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Stakeholder questionnaire on new genomic techniques to contribute to a Commission study requested by the Council

Fields marked with * are mandatory.

Questionnaire on new genomic techniques to contribute to the study requested by the Council

Discussed and finalised in the Ad-hoc Stakeholder meeting on 10 February 2020

Background

The Council has requested [1] the Commission to submit, by 30 April 2021, "a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law" (*i.e.* Directive 2001/18/EC, Regulation (EC) 1829/2003, Regulation (EC) 1830/2003 and Directive 2009/41/EC).

To respond to this Council's request, the Commission is collecting contributions from the stakeholders through the questionnaire below. The study covers all new genomic techniques that have been developed after 2001.

Instructions

For the purpose of the study, the following definition for new genomic techniques (NGTs) is used: techniques that are capable of altering the genetic material of an organism and which have emerged or have been developed since 2001 [2].

Unless specified otherwise, the term "NGT-products" used in the questionnaire covers plants, animals, micro-organisms and derived food and feed products obtained by NGTs for agri-food, medicinal and industrial applications and for research.

Please substantiate your replies with explanations, data and source of information as well as with practical examples, whenever possible. If a reply to a specific question only applies to specific NGTs/organisms, please indicate this in the reply.

Please indicate which information should be treated as confidential in order to protect the commercial interests of a natural or legal person. Personal data, if any, will be protected pursuant to Regulation (EU) 2018/1725 [3].

[1] Council Decision (EU) 2019/1904, OJ L 293 14.11.2019, p. 103-104, https://eur-lex.europa.eu/eli/dec/2019/1904/oj
[2] Examples of techniques include: 1) Genome editing techniques such as CRISPR, TALEN, Zinc-finger nucleases, mega nucleases techniques, prime editing etc. These techniques can lead to mutagenesis and some of them also to cisgenesis, intragenesis or transgenesis. 2) Mutagenesis techniques such as oligonucleotide directed mutagenesis (ODM). 3) Epigenetic techniques such RdDM. Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs.
[3] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC, OJ L 295, 21.11.2018, p. 39–98

Guidelines

Please note that the survey accepts a maximum of 5000 characters (with spaces) per reply field. You might be able to type more than 5000 characters, but then the text will not be accepted when you submit the questionnaire. You will also receive a warning message in red colour below the affected field.

You have the option to upload supporting documentation in the end of each section. You can upload multiple files, up to the size of 1 MB. However, note that any uploaded document cannot substitute your replies, which must still be given in a complete manner within the reply fields allocated for each question.

You can share the link from the invitation email with another colleague if you want to split the filling-out process or contribute from different locations; however, remember that all contributions feed into the same single questionnaire.

You can save the draft questionnaire and edit it before the final submission.

You can find additional information and help here: https://ec.europa.eu/eusurvey/home/helpparticipants

Participants have until 15 May 2020 (close of business) to submit the questionnaire via EUsurvey.

QUESTIONNAIRE

Please provide the full name and acronym of the EU-level association that you are representing, as well as your Transparency Registry number (if you are registered)

If the name of the association is not in English, please provide an English translation in a parenthesis

European Sustainable Agriculture Through Genome Editing (EU-SAGE)
Transparency Registry number: 030272137138-11

Please mention the sectors of activity/fields of interest of your association

Represent European scientists on genome editing for sustainable agriculture and food production.
Facilitate science-based policy making.

If applicable, please indicate which member associations (national or EU-level), or individual companies /other entities have contributed to this questionnaire

This questionnaire was consulted with and endorsed by EU-SAGE members, 132 European research institutes and associations. Detailed list of the members can be found on our website: https://www.eu-sage.eu/ournetwork

We would like to acknowledge the contribution of Dr Dennis Eriksson, Swedish University of Agricultural Sciences, Chair of COST Action PlantEd (CA18111). The COST Action PlantEd currently brings together more than 330 experts from 36 European countries and beyond, with a focus on plant genome editing.

If applicable, indicate if all the replies refer to a specific technique or a specific organism

EU-SAGE is specifically focusing on the use of NGTs in crops for sustainable agriculture and food production. The answers and information that we provide below are therefore limited to that scope. EU-SAGE does not have a position on the use of NGTs in the microbial or livestock sectors.

In this questionnaire, only NGTs used for SDN-1 or SDN-2 applications and NGT-products resulting from SDN-1 or SDN-2 are addressed. A DNA change in a plant obtained by SDN-1 or SDN-2 is indistinguishable from spontaneous DNA changes or those resulting from mutation breeding. SDN-3 applications are not considered here.

A - Implementation and enforcement of the GMO legislation with regard to new genomic techniques (NGTs)

*** 1. Are your members developing, using, or planning to use NGTs/NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

- There is a widespread use of NGTs, in particular CRISPR-based technologies, in life sciences research including plant-based research.
Recent reviews give more insight into the traits modified by genome editing in model plants and crops (Modrzejewski et al., 2019; Swinnen et al., 2016; Wang et al., 2019b; Butt et al., 2019; Chen et al., 2019; Puchta, 2017; Schindele et al., 2020).

- There is research to improve and expand the versatility of NGT technology: on CAS proteins (Endo et al., 2019; Xu et al., 2019; Walton et al., 2020; Veillet et al., 2020; Wolter and Puchta 2019; Ming et al., 2020; Moradpour and Abdulah 2020), DNA-free genome editing (Metje-Sprink et al., 2018), base editing (Veillet et al., 2019), prime editing (Lin et al., 2020) or multiplexing (Lowder et al., 2015; Schindele et al., 2020).

- There is very widespread research that uses NGTs as a research tool to help answer challenging biological questions (Gallego-Bartolomé et al., 2018; Decaestecker et al., 2019; Cheng et al., 2019; Castel et al., 2019). The research presented for example in Decaestecker et al., 2019, illustrates the use of NGTs specific in certain cells, tissues or organs of plant. This technology enables researchers to study the loss of function of certain genes in a specific piece of a plant (stomata, lateral roots etc.), which was less straightforward before the adoption of NGT-technology.

- There is research & development of NGT products with the goal to contribute to the development of crops and foods that have benefits for society, for example: rice varieties with broad-spectrum resistance to bacterial blight disease (Oliva et al., 2019); wheat resistant to powdery mildew (Wang et al., 2014); tomato plants for urban farming (Kwon et al., 2020) or de novo domestication of wild crops (Østerberg et al., 2017; Lemmon et al., 2018; Li et al., 2018; Zsögön et al., 2018)

- An example of the use of NGTs on Camelina sativa, which is an oilseed crop, is described here in more detail. Camelina sativa is a hexaploid containing six copies of any gene of interest. With NGTs the activity of one or more copies of any gene can be modified, allowing for gene dosage and selection of specific genetic variation for tailoring the appropriate traits (Morineau et al., 2017). Several hundred of simple and multiplexed NGT-Camelina plants have been already generated and selected for traits including oil quality but also for more sustainable agronomic practices. Several lines are queuing for field-trial validation. Field trials are essential to evaluate crop performance and the first European NGT-product field trials have already taken place in the UK (Faure and Napier, 2018).

*** 2. Have your members taken or planned to take measures to protect themselves from unintentional use of NGT-products?**

- ○ Yes
- ● No
- ○ Not applicable

* Please explain why not

- Our members have not taken specific measures to protect themselves from unintentional use of NGT-products and recognize no need to do so. The standard safety and security measures apply as for any research material.

- Our members use NGTs and NGT-products as part of managed research projects. The laboratories and resources, including NGT-products, are only available and accessible to laboratory staff.

- The import of resources is managed through Material Transfer Agreements (MTAs) in which the resource is appropriately described. If the resource would be an NGT-product this will be established at that point and enable our members to take the necessary measures to ensure compliance to the applicable legislation.

- Research employees and students are obliged to comply with safety and other applicable legislation such as the GMO legislation. They are also trained in good scientific practices.

- Training in research integrity and good scientific practice is mandatory in all curricula and for all groups of researchers in the scientific institutes. Further, the application of safety measures for working with GMOs and "Good Laboratory Practices" is strictly enforced at the institutional level.

Please find here the answer to Question 4 (there is no possibility to provide a more detailed answer to this question)

- We are not aware of any initiatives in our sector to take specific measures to guard against unintentional use of NGT-products. NGT-products are widely accepted and very frequently used research resources which are managed like any other resource that is subject to the provisions of the GMO legislation. Safety measures are applied. And NGT products are subject to a specific management regime that prevents unauthorized use, unintentional use, or unintentional dispersal.

* 2 bis. Have you encountered any challenges?

- ○ Yes
- ● No

*** 3. Are you aware of initiatives in your sector to develop, use, or of plans to use NGTs/NGT-products?**

- ● Yes
- ○ No
- ○ Not applicable

* Please provide details

- As the EU-SAGE members represent institutes that aim to facilitate the use of NGTs and NGT-products for sustainable agriculture and food production in Europe, there are many ongoing initiatives to develop NGTs and NGT-products that support this goal.

- There is a very widespread use of NGT products for use in basic (Gallego-Bartolomé et al. 2018; Dreissig et al. 2017; Cheng et al. 2019; Castel et al. 2019) and applied plant research (Wang et al. 2019a; Kwon et al. 2020).

- NGTs have become essential research tools as they allow us to identify causal relationships between specific parts of the DNA and plant characteristics by creating precise DNA changes and measuring the effect of plant characteristics.

- There is development and use of NGT-based molecular biology techniques such as CRISPR-capture (Liu et al. 2017) and diagnostics (for example the NEWCOTIANA project is recently involved in production of biopharmaceuticals useful against COVID-19).

- NGTs are already routinely taught at the undergraduate and graduate levels. The next generation of plant scientists is being well-trained to use NGTs and NGT-products for research purposes and is raising awareness for the potential of NGTs and NGT-products for sustainable agriculture and food production (Examples of initiatives are: Grow Scientific progress (https://www.growscientificprogress.org/); The GeneSprout Initiative (https://www.genesproutinitiative.com/) and members of the COST Action PlantEd).

- NGTs are routinely applied in most life science research laboratories and have become indispensable.

*** 4. Do you know of any initiatives in your sector to guard against unintentional use of NGT-products?**

- ○ Yes
- ◉ No
- ○ Not applicable

* 4 bis. Are you aware of any challenges encountered?

- ○ Yes
- ◉ No

*** 5. Are your members taking specific measures to comply with the GMO legislation as regards organisms obtained by NGTs?**

Please also see question 8 specifically on labelling

- ○ Yes
- ◉ No
- ○ Not applicable

* Please explain why not

- No specific additional measures have been taken on top of existing measures in place ensuring compliance to the GMO legislation. This said, we are very critical about the inclusion of all NGT-products within the meaning of the GMO legislation, more specifically those NGT-products that have alterations in the DNA which can also occur spontaneously or as a result of other techniques (SDN-1 and SDN-2 applications).

- The application of NGTs and the use of NGT-products is governed by the research sector through the legal procedures that apply for the contained use of genetically modified (micro-)organisms.

- The use of NGTs and NGT-products in research is added to existing contained use dossiers and as such is generally not difficult to do.

* 5 bis. What challenges have you encountered?

- After the ECJ ruling (case C-529 16) some members have applied for specific permits to perform GMO field trials with NGT-derived plants. This requires a serious effort and in most cases also requires the payment of substantial dossier taxes.

