transition to a bio-sourced industry, for example by modifying starch products, and reduce pollution, for example by modifying lignocellulosic material[19].

One major advantage of NGTs in comparison to other genetic tools is to obtain a desired plant variety in a much shorter time frame. This concerns the introgression of resilience traits from wild relatives just like the breeding for elite traits in wild species with high nutritional potential, and is particularly important in breeding of perennials with generation times of several years, such as forest and fruit trees or grapevine. In addition, the replacement of recurrent backcrosses or breeding cycles by NGTs makes the process more precise since they assure that the modifications at a genetic locus are not subject to dragging linkage to unfavorable genes. A second advantage is even more specific to NGTs, which permit to markedly improve vegetative propagated varieties, which are less or not amenable to conventional breeding, since the desired traits are linked to specific clones and generally lost during sexual crosses. Finally, NGTs allow to enlarge the available gene pool beyond the species of interest by copying interesting alleles from other plant species. For example, nucleotide changes providing viral disease resistance in pepper have been successfully copied into the same gene of Arabidopsis, cucumber and tomato[20].

4-Potential challenges and concerns on NGTs/NGT-products:

EPSO feels that NGTs/NGT-products do not raise any specific concerns, since NGTs produce the same result (plant) as conventional breeding or mutation-induced breeding. If there are concerns, they should be similar to the ones for conventional breeding methods with a history of safe use and similar rules should be applied.

A first challenge concerns traceability and detection. As pointed out above, it is not feasible to detect trace amounts of unknown genome modifications and, more importantly, it is impossible to prove that the variation is synthetic and generated by NGTs and not induced/selected in natural variation. This will clearly become a challenge in the next decade for our breeding activities if NGTs are implemented without publicly available description of the modifications in some countries and not others. As we expect quite a large number of NGT-traits without the necessity to trace them back (according to the regulation in countries like China, the US or South and Latin America) the enforcement of the EU regulation will be a big challenge.

A second challenge concerns SMEs, despite the fact that the development of NGTs has been marked by a strong involvement of SMEs, which are also very present in the development of NGT-products. This potential is threatened by the cost of licence fees to access the technology and the cost of regulatory approval in the countries where NGT-products fall under GMO legislation. Whereas a look at the history of licensing patents on earlier foundational technologies such as recombinant DNA, small interfering RNA and PCR suggests that there is room for hope of reasonable arrangements on the licence issue, the cost of regulatory approval and stewardship presents an almost insurmountable financial effort for SMEs/small scale operators. Obligatory labelling of NGT-products would be an additional burden for efficient marketing. Although SMEs have been shown to quickly surpass multinational companies in the number of applications for NGT development in Argentina, where NGTs and NGT-products are exempted from GMO legislation[21], the scenario in Europe is likely to be the opposite. Present GMO legislation of NGT-products therefore deprives such consumers and bio-industries from the benefits of NGT-products.

A last challenge to a large and rapid application of NGTs are patents. Firstly, NGTs are patented and access to the technology at reasonable conditions is a challenge for EPSO members, as soon as they go beyond basic research and wish to provide services or to translate academic research into new plant varieties. The patent situation is further complicated by the arrival of new variants of genome editing technology not covered by the current licence package proposed for CRISPR/Cas9 applications in agriculture. In any case, EPSO considers that the general benefits for society resulting from NGT-use need to be considered by patent holders in licence negotiations. Secondly, traits present in NGT-plants can also be patented in Europe. Although mechanisms exist to deal with the coexistence of patent and plant variety rights, they may be difficult to handle at a large scale and the infringement difficult to prove. Systematic patenting, especially in minor crops, would likely be counterproductive to rapid and widespread use of the benefits of NGT-products. In conclusion, most EPSO members prefer a simple protection by plant variety rights as for natural mutants and conventional products, but remain open to parsimonious patenting of NGT-traits, keeping in mind the widespread use of patenting in other parts of the world.

5-Safety of NGTs/NGT-products:

When NGTs are used to introduce mutations that could also arise in nature or during conventional breeding programs, safety concerns should not differ from those which apply to plants obtained using methods that have a history of safe use[22,23].

While it is clear that any new trait can have some associated risk, any trait depends on the presence of specific sequences, or on epigenetic changes. Thus, if the range of variation obtained by a specific NGT is the same as the one potentially obtainable using traditional techniques, that specific NGT is not expected to lead to the introduction of phenotypes associated with additional risks.

Off-target effects are frequently cited as an argument to question the safety of NGTs/NGT-products. Intended off-target events can easily be avoided by state-of-the art design of genome editing tools if the genome sequence to be modified is available, either by excluding such sites from the design or by checking for absence of modifications at the expected off-target sites. With regard to unintended off-target effects, there is consensus among plant scientists that there is no evidence for bona fide off-target mutations even in the case of continued expression of Cas9 or Cpf1[24].Thus, off-target events can be drastically reduced to a level similar to that of spontaneous mutations occurring during natural plant reproduction in conventional breeding.

6-Ethical aspects of NGTs/NGT-products:

Questions related to food production have a profound ethical basis related to the right to food as an essential component to the right to life and dignity. The goals of food security, food safety and sustainability are first priorities and guiding principles to which any technology in agriculture must adhere[25]. NGTs, as any other technology, may be useful to achieve "Zero hunger" and other Sustainable Development Goals of the Unites Nations. In this sense the ethical question of a proportionate risk assessment may be balanced by the risk of refusing to apply promising new developments.

The Danish Council on Ethics replies to the question of whether it is ethical to withhold the benefits of a technology from the European farmer, consumer and citizen, that it would be ethically problematic to reject NGTs with beneficial traits provided they are not assessed as posing a higher risk to humans or the environment than similar varieties developed by conventional methods[26].