- As part of deliberate release dossiers it is required to submit a detection method. Due to the inability to develop a fool proof detection method for the detection of DNA alterations in the genome of a plant that can also occur spontaneously, this is not possible. The only thing that currently can be done is to describe the methods used to characterize the event in the NGT-product.

*** 6. Has your organisation/your members been adequately supported by national and European authorities to conform to the legislation?**

- ○ Yes
- ● No
- ○ Not applicable

* What challenges have you encountered?

- In the period prior to the ECJ ruling (case C-529 16), several national competent authorities, such as those from Sweden, Belgium, the UK, Italy and Germany, have provided adequate service by answering within a reasonable timeframe to questions about the application of the GMO legislation.

- Similar questions addressed to the European Commission in that period were not answered in substance by the European Commission.

- Few members have, prior to the ECJ court ruling, consulted competent authorities to check whether the GMO legislation was applicable for specific activities, which in few cases led to the implementation of field trials with NGT crops without GMO permit.

*** 7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products?**

- ● Yes
- ○ No
- ○ Not applicable

* Please describe the traceability strategy, including details on the required financial, human resources and technical expertise

- The members of EU-SAGE are active in the research sector. The current legal requirements for traceability of GMOs mainly apply to food products that have been placed on the market. The members of EU-SAGE are neither involved in placing on the market of crops nor in trade of goods. There may be important differences in the feasibility of traceability of NGT-products within scientific research and the feasibility of traceability of NGT-products within the worldwide food and feed market.

- The experience and expertise of the EU-SAGE members is mostly defined to identity preservation of resources within the research sector. In research the identity of these resources is preserved through the use of ID-numbers or codes. This requires that these ID-numbers or codes physically accompany the resources (codes on seeds bags, on dishes, on tubes, on plant pots, etc.). Problems of traceability arise when the code and the resource get separated. Some organizations may use bar-code systems for particular materials or for certain types of experiments. Records are kept in (electronic) notebooks or sometimes in more elaborate laboratory information management systems.

- There may be quality and identity checks at particular points in the research process, for instance when resources are received from a third party. When performing such identity checks, research organizations are able to verify the genetic identity of a resource and determine whether a particular genetic alteration is present in that resource, but when the genetic alteration can also occur naturally, they cannot determine the origin of that alteration. This is similar to the problems that have been described in the EU-ENGL report entitled: “Detection of food and feed plant products obtained by new mutagenesis techniques.” published 26 of March 2019.

- Many members of EU-SAGE have technical and scientific expertise in the identification of genetic alterations and also have expertise in determining the probability of the natural occurrence of such genetic alterations. For example, the research study of Ossowski et al., 2009 elaborates on the rate and molecular spectrum of spontaneous mutations in the genome of the model plant Arabidopsis thaliana frequently used for research purposes.

* **8. Are your members taking specific measures for NGT-products to ensure the compliance with the labelling requirements of the GMO legislation?**

- ○ Yes
- ◉ No
- ○ Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

-�The members of EU-SAGE are active in the research sector. The current legal requirements for traceability of GMOs mainly apply to food products that have been placed on the market. The members of EU-SAGE are neither involved in placing on the market of crops nor in trade of goods. There may be important differences in the feasibility of traceability of NGT-products within scientific research and the feasibility of traceability of NGT-products within the worldwide food and feed market.

* What best practices can you share?

-�The experience and expertise of the EU-SAGE members is mostly defined to identity preservation of resources within the research sector. In research the identity of these resources is preserved through the use of ID-numbers or codes. This requires that these ID-numbers or codes physically accompany the resources (codes on seeds bags, on dishes, on tubes, on plant pots, etc.). Problems of traceability arise when the code and the resource get separated. Some organizations may use bar-code systems for particular materials or for certain types of experiments. Records are kept in (electronic) notebooks or sometimes in more elaborate laboratory information management systems.

* Please explain why not

-�EU-SAGE members are not involved in placing on the market of genetically modified food or feed, and as of consequence are not encountered with the labelling requirements of Regulation (EC) 1830/2003.

* 8 bis. What challenges have you encountered?

-�In general, the major challenge lies in the enforcement of the GMO labelling requirement as it is not possible to develop detection methods through which it can be established with legally required certainty what the origin of a small genetic alteration (cf. SDN-1 or SDN-2 application) is. This is described in the EU-ENGL report entitled: “Detection of food and feed plant products obtained by new mutagenesis techniques.” published 26 of March 2019. For more details, see answer to Question 7.

* **9. Do you have other experience or knowledge that you can share on the application of the GMO legislation, including experimental releases (such as field trials or clinical trials), concerning NGTs/NGT-products ?**

- (•) Yes
- ( ) No
- ( ) Not applicable

* Please describe for the:

- [x] Agri-food sector
- [ ] Industrial sector
- [ ] Medicinal sector

Agri-food sector

- There have been field trials with NGT-generated mutant crops performed by members of our network in Sweden, Belgium and the UK. In Sweden and Belgium these field trials were performed without GMO permit, but approved by the national authority, at least in 2017 and 2018. The field trial in Belgium in 2019 and in the UK in 2019 were performed with a GMO permit.

- Where field trials were performed with a GMO permit, the applicants have not been able to provide a detection method that can prove with any certainty that plants that contain a particular genetic alteration has been made using an NGT. These applicants could only describe the methods used for the molecular characterization of the events resulting from NGTs. The national reference laboratories for GMO detection are officially responsible for the detection of GMOs in field trials and recognize this problem.

- The main reasons that researchers refrain from conducting GMO field trials despite the potential promising results of their research to bring to society are: additional costs (at least 3500 EUR), administrative procedures (e.g. permit request) and certain experimental limitations (e.g. the tassel needs to be removed of GMO maize).

- EU-SAGE members conduct regularly field trials with GMO plants such as potato, wheat and maize. The Joint Research Center of the European Commission compiles a database of field trials with GMO plants (https://gmoinfo.jrc.ec.europa.eu/gmp_browse.aspx).

- EU-SAGE member share a broad interest to conduct field trials with NGT-products and future field trials are in the pipeline.

- To contextualize the current field trial procedure for NGT-products according to GMO regulations, we provide an example of a field trial that was conducted for NGT-Camelina in 2018 in the UK (Faure and Napier, 2018). NGT-cultures were grown in an experimental farm in locked double-fenced plots. Management measures including netting when the Camelina is in flower and the use of gas guns and hawk kites will be employed to mitigate the risk of seed removal by birds. Management procedures to minimize the spread of seeds or pollen (such as insect-excluding netting) will further reduce the probability of these events occurring. There will be no compatible species grown for 1000 meters from the boundary of the site and no sexually-compatible wild relatives of C. sativa exist in the vicinity of the plots. The risk of non-sexual, horizontal gene transfer to other species is extremely low. In the event of horizontal gene transfer to bacteria, neither the trait genes nor the marker genes would be expected to confer a selective advantage in the field environment under consideration. We estimate the likelihood of horizontal gene transfer as low and the consequences, were it to occur, as negligible. The area proposed to be planted is small and temporary (lasting between 4 and 5 months). Bearing in mind its limited scope, overall risk of harm to human health or the environmental arising from this trial is assessed as very low. The release site will be visited by trained laboratory personnel who are working on the project at no less than weekly intervals (and at some periods, daily) during the growing season of each year of the trial. At the end of each season, the plot will remain in stubble and monitored for volunteers during the remainder of the year and the following season. Any volunteers identified will be destroyed by appropriate herbicide treatment or removed by hand and destroyed. Following completion of the two-year trial the release site will remain fallow for a further season to enable easy identification of volunteers. The site will be inspected regularly and any volunteers identified will be immediately destroyed either by application of a systematic broad leaf herbicide. In the unlikely event that the integrity of the site is seriously compromised, the trial will be terminated and all plants, (including NGT-Camelina and control Camelina plots, and cereal separator) will be destroyed using a suitable herbicide or harvesting as deemed appropriate. All harvested material will be removed from the site and disposed of by incineration or deep burial at a local authority-approved landfill site using an approved contractor. Transportation of waste materials will be in secure containers. The phone numbers of all key staff will be available to site security and farm.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

The maximum file size is 1 MB

B - Information on research on NGTs/NGT-products

*** 10. Are your members carrying out NGT-related research in your sector?**

- (x) Yes
- ( ) No
- ( ) Not applicable

* Please specify including subject, type of research, resources allocated, research location

- It is the core business of our sector to perform research and NGTs are used as a very important tool throughout the sector. NGTs have become essential research tools as they allow us to identify causal relationships between specific parts of the DNA and plant characteristics by creating precise DNA changes and measuring the effect of plant characteristics. For more information, see the answer to Question 1.

- NGTs have not changed the type of challenges that we all want to tackle through plant research. They also have not changed the types of research that are taking place or changed the type of questions that research wants to address. But NGTs have become an overall intrinsic part of plant research, and act as an accelerator in that research.

- The experimental research is carried in a variety of projects for molecular analysis of plant development, plant metabolism and interaction of plants with their environment. NGTs have become a routine and indispensable tool in fundamental research. However, research is limited to laboratory environments due to undue regulatory framework and hence limits scientific progress.

- With more than 100 research centers that are part of our network, which involve around 20000 investigators, all of them either have research projects that somehow involve NGTs or scientists using this technology.

- A few examples of NGT-related research in our sector are:

BULGARIA
In the Institute of Plant Physiology and Genetics at the Bulgarian Academy of Sciences, Sofia, Bulgaria we use NGTs to investigate regulatory mechanisms underlying gene expression during plant development and after exposure to abiotic stress treatments, such as drought, heat shock, high salinity, UV radiation, oxidative stress, etc. In our work, we employ the model plants Arabidopsis thaliana and Lotus japonicus, and the important crop plants Triticum aestivum, Hordeum vulgare, Zea mays, Solanum lycopersicum and Helianthus annuus. The gene functions in the model plants are studied through the generation and characterization of transgenic lines with overexpression or silencing of the genes of interest. This strategy contributes to deciphering the molecular mechanisms of plant stress adaptation, and development of molecular and phenotypic markers for analysis of the genetic determinants of crop stress resistance.

FRANCE
NGTs are being developed by SPS-INRAE for accelerated breeding of the perennial biomass crop

Miscanthus sinensis.

HUNGARY
In the Biological Research Centre, Szeged, Hungary, 17 research groups use predominantly NGTs for research purposes. In most cases, the NGT CRISPR is used. We conduct research on Arabidopsis, Brassica, Medicago, Lotus, Brachypodium, Hordeum, Triticum and Zea mays. Some of the plant research may lead to putative practical applications.

POLAND
In the Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University in Poznan, Poland, we are using NGTs to study gene expression regulation in plants during development and under abiotic stresses (drought, salinity, high temperature, oxidative stress, phosphor deficiency) using model plants Arabidopsis thaliana, Marchantia polymorpha and crop plants Solanum tuberosum and Hordeum vulgare.

SLOVENIA
At the National Institute of Biology, one of our core projects is aimed for better understanding of plant stress responses using a systems biology approach. We are using NGTs to test in the lab, the hypothesis generated by modelling and omics data integration. The NGTs allow us to efficiently study the function of candidate genes potentially involved in plant stress response. We have started with NGTs few years ago, more specifically with optimization and implementation of the CRISPR technology to introduce genetic alterations in potato plants. Since this technology is in constant development, we continue working on the optimization and improvement of this methodology. The CRISPR/Cas9 system is a potent tool that we are using to study the role of potato genes and miRNAs in plant defense response against pathogens. This knowledge that we are gaining represents an important step in understanding plant-virus interactions. Moreover, this knowledge will be further used to develop new strategies for crop protection.

More examples from Czech Republic, Denmark, Italy, Spain and Sweden can be found in attachment to this section.
Our members from Czech Republic answered collectively to this questionnaire in the document attached to this section.

*** 11. Are you aware of other NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify

- The vast majority of research groups in plant molecular biology is routinely applying NGTs, in a variety of research projects.

- There is considerable NGT-related research occurring worldwide in all continents with hundreds of peer-reviewed articles and numerous patents being filed worldwide.

- Public research institutes are the main players in creating multi-faceted research in the plant sector.

- Here are a few examples on NGT-related research that scientists around the world explore to improve food crops with NGTs:

The US startup Calyxt focuses on healthier and more sustainable plant products and developed soybean oil with no trans-fat, trademarked CalynoTM, developed by Calyxt (https://calyxt.com/). Calyxt also developed high-fiber wheat as a healthier wheat option, which is cleared by the USDA, but not yet commercialized (https://calyxt.com/calyxt-harvests-high-fiber-wheat-field-trials/).

The UK start-up, Agrisea, developed salt-resistant rice that can be grown in the sea (https://www.agrisea.co.uk/).

At MIT, researchers devised an approach to develop cereal crops like corn, wheat, and rice that can absorb nitrogen from the soil instead of requiring added nitrogen fertilizer (https://news.mit.edu/2020/making-real-biotechnology-dream-nitrogen-fixing-cereal-crops-0110).

Of special importance for Europe, with 2020 as the third successive year of drought, is research into drought stress tolerance in wheat and other grains continues apace, although no drought-tolerant varieties have yet reached farmers (Mwadzingeni et al., 2016; Sallam et al., 2019)

Key species including wheat, potato or banana that contain more than two copies of their genetic material (also called polyploid) are as of consequence not amenable for genetic improvement. For example, six copies of the gene FATTY ACID DESATURASE (FAD2) in Camelina sativa was modified using NGTs to improve the fatty acid composition of Camelina oil (Morineau et al., 2017; Jiang et al., 2017). Inactivation of the six mlo genes in wheat resulted in resistance to the devastating powdery mildow fungal disease (Wang et al., 2014).

*** 12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling on mutagenesis?**

Court of Justice ruling: Case C-528/16 http://curia.europa.eu/juris/documents.jsf?num=C-528/16

- (x) Yes
- ( ) No
- ( ) Not applicable

* Please describe

- Following the ECJ ruling (case C-529 16) funding was rejected in certain member states as a result of the interpretation that NGT-products are GMO. For example, in Austria at least four research grants to an ERA-NET EU-wide collaboration proposal were rejected based on the ECJ ruling. In this case, the Austrian funding body rejected any research proposals using ‘GMOs’. These four large collaboration proposals negatively affected at least 17 different labs across the EU. Another example is in Dusseldorf, Germany where the German Federal Ministry for Economic Cooperation and Development (Bundesministerium für wirtschaftliche Zusammenarbeit und Entwicklung, BMZ) explicitly does not fund any GMO related projects for international development projects and because of the interpretation of the ECJ ruling as a result does not fund NGT-related projects.

- Prior to the ECJ ruling (case C-529 16) different NGT-related research projects were being set up jointly with SME breeding companies. A number of such research projects has been stopped and the interest to start NGT-related research collaborations has seriously declined.

- A number of spin-off and start-ups have been stopped prior to being established (for instance a Belgian start-up that was going to focus on the development of improved bananas), and a number of new breeding companies (amongst others a breeding company focusing on soybean varieties for North-western Europe) have not started up their planned NGT breeding programs.

- There is also a strong tendency that companies will not invest in academic research programs that involve the use of NGTs for the development of new crop varieties.

To our knowledge some European researchers have moved to countries outside of Europe where research on NGTs is encouraged. In other cases, researchers have stayed in Europe but have moved their field experiments outside of Europe.

- In Belgium, a field trial with gene edited (CRISPR) maize, containing a single nucleotide change, had to be fenced, and an application dossier had to be submitted including the payment of 3000,- euro dossier tax. Furthermore, the obligatory removing of the tassel of the NGT-maize hampered a full experimental characterization of the plants in the field.
- Poland: All researchers working in Poland on NGTs need to have a permission of the Polish Ministry of Environment. The permission allows only to perform experiments in laboratories.

- The ECJ ruling (case C-529 16) has a negative impact on agricultural innovation in Europe based on the number of patent applications related to NGTs compared to other parts in the world (Martin-Laffon et al., 2019). Only 8% of CRISPR patents in agriculture were filed in Europe, while 60% originate from China and 26% from the USA. It also raised concerns in many developing countries and affects their regulatory processes since these countries see a leadership role in technology in the European Union.

- There is uncertainty among young researchers about the impact of the court ruling on the future perspectives in plant sciences in Europe. There is also a growing anxiety among young scientists whether to continue a career in plant science. There is a decrease of attractiveness of Europe as a location for high-level, innovative research in plant molecular biology for young scientists, as compared to USA and Asia. Different groups of young researchers have started raising their voices with the goal to enable the use of genome editing for sustainable agriculture and food. There is the ‘GeneSprout’ group (originating from Wageningen WUR), a group of young Belgian researchers (involved in campaigns with the credo ‘Give CRISPR a chance’), “Progressive Agrarwende” (originating from young members of the Green Party in Germany and young scientists from various research institutes in Germany and the UK), and the group behind the Citizens’ Initiative.

- Shortly after the ECJ ruling, leading scientists representing European plant and life sciences research centers and institutes endorsed a position paper to urge European policy makers to take action in order to facilitate the potential of genome editing in European agriculture
(EU-SAGE statement in attach). Not only EU-SAGE voiced the concerns of scientists on the negative impact of the ECJ ruling but also numerous other organizations and learned societies did. A selection of the different statements is enlisted in the attachment.

*** 13. Could NGT-related research bring benefits/opportunities to your sector/field of interest?**

- (selected) Yes
- No
- Not applicable

* Please provide concrete examples/data

- NGTs are essential tools in the functional characterization of cellular processes and, overall, in understanding the regulation of plant trait expression. There is no technology available offering similar effectiveness and efficiency in understanding causal relationships in cellular processes, at the molecular-genetic level. This can be extended from fundamental research to pre-breeding research: NGTs enable the rapid testing of genetic variation of interest and thereby support the molecular breeding process. This however requires testing of NGT-plants in natural environments.

- NGTs have enabled the introduction of genetic variation in crops in a much more targeted and efficient way, which accelerated the plant related research. It is an essential improvement in breeding of crops which have large genomes compared to other crops. It is now for instance much easier to knock-out a gene, that is, to inactivate a gene. This helps to perform basic research in a more efficient way and will contribute to deciphering the genetic and molecular mechanisms that determine how plants develop and grow under normal circumstances, and circumstances of stress, and how the interaction of plants with its environment is regulated. In this way important scientific knowledge is generated that will contribute to help achieve the sustainable development goals of the United Nations.

- Most plants have polyploid genomes or are derived from polyploids, that is, they contain more than two copies of their genetic material. Important examples are bread wheat, durum wheat, potato, peanut, alfalfa, sugar cane, canola, maize and soybean. As a consequence, the chances of selecting a new mutant trait are extremely low both by making use of natural variation or by random mutagenesis, because it requires that all the copies of the target gene are mutated at the same time. Genome editing provides a solution to this problem. It is now possible to target all copies of a certain gene to introduce a desired edit in all copies of that gene at the same time. An example is described in the research study of Veillet et al., 2019 NGTs were used to introduce small genetic alterations to the GBSSI gene in Solanum tuberosum (potato). Mutants with loss of function of the GBSSI enzyme were obtained using NGTs by changing four copies of the GBSSI gene simultaneously, resulting in impaired amylose biosynthesis. Amylose determines many physicochemical properties of potato starch, namely its pasting temperature and viscosity. Therefore, it is useful for industrial applications to modify potato starch composition by mutating genes encoding enzymes that control the amylose/amylopectin ratio.

- NGTs have made it possible to introduce genetic changes in multiple genes simultaneously through a process that is called multiplexing. This opens the door to achieving relevant alterations in properties that are determined by more than one gene or to introduce different beneficial properties at the same time (Lowder et al., 2018; Wang et al., 2019a; Barthel et al., 2020). For example, NGT multiplexing was applied to create broad-spectrum pathogen resistance by targeting simultaneously three genes at different locations in the genome of rice (Oliva et al., 2019). These edits are indistinguishable from natural variants, which occur separately in genetically very different rice cultivars. The combination of such natural variants in a breeding program takes many generations. Further complex traits, such as drought tolerance, are governed by many small effect genes that require multiplexing to select for the most effective combination of gene variants (Armario Najera et al., 2019).

- Using NGTs it is possible to introduce useful genetic changes that have been identified in variants or wild relatives, without the need to go through the time-consuming process of crossing and backcrossing. In classical breeding, favorable genes are often ‘linked’ to genes that negatively affect crop performances. Genes encoding unfavorable traits can be inactivated and as of consequence accelerate the introduction of favorable traits in superior varieties. This process is also referred to as ‘fast domestication’, which has made it possible to simultaneously introduce important domestication or other beneficial traits into wild relatives of crops, land-races or older varieties that possess important properties that have been lost in more modern varieties (Østerberg et al., 2017; Lemmon et al., 2018; Li et al., 2018; Zsögön et al., 2018).

* **14. Is NGT-related research facing challenges in your sector/field of interest?**

- (x) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

- The legal unclarity on the status of NGT-products is at the basis of why there is so much debate on NGTs in Europe.

- In Sweden, we have seen that one challenge for research using NGTs is that some of the important research councils funding more applied research is starting to put low grades on research projects using NGTs because they will never come to practical use within EU given the current legislation. In Poland, all constructs used to get mutated plants require Polish Ministry of Environment permission and this takes months to get.

- An important debate is about licensing the NGT-products and in particular whether the plant should be patented as a genetically modified plant or registered as a regular plant cultivar or have a specific status. In order to alleviate the unclarity the best option would be considered NGT-plants as regular mutagenized cultivar and being registered as such.

* **15. Have you identified any NGT-related research needs/gaps?**

- (x) Yes
- ( ) No
- ( ) Not applicable

* Please specify which needs/gaps, explain the reasoning and how these needs/gaps could be addressed

- Exemption of NGT-related research from present GMO legislation to facilitate field trials. See answer to Question 9. The main reasons that researchers refrain from conducting GMO field trials despite the potential promising results of their research to bring value to society are: additional costs, administrative procedures and considerable experimental limitations.

- The main bottleneck of applying NGTs to plants is species- and genotype independent delivery of NGT reagents to plant cells and subsequent regeneration of a healthy and fertile plant. Very little research has been conducted over the past decade on plant transformation and regeneration methods. This also includes novel (nano-)materials for introduction of DNA and RNA, as well as ribonucleoproteins into plant cells. These gaps in research need to be addressed by corresponding calls.

- There is a need for research that contributes to the further improvement of certain NGT technologies, especially those forms of gene editing that seek to introduce particular genetic alterations in plants via homology-directed repair (HDR), and NGT technologies to improve (or assist) conventional breeding to fix or break genetic linkages between traits in a controlled manner (Huang and Puchta, 2019).