With regard to ethical concerns raised about GM crops and extended to NGTs, EPSO considers that (i) there is no specific potential harm to human health since NGT-plants are indistinguishable from mutants obtained by methods considered to have a safe history of use and are produced by methods that are less invasive than classical transgenesis shown to have no negative impact on mammalian health[27,28], (ii) there is no intrinsic potential damage to the environment, since NGT-plants are indistinguishable from "natural" mutants and therefore should not be subject to specific evaluations beyond the UPOV certification of conventional varieties, (iii) there is no technical reason that would prevent NGT-crops to be cultured in traditional or non-conventional farming systems[29], (iv) there is no technical barrier hindering the democratisation of NGTs and high potential to avoid excessive corporate dominance, as demonstrated by the predominant implication of SMEs and public actors in Argentina over the last 4 years[21] and (v) there is a sharp contrast between the alleged unnaturalness of NGT-crops and scientific data showing that major genome rearrangements are part of an ongoing evolutionary process[30], that not only sequence polymorphisms but also structural differences (large deletions, insertions and inversions) exist naturally between crop varieties of the same species[31], and that horizontal gene transfer between species concerns "natural" crop varieties[32].

Ethics generally relate more to the application of a technology rather than to its nature[33]. The real question is not whether genome editing as such is acceptable, but whether the use we make of it supports commonly admitted values and avoids harm to humans and the environment. Another important consideration is that many of the plant varieties obtained by NGTs are not different from identical products obtained by techniques with a history of safe use. Whereas there are ideological arguments to reject them due to their origin, there is no factual basis allowing specific regulations to discriminate between them.

7-Consumers' right for information/freedom of choice:

Consumers need to be informed in order to be able to exercise their freedom of choice and labelling is one of the possibilities to provide this information. According to our members, labelling of NGT-products should not be obligatory as it is presently the case for GMO products, but voluntary labelling may be envisaged, both in a negative (NGT-free) and positive fashion (benefits of NGT-products). A major pitfall of labelling is the technical inability to discriminate NGT-products from conventional products, which is indispensable for the enforcement of any labelling rules.

EPSO is opposed to obligatory labelling because (i) it may give the wrongful impression that public authorities consider NGT-products as such to be harmful or problematic (ii) it is dependent on traceability, which is not feasible for NGT-products if the modifier construct is not present in the final product, (iii) it is delicate in the present international context where consumers would have difficulties to understand that food made with NGT-products is labelled as GM if the products were harvested in Europe and not at all labelled if the products were imported from many other countries and (iv) it refuses equal treatment since similar or even identical products that have been obtained with technologies with a history of safe use can be marketed without labelling.

Voluntary labelling has the advantage to give voice to different types of values, to maintain information levels equal to all actors and to take into account various lifestyle choices. It allows to mention not only the possibility to exit (for example NGT free) but also to underpin proven benefits (for example produced without pesticides). In fact, in order to offer a true choice to consumers, the information content of a potential NGT label has to exceed the fact of the mere use of the technology in the production process[34].

Conclusion

NGTs are one of the building stones needed to assure the success of the ambition announced by the European Commission in the European Green Deal and which will mobilize research and foster innovation. Two examples are pest-resistant NGT-plants allowing to achieve the zero pollution ambition for a toxic-free environment and allergen-free or bio-fortified NGT-products realising the "From Farm-to-Fork" concept for a fair, healthy and environmentally-friendly food system.

NGTs and NGT products can help implement the “European Biodiversity strategy for 2030” by improving underutilised fruit and vegetable crops and cereals, which are often nutritious but need breeding to improve their economic performance and possibly further improve their nutritional content. Such underutilised crops often did not benefit from critical-mass breeding efforts in the past, due to their poor market share compared to the time and effort needed to improve them with classical technologies. NGTs, under improved legislation, could be used to improve underutilised crops and thereby substantially increase the diversity of cultivated crops as a whole, a main target of the biodiversity strategy. Finally, the application of NGTs to neglected species will help to explore biodiversity by revealing metabolic pathways of a large variety of bioactive secondary metabolites, which are often no longer present in main crops.

This statement summarises EPSO’s submission to the EC study on NGTs. The submission was developed by the EPSO Agricultural Technology Working Group led by Peter Rogowsky, Frank Hartung and Ralf Wilhelm with input from and approved by the EPSO Representatives and Board.

References

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Useful links
Court of Justice of the EU: Judgment in Case C-528/16, 25.7.2018. English Press Release; Ruling in English:
https://epsoweb.org
EPSO Working Group on Agricultural Technologies:
Statements drafted by this group and approved by the EPSO representatives are for instance:
- EPSO updated statement on Crop Genetic Improvement Technologies, 12.01.2017
- EPSO: Opinion on the SAM Explanatory Note on New Techniques in Agricultural Biotechnology, 15.9.2017
- EPSO: First reaction on the Advocate General's Opinion regarding mutagenesis and the Genetically Modified Organisms Directive, 18.1.2018
- EPSO: Statement on the Court of Justice of the EU ruling regarding mutagenesis and the GMO Directive, 19.2.2019
- EPSO: EPSO welcomes Commissioner Andriukaitis statement and call for action 'New plant breeding techniques need new regulatory framework', 29.3.2019
- EPSO: Synthetic Biology should not be confused with the application of new breeding techniques, updated statement, 30.8.2017
- EPSO: Comment on the report of the Ad Hoc Technical Expert Group on Synthetic Biology, 8.3.2018, original report of the AHTEG and all submitted comments.

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