- There is a need for research that further improves the efficiency of DNA-free methods to obtain NGT-plants. The current status of DNA-free genome editing is reviewed in the study of Metje-Sprink et al., 2018).

- Among the general population, there is a need for research to identify the levels of knowledge, perception, attitude, consumption and choice behavior related to NGTs and NGT products.

- The technology is currently limited by the lack of knowledge in gene function. There are only a handful of known mutations that are important for plant production. More work is needed to rapidly screen and identify useful alleles.

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C - Information on potential opportunities and benefits of NGTs/NGT-products

* **16. Could NGTs/NGT-products bring benefits/opportunities to your sector/field of interest?**

- (•) Yes
- ( ) No

* Please describe and provide concrete examples/data

- The research sector as such is not the main market for the use of products obtained by NGTs.

- There are plenty of examples that illustrate how NGT-products can be used to investigate key processes such as plant development, plant metabolism and plant interaction with the environment (microbes, water, nutrients).

- Example of a study in which a gene was characterized by analyzing a NGT-modified plant (using CRISPR). Bread wheat (Triticum aestivum L.) is a major staple crop worldwide. Given the importance of wheat, new traits have continuously been sought to improve its yield and quality. Bread wheat incurs critical yield losses from powdery mildew, a major disease caused by the fungus Blumeria graminis f. sp. Tritici. Currently, farmers heavily rely on fungicides to control the disease. In order to make the cultivation of wheat more sustainable, researchers have looked into the potential of NGTs to improve resistance to powdery mildew in wheat (Wang et al., 2014). Loss-of-function of the gene MLO in barley, Arabidopsis and tomato leads to broad-spectrum and durable resistance to the fungal pathogens that cause powdery mildew. However, to date, no wheat varieties with loss of function of the MLO gene have been described. This highlights the limitations of conventional breeding methods such as for example mutation breeding. The difficulty for the genetic improvement of wheat is that the genetic blueprint contains three similar but not identical copies of most of its genes. Innovation through NGTs enables the possibility to change simultaneously the six copies of wheat, hence resulting in loss-of-function of the MLO gene. Researchers managed to develop wheat that is resistant to powdery mildew (Wang et al., 2014). This research presents one of the many successful examples of the use of NGTs for the improvement of crops.

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (x) Yes
- ( ) No

* Please explain

-�NGTs and NGT-products act as research tools that provide important benefits for the research sector and can thereby stimulate research. Currently, NGTs offer the most precise, efficient, and fast way to create precise (site-directed) DNA changes in a plant something that was simply not possible before the development of NGTs. Not surprisingly, NGTs have become essential research tools as they allow us to identify causal relationships between specific parts of the DNA and plant characteristics (by creating precise DNA changes and measuring the effect of plant characteristics).

*** 17. Could NGTs/NGT-products bring benefits/opportunities to society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic benefits?**

- (x) Yes
- ( ) No

* Please describe and provide concrete examples/data

- Several examples below illustrate how the rapid, targeted, and knowledge-based use of NGTs for precision breeding can contribute to human health and the environment:

Improved resistance against diseases, e.g. mildew resistant wheat (Wang et al., 2014; Zhang et al., 2017), fungal resistant grapevine (Wang et al., 2018), fungal resistant rice (Wang et al., 2016), broad-spectrum bacterial disease resistant tomato (Toledo Thomazella et al., 2016), grapefruit resistant to citrus canker (Jia et al., 2017), rice resistant to bacterial blight (Zhou et al., 2015; Blanvillain-Baufumé et al., 2017; Xie et al., 2017;).

Improved resistance against abiotic stress, e.g. drought tolerant maize (Njuguna et al., 2018) drought tolerant wheat (Kim et al., 2018), salt tolerant rice (Duan et al., 2016), drought and salt tolerant soybean (USDA database), salt tolerant tomato (Li et al., 2018)

Improved agronomic traits, e.g. wheat with increased grain yield (Zhang et al., 2018), shatter-resistant oilseed rape (Braatz et al., 2017; Yang et al., 2018), cucumber with female flowers only (Hu et al., 2017), rice with optimized flowering time (Li et al., 2017)

Consumer quality traits, e.g. potato with altered starch composition (Andersson et al., 2017), non-browning potato (USDA database), cereals with improved protein content (USDA; Sun et al., 2017), tomato with altered sugars (Lee et al., 2018; Nonaka et al., 2017)

Health-related traits, e.g. high-fiber wheat (USDA database), low-acrylamide potato (Clasen et al., 2016), low gluten wheat (Sánchez-León et al., 2017), improved seed oil (Okuzaki et al., 2018), increased contents of beneficial secondary metabolites, reduced contents of allergens and toxic heavy metals in cereals, legumes and oilseeds (USDA database; Haun et al., 2014; Demorest et al., 2016; Wen et al., 2018; Zhou et al., 2018; Abe et al., 2018; Nieves-Cordones et al., 2017; Tang et al., 2017).

- Several examples below illustrate how the rapid, targeted, and knowledge-based use of NGTs for precision breeding can contribute to an urgently needed, more sustainable agriculture:

By reducing the amount of inputs (water, fertilizer, plant protection products) needed to grow the crops, thereby reducing the amount of GHG emissions associated with these inputs and reducing the environmental pressure caused by plant protection products.

By increasing the output per unit of land, thereby reducing the amount of land needed as arable land.

By saving crop species that are in danger of disappearance (e.g. plum in Europe, which is threatened by the Sharka virus), local varieties, and orphan species, thereby protecting biodiversity and increasing the diversification of agricultural species.

* Under which conditions do you consider this would be the case?

-�Demand for food and resources will continue to grow worldwide, while natural resources required for food and biomass systems will become limited and ecologically valuable natural landscapes contributing to biodiversity will get lost. Climate crisis is upon us, and its impacts are getting more severe with each passing year. Global actions to slow down climate change are absolutely necessary but likely insufficient. We must therefore invest in the continuous and rapid adaptation of crops to local conditions that are now inevitable: higher temperatures, longer periods of drought and unpredictable seasons. Solving the global food and resource problem requires a multidisciplinary approach as plant production comprises many aspects such as inputs, management practices, plant protection, soil management and plant varieties. The main focus of breeders, geneticists and biotechnologists is the improvement of plant varieties.

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (x) Yes
- ( ) No

* Please explain

- Plant breeding depends on genetic diversity. We humans have been practicing plant breeding for thousands of years by selecting for variation within the DNA of our foods, making them more nutritious, more productive and better adapted to agricultural practices. Much of what we eat today could not exist without it. Initially, plant breeding had to depend on random DNA changes happening by chance. A huge scientific breakthrough was the introduction of mutation breeding, which presented plant breeders with the ability to insert variation into DNA. The DNA changes resulting from mutation breeding, however, occur in many genetic locations simultaneously and at random. Moreover, despite this and other scientific breakthroughs, plant breeding is still a time-consuming process. NGTs, on the other hand, are tools of precision, that can be used to introduce the same type of DNA changes but faster and in a specific genetic location. The use of NGTs therefore allows knowledge-based and accelerated precision breeding by the targeted introduction of existing or additional genetic variation into crops to improve traits.

- NGTs enable us to diversify crops and traits adapted to local regions in Europe. Re-emerging orphan crops like camelina, hemp and crambe provide new markets but also alternatives for European agriculture in the context of climate change. Classical breeding for these crops is either non-existent or difficult to implement (for instance low genetic pool). It also provides a possibility to tackle traits for specific markets (for example gluten free wheat) or specific European regions or climate conditions.

*** 18. Do you see particular opportunities for SMEs/small scale operators to access markets with their NGTs/NGT-products?**

- (x) Yes
- ( ) No

* Please describe and provide concrete examples/data

- NGTs are easy to access and apply by operators of all sizes.

- After it was shown in 2013 that the NGT CRISPR can be used in plants to make small genetic alterations, there was a lot of interest from SME breeding companies to establish the technology within their breeding programs (vegetable crops, ornamentals, fruit crops, etc.) and to improve different varieties.

- SMEs work locally and local varieties improved using NGTs will be accepted by local farmers.

- Particular opportunities exist if NGT products resulting from SDN-1 or SDN-2 applications are excluded from the scope of EU GMO legislation. The cost for European SMEs to access and use NGTs is relatively inexpensive. If they were permitted to market varieties derived from NGTs, this would increase the number of European players in the area of crop improvement and result in a broader offering of varieties and crops to European farmers, thereby increasing agricultural biodiversity and improving farmer and consumer economics.

- Various aspects have to be considered. Experience shows that SMEs and especially startups very often are the initiators or driving forces of technological innovation because of: the specifically progressive and innovative spirit of their employees and their leadership (‘innovation affinity’), the high level of scientific and technological know-how of their employees, their strategic focus on R&D (at least in the beginning of their business or of new business units within an existing company; less focus on short term return on investment) and their shorter development cycles (fast decision-making processes).

- Prerequisites for that are strong R&D power and capacity in these enterprises or company units, high level of know-how and capacity in intellectual property right protection and the handling of regulation processes for new technologies and products thereof and, overall, high financial power paired with a realistic view of timeframes for product development and the successful market introduction of new products.

- High or not reliable regulatory hurdles for the regulation of new technology or market introduction of new products, set by respective legislation, are considered a major obstacle for technological innovation. In addition, such legislation puts SMEs and startups in disadvantage to large-size companies with an incomparable financial power, administrative power and already existing market power and penetration. These concepts hold true for NGTs and NGT-products as well. Furthermore, from the technical point of view NGTs are easy to establish and to operate, reducing potential competitive disadvantages of SMEs at least at this level.

- Argentina was the first country with biosafety legislation specifically for NGT-products. After four years of implementation of legislation for NGT-products, the percentage of product applications from public sector and SME developers has increased and a wider array of products has been submitted for regulatory review compared to GMOs with a narrow spectrum of traits and exclusively large-size companies as applicants. These observations have been recently analyzed and described (Whelan et al., 2020).

- Abstract of the study ‘Gene Editing Regulation and Innovation Economics’(Whelan et al., 2020): Argentina was the first country that enacted regulatory criteria to assess if organisms resulting from NGTs are to be regarded as genetically modified organisms (GMOs) or not. The country has now accumulated 4 year of experience applying such criteria, reaching a considerable number of cases, composed mostly of NGT-plants, animals, and microorganisms for agricultural use. This article explores the effects on economic innovation of such regulatory experience. This is done by comparing the cases of products derived from gene editing and other NGTs that have been presented to the regulatory system, against the cases of GMOs that have been deregulated in the country. Albeit preliminary, this analysis suggests that products from gene editing will have different profiles and market release rates compared with the first wave of products from the so called ‘modern biotechnology’. NGT-products seems to follow a much faster development rate from bench to market. Such development is driven by a more diverse group of developers, and led mostly by small and medium enterprises (SMEs) and public research institutions. In addition, NGT-product profiles are also more diversified in terms of traits and organisms.

*** 19. Do you see benefits/opportunities from patenting or accessing patented NGTs/NGT-products?**

- [x] Yes
- [ ] No

* Please describe and provide concrete examples/data

- Patenting of NGTs or NGT-products is an efficient way for protecting intellectual property and thereby is also an essential basis for creating economic value and benefits from such technologies or products for inventors, intellectual property right owners, licensors and licensees. The possibility of patenting NGTs and NGT-products is also seen as a stimulus for further research resulting in improvements of such technologies and products. However, patenting of technologies and products may also create somewhat of a threshold for the ability of companies, especially SMEs, to commercialize NGTs or NGT-products in which patented inventions are used. This is because such commercial use requires a license agreement with the patent holder.

- The fact that patents may apply, and license agreement may be necessary is not unique for Europe. It also applies in other parts of the world, and in that respect, there is a level playing field.

- The complex landscape of NGT-related intellectual property presents a major hurdle to obtain Freedom-To-Operate for start-ups, SMEs and public sector research institutes that aim to commercialize their products. Patent pool or compulsory licenses might be an option to guarantee access to the technology for SMEs and Start-ups and avoid that the technology will only benefit a handful of multinational companies.

- Access to patented NGTs and NGT-products will be critical for their use. The difficulty today is that due to the uncertainty in the commercial development of products derived from NGTs in the EU, research is limited in the EU, resulting in fewer inventions (and fewer patents and patent variety rights) by European researchers. Most patent activity related to NGTs is occurring in China and the USA (Martin-Laffon et al, 2019). When severe regulatory constraints continue to apply to NGTs in Europe, the lack of innovation in this field will increase the access cost of these technologies for European players, putting them in a competitive disadvantage versus players from other countries.

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D - Information on potential challenges and concerns on NGTs/NGT-products

*** 20. Could NGTs/NGT-products raise challenges/concerns for your sector/field of interest?**

- [ ] Yes
- [x] No

* Please explain why not

- As NGT-products are currently regulated as genetically modified organisms (GMOs), there are no specific challenges that would be different from what is being applied today for GMOs.

- EU-SAGE member share a broad interest to conduct field trials with NGT-products and future field trials are in the pipeline. However, applicants from authorized research institutes have to apply for a GMO permit to perform field trials with NGT-products because of the interpretation of the ECJ ruling on mutagenesis (case C-528/16). This requires a serious effort and, in most cases, also requires the payment of substantial dossier taxes. As of consequence, the threshold to validate scientific results generated in the lab using field trials is much increased. See answer to Question 9.

- For a research organization and for individual scientists, the challenge is to stay scientifically competitive. Currently, NGTs are the most effective and most efficient tools for analysis of causal functional relationships in cellular processes, at the molecular level. Therefore, know-how, necessary equipment and a supportive regulatory framework for the application of these technologies in research are of key importance for scientific competitiveness. The possibility to apply the best available and innovative technology is also a key factor to attract qualified scientists and prevent the so called “brain drain”. Of course, all this will finally also have an impact on the economic competitiveness of societies.

* **21. Could NGTs/NGT-products raise challenges/concerns for society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic challenges?**

- ◯ Yes
- ◉ No

* Please explain why not

- Scientific progress in plant breeding over the past decades is of paramount importance for the promotion of individual and societal welfare. Innovative technologies such as NGTs need to be facilitated to ensure that people are able to enjoy the benefits of scientific progress and its applications.

- The Right to Science is recognized and protected as a fundamental human right. It is enshrined in article 27 of the 1948 Universal Declaration of Human Rights (UDHR) and in article 15 of the International Covenant on Economic, Social and Cultural Rights (ICESCR).

UDHR, Article 27: “Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits”.

ICESCR, Article 15:
“(1) The States Parties to the present Covenant recognize the right of everyone:
To take part in cultural life;
To enjoy the benefits of scientific progress and its applications;
To benefit from the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author.
(2) The steps to be taken by the States Parties to the present Covenant to achieve the full realization of this right shall include those necessary for the conservation, the development and the diffusion of science and culture.
(3) The States Parties to the present Covenant undertake to respect the freedom indispensable for scientific research and creative activity.
(4) The States Parties to the present Covenant recognize the benefits to be derived from the encouragement and development of international contacts and co-operation in the scientific and cultural fields.”

- In the current legal situation, in other parts of the world where certain applications of NGTs are treated in the same way as conventional crops, the farmers, operators and consumers are likely to benefit much more from NGTs than farmers, operators and consumers in Europe, and consequently EU agriculture will become less competitive in the global market.

- In the same way certain environmental benefits (for example reduced use of chemicals) cannot be achieved in Europe, while they will be achieved in other parts of the world, and EU agriculture will become less competitive in the global market.

- Generally, the marketplace (the needs of farmers, producers, consumers and society in general) will direct what type of crop-trait combinations will be developed and which NGT-products will be placed on the market. It is important that knowledge about these needs is developed, to prevent a gap between what is developed and what is most desired.

*** 22. Do you see particular challenges for SMEs/small scale operators to access markets with their NGTs /NGT-products?**

- (x) Yes
- ( ) No

* Please explain and provide concrete examples and data

- As long as NGT-products are considered to be subject to the EU GMO legislation SMEs and small scale operators will not be able to market their NGT-products, simply because having to comply with the EU GMO legislation creates requirements that are too complex, too cumbersome and too expensive to cope with for such SMEs. On top of that in the past two decades it has proved impossible to cultivate GMO crops in Europe (with the exception of GMO crops approved before).

- The major challenge lies in the enforcement of the GMO labelling requirement as it is not possible to develop detection methods through which it can be established with legally required certainty what the origin of a small genetic alteration (cf. SDN-1 or SDN-2 application) is. This is described in the EU-ENGL report entitled: "Detection of food and feed plant products obtained by new mutagenesis techniques." published 26 of March 2019. For more details, see answer to Question 7.

- It is therefore expected that SMEs and small scale operators will, whenever possible, direct their R&D activities towards markets outside of Europe. This is a major problem as Europe represents a large market and it may be detrimental to SMEs and small scale operators to not have access to this market.

- In the course of market introduction of NGT-products, the most relevant challenge for SMEs and startups is seen in the time-consuming and very costly process of regulation for such products, as long as they fall under GMO legislation in its present form. Very often SMEs lack the know-how and the financial power to cope with that challenge. It requires investments in technical know-how and technical equipment, and the costly licensing-in of rights for commercial use of patent-protected technology and products. This can put SMEs at disadvantage, as long as they have no own strong R&D program and/or no own strong patent portfolio which are also cost-intensive to establish and maintain.

- The challenges are enormous if NGT-products are regulated in the same manner as GMOs. Due to the cost, delays and uncertainties to go through GMO regulatory processes, SMEs/small scale operators will not develop such products since they will not be able to pass the regulatory hurdles, unless those undergo extensive revision and simplification adapted to the NGTs, in the very near future. If some NGT products are treated the same way as plants derived from traditional breeding techniques, then the challenges of developing such products can be overcome by SMEs and small scale operators. There are for example more than 70 breeding companies of different sizes operating in France, the majority being small scale operators. See https://www.gnis.fr/acteurs-filiere-semences/.

*** 23. Do you see challenges/concerns from patenting or accessing patented NGTs/NGT-products?**

- ○ Yes
- ◉ No

* Please explain why not

- See also our answer to Question 19.

- If we want to prevent that European players end up in a disadvantageous position compared to players in other important parts of the world, for instance by an increased access costs to NGTs for European players, then we should enable the use of NGTs for sustainable agriculture and food production in the same way as in other parts of the world.

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E - Safety of NGTs/NGT-products

*** 24. What is your view on the safety of NGTs/NGT-products? Please substantiate your reply**

- From a scientific point of view, one cannot make generic statements that all products obtained by NGTs are, or are not safe, but the same applies to products obtained by conventional and mutation breeding.

- One should distinguish between the use of NGTs resulting in products that have genetic alterations that can also occur spontaneously in nature or result from conventional breeding and products that have genetic alterations that cannot occur in nature or result from conventional breeding.

- Products obtained by NGTs with genetic alterations that can also spontaneously occur in nature or result from conventional breeding are by definition as safe as those conventional products. A product with a specific mutation generated by an NGT is as safe as a conventional product containing that same mutation.

- The EU-SAGE network is very much focused on the use of NGTs that result in products that have genetic alterations that can also occur spontaneously in nature or result from conventional breeding (SDN-1 and SDN-2). Because such products are at least as safe as similar conventional products, the members of the EU-SAGE network are of the opinion that the legislation should treat them in the same way as conventional products.

- Products with a specific mutation generated by an NGT are, if anything, safer than a conventional product with that same mutation generated by natural means or random mutagenesis (for instance using radiation). The conventional product will have many additional mutations of which the effect is not known. The conventional product has a much higher degree of uncertainty about its safety than the product of NGT.

- With the use of NGTs, plant breeding becomes much more knowledge-based. Plant breeding thereby transforms from a chance process to a much more targeted and precise approach. The amount of uncertainties thereby reduces, and this will contribute to safety.

- A product in which a transgene has been introduced using an NGT is generally as safe as a product in which that transgene has been introduced using conventional transgenic technology. But when one uses NGTs to introduce a transgene in a specific location in the genome (cf. SDN-3 application) of which it is known that insertion in that location will not interfere with the expression of endogenous genes and cannot lead to the formation and expression of new proteins, these transgenic organisms are less likely to exert unintended effects and hence are likely to be safer than conventional transgenic organisms.

- Organisms that have the same likelihood of being safe should be treated by the safety legislation in the same way. Otherwise the legislation would be discriminatory. It is not the use of a particular technology that will determine whether or not a certain organism is safe. The product characteristics generated will determine the safety of an organism.

- It is not the question whether or not a product generated by an NGT could possibly create a risk that should determine whether or not such products should be subject to the GMO or similar legislation. Food products should be safe anyway (EU general food law). The major question is to what type of safety governance we want to subject NGT products. Do we want to subject them to safety legislation that requires elaborate pre-market safety assessments and explicit authorizations, or do we want to subject them to a system that imposes post market safety liability (through the general food law and the environmental liability legislation)? The answer to that question will be determined by the general principle of non-discrimination. Products that have the same likelihood of safety should be governed by the same legislation.

- We also want to refer to what has been said about safety by the panel of the EU Scientific Advice Mechanism in its 2017 Exploratory Note on new techniques in agricultural biotechnology (pages 17-19, 77-80, 95-97), and its 2018 statement entitled “A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive”, at pages 3 and 4.

*** 25. Do you have specific safety considerations on NGTs/NGT-products?**

- ○ Yes
- ◉ No

* Please explain why not

- Please see our answer to Question 24.

- In general, the application of NGTs starts from the understanding of the role and function of particular genes and genetic elements, and their interconnection with other genes of the organism. Plant breeding thereby transforms from a chance process to a much more targeted and precise approach. The amount of uncertainties thereby reduces, and this will contribute to safety.

- Scientists and breeders have the ability to select NGT-products in which only the desired genetic change has occurred without off-target modifications.

- There is discussion on possible off-target modifications. Most of that discussion has become obsolete as the technology has further improved and the specificity of NGTs is raised to a very high level. In plants the possibility of off-target modifications is also not a very relevant discussion when one realizes that conventional random mutagenesis creates steep numbers of off-target modifications. These additional off-target modifications resulting from conventional mutagenesis are generally neither identified, nor are their effects determined, nor did any safety issues arise in the past 75 years. Additionally, one should realize that, depending on the size of the plant genome, already between tens and several hundreds of spontaneous mutations occur from one generation to the other. Furthermore, any commercially deployed NGT or GM event is likely to have been subjected to multiple back crossing cycles, eliminating most off-target events.

- There are several reviews and studies that address the topic of possible off-target modifications. In the study of Tang et al., 2018 is described how they looked for off-target mutations by whole genome sequencing in rice plants transformed with either Cas9 or Cpf1. A small number of mutations were found and the vast majority were caused by tissue culture and Agrobacterium-mediated transformation (1.86×10^{-7}). Off-target mutations were found only in plants edited by 1 out of 12 different Cas9-gRNAs. In the review of Modrzejewski et al., 2019 is summarized that out of 1328 studies using NGTs such as CRISPR, TALENs, base editing, ZFN, and ODM in 68 different plants, 252 of them investigated off-target mutations. In around 3% of the analyzed potential off-target sites mutations were detected. In the brief opinion of Hahn and Nekrasov, 2019 on off-target modifications in plants the take home message is that it is less of a concern, and most off-target mutations can be avoided by careful design of gRNAs.

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F - Ethical aspects of NGTs/NGT-products

*** 26. What is your view on ethical aspects related to NGTs/NGT-products? Please substantiate your reply**

- EU-SAGE is mainly focusing on the use of NGTs for crops in agriculture and food production and is limiting its ethical considerations to that sector.

- The use of any technology and products thereof has to take place in accordance with the cultural and religious system of values established in a given society, in addition to the legal framework. This holds especially true when issues of protecting life and nature are potentially touched. The system of values builds the framework for rational risk to benefit estimations, at a variety levels, when deciding about the application of new technologies and market introduction of products generated with the help of such technologies. And it has to be taken into account that the system of values might substantially differ for individuals, when setting different priorities. In Western societies the teachings of Humanism, Enlightenment and Christian Religion determine ethical standards of human behavior. In many respects, these can be affected by the introduction of any novel technologies, and hence also by the introduction of NGTs. However, these are not specific to NGTs as such.

- Plants have been domesticated by humans to be more productive and adapted to agricultural practices since the dawn of civilization. Genome editing is now part of the innovation history that plant breeding developed and there are no other ethical concerns that exist that would be different from what would apply to plants derived from traditional breeding.

- In regard to the ongoing discussion on genome editing, it is important to clarify what aspect of the technology is being discussed. When decisions are taken based on claims different from scientific evidence, then it should be clearly communicated for transparency reasons.

- There is a general misconception that genome edited crops would not be regulated in case they would not be subjected to the provisions of the GMO-directive and this may cause ethical considerations. The safety of food products is determined in the European general food law (Regulation (EC) 178/2002) and the European environmental liability directive (2004/35/EC).

- An ethical concern is that genome edited plants are perceived as unnatural. Humans have made use of the natural genetic variation since the beginnings of agriculture and they always have selected for the traits that were beneficial and suitable for them. In this regard, all the food products we consume today can be considered unnatural. On the other hand -from a scientific point of view- mutations can occur spontaneously in nature, so they would have to be considered natural. This disagreement can be explained because ‘naturalness’ is related to values as well: ‘natural’ which is often associated with something positive, whereas ‘unnatural’ is associated with something negative.

- Because NGTs and NGT products have a real potential to contribute to a more sustainable agriculture and food production and thereby contribute to helping achieve important sustainable development goals, it would be unethical to block the use of NGTs and NGT products.

- Developing economies, particularly those in Africa, have a lot to gain with the use of NGTs and NGT products. Some of the developing economies have a tendency to look at Europe for the way they would want to regulate modern breeding technologies. Europe should take this into consideration and promote policies that allow the responsible use of NGTs.

- A regulatory situation that prevents, slows down or delays the development and marketing of plant varieties that have been developed using NGTs and carry substantial environmental, health and/or economic benefits, and that do not create specific risks referring to the technology by which they were developed, is ethically questionable.

*** 27. Do you have specific ethical considerations on NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please explain

- EU-SAGE is mainly focusing on the use of NGTs for crops in agriculture and food production and is limiting its ethical considerations to that sector.

- Our ethical considerations concern the current regulatory situation which leads to a delayed adoption of NGTs in research and breeding as well as respective product development. We therefore agree with the statement from EASAC "that the potential costs of not using a new technology, or being slow in adoption, must be acknowledged. There is no time to lose in resolving the problems for food and nutrition security in Europe" (EASAC: The regulation of genome-edited plants in the European Union).

- In the statement released by the Danish Council on Ethics, a large majority of the Council members stated that "It is ethically problematic to reject GMO varieties if they can help alleviate or solve significant problems and there are no good arguments for rejecting them" (Danish Council on Ethics, 2019). This statement applies to NGT-products as well.

- Another valuable point was raised by the Max Planck Society Ethics Council calling upon politicians "to pursue new and amended legislation that takes into account the differences between conventional genetic modification using recombinant DNA technology and transgene-free genome editing" (Ethics Council of the Max Planck Society, 2019).

- It is ethically problematic that farmers who want access to improved seeds are denied this. Farmers are constantly struggling to deliver a high amount of high-quality products while protecting their crops against insects, diseases and unfavorable weather conditions, and at the same time minimizing the impact on the environment. It is therefore imperative to give farmers access to crop varieties that have been genetically improved to, amongst others, resist insects, pathogens and drought with minimum use of pesticides and other input.

- There is an ethical dimension to the discussion on equal access to technology. Wherever possible, we should refrain from policies that would result in SMEs being excluded from the use of NGTs (Rommens, 2010).

- Freedom of choice is an important principle with strong ethical implications. There are consumers that demand labelling of GM products in order to actively choose to not buy these. It cannot be overlooked though that there are also consumers who will actively choose to buy GM products, as well as the products of NGTs, as these are often associated with reduced environmental impact (Brookes and Barfoot, 2018), improved farmer economy (Brookes and Barfoot, 2017) and higher nutritional quality (De Steur et al., 2017). It is ethically problematic to deny consumers the right to make an active choice that is beneficial to the environment and to their own health.

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G - Consumers' right for information/freedom of choice

*** 28. What is your view on the labelling of NGT-products? Please substantiate your reply**

- Because the use of a particular breeding technology is not related to the impacts of the product in terms of health, environment and/or sustainability, we are of the opinion that labelling of products obtained by NGTs is uninformative. It does not help consumers to make informed decisions in the context of global challenges such as climate and biodiversity; challenges that matter to the general public today.

- The standard legislation for labelling of commercialized products should be applied to NGT-products, based on their material quality (contents, nutritional quality etc.) and origin. As long as no scientifically reliable or reasonably conceivable indications with respect to danger for human/animal health and/or environment by NGTs, no labelling of NGT-products on the basis of the breeding process is considered necessary.

- Labelling on the basis of the use of a particular breeding technology is not fair in a context where the general population lacks knowledge about NGTs and is not able to place NGTs in the broader context of domestication and breeding technology as it has evolved over the years.

- Over the years, a GMO label has proven to be more of a stigma than an actual informative label. It does not provide relevant information on the actual properties of the product (introduced trait, advantages, risks). The GMO label has also been misused to promote irrational fear. Using that label for products that carry genetic alterations that are identical to genetic alterations that are able to occur naturally or be the result of conventional breeding is discriminatory.

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H - Final question

*** 29. Do you have other comments you would like to make?**

- (x) Yes
- ( ) No

Please provide your comments here

- EU-SAGE wishes to re-emphasize that it is specifically focusing on the use of NGTs (SDN-1 and SDN-2) in crops for sustainable agriculture and food production. The answers and information that we have provided above are therefore limited to that scope. EU-SAGE does not have a position on the use of NGTs in the microbial or livestock sectors.

- The world is facing important sustainability challenges, and Europe has formulated an ambitious Green Deal to fight these challenges. EU-SAGE is of the opinion that the EU should enable the use of innovative breeding technologies such as NGTs as part of that Green Deal. NGTs provide an important and unique opportunity to achieve a number of sustainability goals in a much more efficient and much more targeted manner.

- The use of NGTs further transforms plant breeding from a chance process to a much more targeted and precise approach. The amount of uncertainties are thereby reduced, and this will contribute to safety.

- EU-SAGE wishes to point out that NGTs and NGT-products are very widely accepted and very widely used in the research sector. They have become an intrinsic, inseparable part of European plant science.

- EU-SAGE also has a specific view on the legislative situation. In that view it particularly focuses on the use of NGTs resulting in products that carry genetic alterations that could otherwise also have occurred spontaneously in nature or be the result of conventional breeding activities. EU-SAGE advocates a legislation that does not discriminate on the basis of a particular breeding technology. Where the end-product is the same, and their safety aspects do not differ, the legislation should treat them similarly. This approach is also followed in many other parts of the world and there is good reason to strive for worldwide harmonization. Maintaining the current regulatory interpretation that all genome edited organisms are subject to the provisions of the EU GMO legislation will lead to trade disruptions and this legislation cannot be enforced. Maintaining the current regulatory situation would have effects that are contrary to what the EU would like to achieve by means of the Green Deal.

- Attached, please find the proposal by AFBV and WGG for amendments to GMO legislation

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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ITALY

The NGT-related research carried out at Fondazione Edmund Mach (San Michele all'Adige, Trentino) aims to improve the delivery of NGTs into plant cells of grapevine and apple. The goal is to obtain apple cultivars that are resistant to apple scab and fire blight. In the case of grapevine, the goal is to obtain cultivars that are resistant to powdery mildew or tolerant to drought. Currently, we were able to obtain mutated plants and we are currently testing in the greenhouse their phenotypes.

The Italian national project on plant biotechnology 'BIOTECH' that involves several Italian universities and Research Centre for Genomics and Bioinformatics (CREA) is funded by the Italy Ministry of Agricultural, Food and Forestry Policies. BIOTECH applies NGTs to develop new knowledge on gene functions and to select new genotypes, with major research targets on yield, diseases resistance and quality. BIOTECH is organized into 13 research areas, each of them focusing on one or few crop(s), for a total of 16 species that represent most of the Italian agriculture. The major crops are grapevine, citrus, peach, apple, pear, tomato, eggplant, wheat, rice and poplar. BIOTECH promotes the diffusion of new breeding techniques within the Italian scientific community, to revitalize the long-lasting tradition in plant breeding and genomics. The project aims at building a scientific know-how that can contribute to translating the knowledge on plant genomes into improved and more sustainable cultivars.

Other NGT research examples carried in Italy:

Tomato resistance to parasitic plants

Parasitic plants like *Phelipanche ramosa* cause relevant damage to tomato cultivations. Chemical or agronomic control is very difficult and natural resistance has not been identified. Genome editing is being used to generate mutants in which parasite-host recognition is blocked.

Tomato tolerance to salt stress

High salt in the soil negatively affect productivity, and millions of hectares of land are not usable for agriculture due to salinity. The amino acid proline is an osmoprotectant that helps plants tolerate high salt concentrations. Genome editing is being used to reduce proline catabolism and thus increase proline content.

Soluble sugar content in tomato

Brix degree (the content in soluble sugars, mainly glucose and fructose) is one of the main quality parameters in tomato. A favorable allele in the gene encoding invertase – which breaks sucrose into its glucose and fructose – has been found in tomato wild relatives. Using genome editing the mutations that characterize this allele can be reproduced in cultivated varieties.

Gluten intolerance

In sensitive individuals, fragments of the wheat seed proteins that constitute gluten cause inflammatory or immune reactions causing different levels of intolerance or celiac disease. A fragment of a rye protein of the same class of wheat gliadins – a component of gluten - has been shown to inhibit the toxic effects of its wheat counterparts. Gene editing is being used to change the toxic epitopes of durum wheat gliadins to obtain a similar antagonistic effect.

Increase of durum wheat productivity

Genes that limit seed number and size have been identified in certain cereals. This knowledge is being used to edit corresponding genes in durum wheat and decrease their activities, so to overcome yield constraints.

Grape resistant to fungal pathogens

Powdery and downy mildew are fungal diseases that heavily affect grape cultivations, and can be controlled only with extensive use of fungicides. Resistance genes to both pathogens have been identified in a number of wild relatives as well as in a few cultivated varieties. *MLO*-like susceptibility genes that can be knocked out to achieve resistance have been identified for powdery mildew. The loss of function mutations in *MLO*-like genes are being introduced in several important varieties by editing, thus avoiding the problems associated with conventional breeding, namely the very long duration of backcrossing programs and the inevitable loss of genetic and legal variety identity.

Seedless table grape

Seedless table grape cultivars are favored by consumers, but very few of them have been obtained in Italy. The gene responsible for the seedless phenotype is known. The favorable mutations are being inserted into Italian table cultivars.

Optimization of rice flowering time

Rice is a tropical short day (SD) plant whose flowering is induced as day length decreases under a critical threshold. Adaptation to northern areas – such as those in Europe - required selection of natural mutants with reduced sensitivity to photoperiod, allowing plants to flower quickly under longer day lengths and mature before the onset of winter. The mutations involved are known at the molecular level. However, for many tropical varieties that are now popular among consumers, such mutants are not available. The known mutations are being introduced by genome editing in tropical varieties and novel Italian varieties.

DENMARK

The Novo Nordisk Foundation, Denmark, has awarded a major grant for the project "NovoCrops: Accelerated Domestication of Resilient Climate Change Friendly Plant Species" at the Department of Plant and Environmental Sciences at the University of Copenhagen. The researchers will test NGTs for accelerated breeding on a variety of wild plants to create crops that are resilient to factors related to climate change such as diseases, drought or flooding. Nine plant species provide almost all the world's food intake, and all are refined. By comparison, there are about 380,000 wild plant species. Nature therefore offers us huge genetic variation that we do not access today. Instead of examining how to make the refined plants more robust, we will instead study how to harness the hardiness of wild plants as a starting-point to make crops that are resilient to diseases and extreme weather events.

SPAIN

At IBMCP (CSIC-UPV) in Valencia, Spain we are using NGTs for two main applications: to introduce new traits in plants and to recapitulate some important traits that were done by traditional breeding methods. We have used NGTs to introduce changes in tomato fruit color and to produce compositional variants in specific tomato backgrounds (i.e. Muchamiel, San Marzano etc.) that conserved the traditional typology but introduce additional value in terms of fruit composition or colors. Moreover, we are eliminating the linkage drag (flavor composition change) associated to the introduction of disease resistance genes by correcting the tradeoff linkage allele with NGTs.

SWEDEN

At the Swedish Agricultural University in Uppsala, Sweden, our research group is routinely using NGTs, and particularly CRISPR technology. NGTs aids us in understanding basic biological processes that shape organisms and how we can take advantage of this knowledge to improve plants. As a consequence of our established multiplex CRISPR, we are now in the position to address the functional role of proteases encoded by redundant gene families. We are also developing new approaches of NGTs and implementing the technology not only in the basic research model plant Arabidopsis thaliana but also in crops like rapeseed (Brassica napus).

Open Statement

European scientists urgently reach out to the newly elected European Parliament and European Commission to enable the potential of genome editing for sustainable agriculture and food production.

European agriculture can make considerable contributions to the **UN Sustainable Development Goals**. Precision breeding methods like genome editing with CRISPR are innovative tools that have the potential to help reach these goals in a faster and more efficient way.

The current interpretation of the European legislation (case C-528/16) prevents **the use of genome editing for sustainable agriculture and food production in the EU.**

A small revision of the European legislation will harmonize it with the legal framework in other nations and enable European scientists, breeders, farmers and producers to include genome editing as one of their tools to meet the future challenges of sustainable development.

Our planet is facing unprecedented challenges because of a rising, more affluent world population, while biodiversity is diminishing at an alarming pace and the average temperature on earth continues to rise. To meet these global challenges and others, we will have to shift our mentality and lifestyle, to increase investments in knowledge creation and facilitate the use of innovative technologies.
This also means that agriculture and food production must become more sustainable. The environmental footprint of agriculture has to diminish and farming has to adapt to the rapidly-changing climate. Drought is one of the major factors that is threatening crop yields. We are witnessing this today in Europe. All possible approaches are required to meet these challenges. Plant breeding can make a substantial contribution by developing new crop varieties that are less susceptible to pathogens and are more resilient to drought. **This will enable farmers to produce high yields while decreasing the use of chemicals and water.**

> As an example, **the use of chemicals could be reduced drastically to fight fungal infections during wheat cultivation.**
> Here a minimal change of the so-called MLO genes induced by genome editing is sufficient to obtain resistance against powdery mildew. This type of alteration already exists in nature but is very difficult and time consuming to introduce via conventional breeding approaches. This is a clear example that shows how innovative methods like CRISPR can significantly accelerate the introduction of beneficial properties into crops.

To develop these varieties, scientists and plant breeders must have access to the widest possible array of breeding tools. The most recent addition to the toolbox is precision breeding with CRISPR. It allows scientists and breeders to develop desired crop varieties in a faster, relatively simple and much more directed way compared to previous breeding techniques. **Scientists and breeders in the EU should be enabled to use precision breeding techniques with CRISPR to contribute to a more sustainable agriculture and food production.**

Exactly one year ago, on the 25th of July 2018, the European Court of Justice (ECJ) ruled that plants obtained by precision breeding techniques like CRISPR are genetically modified organisms (GMOs) which, in contrast to the products of much less precise mutation breeding techniques, are not exempt from the GMO legislation. As of consequence, even crops with the smallest CRISPR-mediated alteration, which can also arise spontaneously in nature, are subjected to these provisions. This is highly problematic as the European GMO legislation presents an unreasonable regulatory threshold affecting research institutes and small breeder companies. It is simply too complicated and too expensive to comply with.

The EU GMO legislation, issued in 2001, no longer correctly reflects the current state of scientific knowledge. There are no scientific reasons to consider **genome-edited crops** differently than conventionally-bred varieties that have similar alterations. Plants that have undergone simple and targeted genome edits by means of precision breeding and which do not contain foreign genes **are at least as safe as varieties derived from conventional breeding techniques**.

EU maintains a high standard in food safety and the environment
It is important to note that not being subject to GMO legislation does not mean that such crops and foods are not regulated. There is general food safety legislation that prescribes that foods introduced onto the European market must be safe, and there is environmental legislation that will hold market players liable in case they would introduce crops into the environment that cause damage to biodiversity and protected habitats.

The consequence of the ECJ ruling is that in Europe precision breeding techniques like CRISPR are becoming the privilege of a select group of large multinational companies to exploit it in large cash crops. Consequently, the inability to market genome edited crops in Europe will cause a chilling effect on the investments in R&D in the European breeding sector. The result will be that the further development of beneficial varieties in a faster and much more directed way will be halted in Europe, while the rest of the world embraces the technology.

The EU GMO legislation differs from the legislation in many other nations. These countries apply legislation which is more adapted to the current state of scientific knowledge, excluding plants that have alterations that could also occur naturally or result from conventional breeding activities. **In other words, in these countries genome-edited plants are not subjected to the GMO legislation, enabling scientists and breeders to use genome editing for a more sustainable agriculture and food production.**
The difference in regulatory approach will likely lead to disruptions of international trade and have consequences for food security in Europe. As stated before, small alterations introduced by precision breeding also arise spontaneously in nature. Therefore, it is not possible to determine the origin of such small alterations implying that the current EU GMO legislation cannot be enforced on imported products. **A small revision of the European legislation, by means of harmonizing the legal framework with the other countries of the world, is vital to enable European scientists and breeders to use precision breeding methods like CRISPR as one of the tools to meet the global challenges of sustainable development.** It will unlock scientific progress to help provide solutions to the current challenges we are facing.

The European scientific community, signatory to this Open Statement, urgently calls upon the European institutions including the European Council, the new European Parliament and the upcoming European Commission to take appropriate legal action to enable European scientists and breeders to apply genome editing for sustainable agriculture and food. The ability to use genome editing is crucial for the welfare and food security of European citizens.

Statements on genome editing

Scientific community:

- Letter to the European Commission by **EU-SAGE**

  "Europe cannot afford to miss out on the important opportunities that genome editing offers for sustainable agriculture and food production. Strong political signals of commitment to solve the current regulatory deadlock are necessary to prevent irreversible damage to our European economy and to the transition to a green economy"

- Statement by the **Group of Chief Scientific Advisors** (SAM) - A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive

  "…in view of the Court's ruling, it becomes evident that new scientific knowledge and recent technical developments have made the GMO Directive no longer fit for purpose."
  "…we recommend revising the existing GMO Directive to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification. This should be done with reference to other legislation relevant to food safety and environmental protection.

- **European Plant Science Organisation** (EPSO) - Statement on the ECJ Ruling regarding mutagenesis and the Genetically Modified Organisms Directive

  "The ruling of the ECJ presents a considerable drawback for the future of innovative plant science and its societal benefits in Europe."
  "…EPSO supports a science-based revision of the present European legislation establishing a more proportionate product-based risk assessment."

- **German National Academy of Sciences Leopoldina and the German Research Foundation** (DFG) - Towards a scientifically justified, differentiated regulation of genome edited plants in the EU

  "…the science academies and the DFG see an urgent need to reassess the products of the much more precise and efficient methods of genome editing and to amend European genetic engineering law."

- **European Academies Science Advisory Council** (EASAC) - The regulation of genome edited plants in the European Union

  "EASAC reaffirms the importance of exploring radical reform and urges the EU Institutions to explore the options recommended by Leopoldina et al. (2019) and others:

• First, to revise the GMO definition/exemptions to enable the EU to capitalize on the plant breeding opportunities afforded by genome editing.
• Secondly, to develop a new legal framework to focus on traits not processes."

- Gene editing regulations: A position paper from the **European Federation of Biotechnology** (EFB)

  "The European Federation of Biotechnology regrets this ruling because it ignores scientific arguments that the interpretations of the technologies are scientifically inaccurate."

European seed sector:

- **Euroseeds** position paper - Plant Breeding Innovation Applying the latest Plant Breeding Methods for the benefit of sustainable Agriculture, Consumers and Society,

  "ESA (European Seed Association) considers that the consequences of this ruling present unacceptable socio-economic risks for European plant breeding, for the wider agri-food chain, for consumers and for our European environment."
  "The ECJ ruling shows that the existing GMO legislation no longer reflects current knowledge and scientific evidence. ESA therefore encourages Commission to apply the above-mentioned criteria and update the EU's current regulatory framework accordingly."

European farmers and agri-cooperatives:

- **Copa Cogeca** - NBTs are not a luxury but an urgent necessity for the vitality of the whole EU farming model

  "…last year's ruling by the European Court of Justice is already having serious repercussions on the strategy of European breeders."
  "New Breeding Techniques (NBTs) should be a priority within the Work Programme of the new Commission when it comes to agriculture. For Copa and Cogeca, it is now a matter of urgency that a real European strategy regarding these highly promising techniques is put in place, as they would ensure that our farming model is able to adapt to both the early effects of climate change and fierce international competition."

European Advisory Committees on Biosafety:

- **Advice of European Advisory Committees on Biosafety**

  "It was agreed that an improved regulation is needed which focuses more on the result of the genetic modification than on the way this modification has been achieved. An adaptation should take into account the decades-long national and international experience with genetic engineering gained so far, the similarity of products derived from natural, classical and targeted mutagenesis, and the practical availability of tools for law enforcement and control."

Consumers:

- **Consumer Choice Center** (CCC) - Letter to Commissioner Kyriakides

  "The European Union has traditionally objected most innovations in food science and prevented European consumers from accessing biologically-enhanced food. This can be seen in the very limited number of genetically modified crops authorized for cultivation in the EU, and a very cumbersome and expensive process of importing genetically modified food and a recent European Court of Justice ruling on treating gene editing as restrictive as GMOs."

Ethical perspective:

- **The Danish Council of Ethics** - GMO and ethics in the new era

  "The Council provides recommendations on the question of whether it would be ethically problematic to reject GMOs 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. The Council's opinion moreover implicates recommendations for a change of the EU's authorization system for GMOs and other plants with new traits."

Proposal by AFBV and WGG for amendments to GMO legislation

This proposal is a working document not for broad distribution, intended to elicit comments in order to serve as a basis for further discussion.

The text colored in blue reflects current wording of the Directive that is not modified by this amendment.

Draft Amendment to EC Directive 2001/18 based on Netherlands 2017 proposal

10 February 2020

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 thereof,

Having regard to (…)

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) Directive 2001/18/EC (hereinafter 'The Directive') of the European Parliament and of the Council establishes a comprehensive legal framework for the deliberate release and placing on the market of genetically modified organisms (GMOs);

(2) The rules laid down in The Directive do not apply to such organisms obtained through the techniques listed in Annex I A, Part 2 and Annex I B;

(3) Annex I A has never been adapted to new technical progress and scientific knowledge, since its establishment in 2001;

(4) New genetic modification techniques, which have been in development for more than 20 years and are known as genome editing, have emerged and have demonstrated significant potential for genetic improvement. Scientific reports show that these techniques have a level of safety comparable to mutagenesis and traditional breeding techniques;

(5) Scientific knowledge and technical progress have developed to an extent that requires a revision of Articles 2 and 3 as well as Annex I A and the creation of a new Annex I C. This Annex I C should exclude from the scope of The Directive certain categories of organisms obtained through genome editing techniques which permit precise and targeted modifications of the genome without insertion of recombinant nucleic acid sequences;

(6) The aim to enhance the functioning of the European internal market and improve opportunities for innovation, while protecting human health and the environment, underpins the need for revising Annex IA in order to include genome editing techniques in Part 1 and create a new Annex I C in order to exclude certain categories of organisms obtained through genome editing techniques;

(7) Growing and continued lack of clarity and legal certainty impede a smooth and harmonised implementation of The Directive, especially regarding its applicability with regard to new breeding techniques which lead to genome editing;

(8) To substantiate the excluded status of an organism under The Directive, adapted mechanisms are required to confirm applicability of the new exemptions under new Annex I C;

(9) In order to avoid unjustified discrimination between otherwise indistinguishable products obtained by genome editing and traditional breeding methods, all of which do not contain any recombinant nucleic acids, modifications to The Directive should constitute a full harmonization measure for GMOs as well as organisms that are excluded or exempted under revised Annex I

A, under Annex IB and new Annex I C, with such excluded or exempted organisms to be treated the same way as those obtained through traditional breeding methods;

(10) The Directive should therefore be amended accordingly;

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Paragraph (2) of Article 2 of The Directive is replaced by Article 3 below. Article 3 of The Directive is replaced by Article 4 below. Annex I A of The Directive is replaced by revised Annex I A below. A new Annex I C included below is added to The Directive.

Article 2

This amendment to The Directive constitutes a full harmonization measure for GMOs as well as organisms excluded under Article 2 (Annex I A, Part 3) or exempted under Article 3 (Annexes I B and I C), with all excluded or exempted organisms to be regulated only in the same manner as organisms derived from traditional breeding methods.

Article 3

Paragraph (2) of Article 2 of The Directive is replaced as follows:

(2) " genetically modified organism (GMO) " means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination

Within the terms of this definition:

(a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1;

(b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification;

(c) the organisms described in Annex I A, Part 3, are excluded from the scope of The Directive.

Article 4

Article 3 of The Directive is replaced as follows

Exemptions

1. This Directive shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B.

2. This Directive shall not apply to the carriage of genetically modified organisms by rail, road, inland waterway, sea or air.

3. After confirmation on a case by case basis by a competent authority of a Member State, in accordance with the terms and conditions defined in Annex I C, The Directive shall not apply to certain categories of organisms obtained by techniques of genetic modification identified in

revised Annex I A, Part 1, Point 4, and described in Annex I C, which Annex can be revised from time to time in accordance with the mechanism described in Article 5 below.

Article 5

Not later than once every five years, following consultation with relevant stakeholders and in collaboration with the competent authorities of the Member States, the Commission shall report to the EU Parliament on the evolution of scientific knowledge and technical progress and, if necessary, shall propose a revision of these Annexes. The first such report and eventual proposed revision shall be completed by 1 January 2025.

Article 6

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this amendment to The Directive by 18 months from the date of entry into force at the latest. They shall forthwith communicate to the Commission the text of those provisions.

   When Member States adopt those provisions, they shall contain a reference to this amendment to The Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this amendment to The Directive.
3. Regulations (EC) 1829/2003, (EC) 1830/2003 and (EC) 1946/2003 are amended to reflect the replacement of Paragraph (2) of Article 2 and Article 3 of The Directive and the addition of Annex I C to The Directive.

Article 7

This amendment to The Directive shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

Article 8

This amendment to The Directive is addressed to the Member States.

Signature

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Revised Annex I A

ANNEX I A

TECHNIQUES REFERRED TO IN ARTICLE 2(2)

PART 1

Techniques of genetic modification referred to in Article 2(2) (a) are inter alia:

(1) Recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;

(2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;

(3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

(4) genome editing techniques, a group of technologies that allow the targeted modification of genetic information by adding (insertion of), removing (deletion of), or exchanging (replacement of) nucleotides at a specific location in the genome of the recipient organism.

PART 2

Techniques referred to in Article 2(2)(b) which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules :

(1) in vitro fertilisation;

(2) natural processes such as: conjugation, transduction, transformation;

(3) polyploidy induction;

PART 3

The organisms covered by Article 3 paragraph 2 (c) of this amendment to The Directive, called "null segregants", are progeny of a GMO parental line from which the recombinant nucleic acid sequence(s) present in the parent has(ve) been removed through sexual crossing or a molecular excision mechanism, as well as any other exogenous sequences at the excision site.

The GMO can be either a GMO parent of the initial cross, a GMO line used for the molecular excision or a GMO line used as an intermediary in the production of the final organism.

However, if a null segregant has been obtained by using a technique listed in Annex I A, Part 1, Point 4, it shall be regulated in accordance with the terms and conditions of Annex I C.

New Annex I C

The text of this Annex has been written primarily with the intention to cover plants; it can be further adapted, if necessary and as appropriate, to animals and microorganisms.

ANNEX I C

As used herein, the term 'natural gene pool' refers to the gene pool of a plant species defined as all of the genes and alleles (i.e., different versions of the same gene) obtained from plants which can exchange genes by sexual crossing as well as from distantly related plant species with which genes can be exchanged by sexual crosses using traditional breeding techniques. The terms 'Editing' or 'edited' refer to the application of 'genome editing' techniques.

TECHNIQUES REFERRED TO IN ARTICLE 3, paragraph 3

Certain categories of plants, described below and obtained through use of the techniques described in Annex I A, Part 1, Point 4, are excluded from the scope of The Directive, provided that if recombinant nucleic acid sequences have been used in the editing process these recombinant nucleic acid sequences have been entirely removed from the modified organism. Additional categories may be added at a later date in accordance with the mechanism described in Article 5 of this amendment to The Directive, if justified by the evolution of scientific knowledge and technical progress.

a. Categories of plants to be excluded:

(1) Category 1: A plant having a native allele that has been edited to reproduce a functionality associated with a known allele present in its natural gene pool;

(2) Category 2: A plant having a native allele that has been edited to reproduce a functionality associated with a known allele present in a plant species that is outside the plant's natural gene pool;

(3) Category 3: A plant having a native allele that has been edited to reproduce a new functionality, of which the sequence modifications obtained by genome editing are of the same type as those which can be obtained by spontaneous or induced mutagenesis; and

(4) Category 4: A plant in which a gene known and present in its natural gene pool has been inserted into a targeted site of its genome.

With respect to all of the above categories, it is possible, through genome editing, to have in the same plant several edited alleles (or inserted genes). In such cases each edited allele (or inserted gene) shall be analysed independently according to the above-defined criteria. If all of the edited alleles or inserted genes fall under the same category, the plant belongs to such category. If the edited alleles or inserted genes belong to different categories, the plant must comply with each relevant category in order to be excluded. If a new edit is undertaken upon a different allele of a plant which has previously been determined to be excluded, only confirmation of exclusion for the new allele shall be required of the notifier.

b. Obtaining confirmation of the exclusion from The Directive of an edited plant:

Confirmation of the exclusion of an edited plant must be obtained by the notifier. The confirmation process is adapted to the exclusion category.

1. Procedure for submitting the confirmation request

- The notifier shall file its confirmation request with the competent authority of the Member State in charge of GMO regulations;
- The request for confirmation is made by the notifier whenever it wishes to benefit from the exclusion and remove its plant from the scope of The Directive;
- The exclusion decision for an edited plant shall be valid for all progeny of such plant containing the same edit and binding upon all Member States;
- Once the confirmation of exclusion is obtained, any variety obtained using the edited plant shall be subject to seed and plant variety regulations applicable to relevant crop species in the same manner as any variety obtained through traditional breeding techniques, including registration in the common catalogues of varieties of agricultural plant and vegetable species which can be marketed in the European Union.

2. Contents of the confirmation request application

The information requirements to be supplied by the notifier shall be adapted to the plant category:

a. *Standard requirements for all categories*:

(i) Name of the notifier and contact information;

(ii) Taxonomic description of the plant which has been edited or in which a gene has been inserted;

(iii) Technique used and main steps that have been followed, including, if applicable, whether or not an intermediate GMO was produced in the editing process, and the modalities of elimination of any inserted recombinant nucleic acid sequence, and confirmation of the elimination of any such inserted sequence (null segregant).

b. *Requirements that are Category specific*:

- For Categories 1 and 2:

  (i) Taxonomic description of the plant containing the model allele and a description of the model allele;

  (ii) Description of the edit realized in the final plant (addition, deletion or replacement) and confirmation that the resulting edited sequence has been obtained and comparison of the functionality of the model and edited alleles.

- For Category 3:

  (i) Description of the new allele and its functionality obtained after genome editing and available background information on the reasons that led to editing such allele (research work, for example);

  (ii) Description of the edit realized in the final plant (addition, deletion or replacement) and confirmation that the resulting edited sequence and its functionality have been obtained.

- For Category 4:
  (i) Taxonomic description of the donor plant containing the inserted gene and a description of such gene;
  (ii) Confirmation of the sequence of the inserted gene in comparison to the original gene before insertion;
  (iii) Confirmation that the inserted gene is located at the site targeted by genome editing.

c. Any information supplied by the notifier for which it wishes to claim confidentiality must be marked "Confidential".

3. Processing time

The processing time by the competent authority of a Member State to determine whether or not an edited plant falls under one of the four Categories for exclusion should be no more than sixty days.

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