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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 Plant Science Organisation (EPSO), Transparency Registry number: 38511867304-09

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

Fundamental and applied public research in the plant science sector

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

This contribution has been endorsed by 197 institutes/universities that are members of EPSO. It has been prepared by the Agricultural Technologies Working Group, which compiled the contributions received after a call for input addressed to all EPSO members.

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

All our replies refer only to plants (not to animals or microorganisms) and derived food and feed products obtained by genome editing leading to mutagenesis (point mutations or other modifications existing in nature) for agri-food and industrial applications (not medicinal) and for research, unless otherwise specified.

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

EPSO members are very active in the NGT field with a focus on three types of activities: (i) The development of NGTs to enhance their efficiency and specificity and to broaden their field of application, (ii) the use of NGT-products (modified plants) in fundamental research to decipher biological processes and (iii) the use of NGT-products (modified plants) in applied research to develop crop varieties with improved agricultural performance or leading to products with improved quality. Some of our members also modify the genomes of plant-associated microorganisms with the goal to protect the plant host against disease or to enhance its tolerance to abiotic stress.

The further development of NGTs is important in plant science, since the introduction of genome editing tools in the plant cell remains challenging for certain species or for certain genotypes within a given species (Altpeter et al., 2016). Despite tremendous progress over the past few years and the present capacity to edit 45 plant genera belonging to 24 different botanical families (Shan et al., 2020), a lot of work still needs to be done so that eventually any plant species can be edited. Other developments of NGTs concern the type of modifications and the efficiency with which they can be achieved in plant systems. Recent examples are the extension of novel tools such as base editing (Veillet et al., 2019), prime editing (Lin et al., 2020) or Cas9-NG to plants (Veillet et al., 2020).

CRISPR/Cas9 technology has become a widespread and highly appreciated tool in fundamental research and has replaced earlier tools such as RNAi in functional genomics aiming at determining gene function by the use of loss-of-function mutants. The majority of our members produce and use genome edited plants on a daily basis to further our knowledge of a large diversity of biological processes. Beyond functional genomics, derivatives of CRISPR/Cas9 technology are also used as tools in cellular biology (Puchta 2017).

Applied research by EPSO members provides an ever growing number of crops with novel traits compatible with a sustainable agriculture. The research is generally limited to proof of concept in confined environments, but a handful of field trials respecting the regulations have been or will be performed. The approximately 50-fold drop between confined and field trials is a clear indication that the present regulation in Europe is a major issue for harnessing the full potential of NGT-related research. The species targeted by NGT modifications are mostly major crops, but minor crops (including niche/local varieties) in the respective European countries are concerned, too. Some members such as the French CIRAD are also interested in agronomical applications of NGTs in partnership with developing countries in the global South.

NB: Please see supporting document #1 for list of cited references.

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

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

* Please provide details

Although the meaning of the question is not fully clear to us, we assume that the question concerns both the NGT-products produced by our members and the use of (potential) NGT-products provided to us by third parties. In the first case, our members strictly apply GMO regulation including the destruction of the material at the end of experimentation. In the second case, incoming material is handled according to GMO regulation, although it may not fall under such regulation in the country providing the material.

Plants produced by NGTs by our members have been declared to the competent authorities and have obtained the necessary permits. They are cultivated in P2 confinement greenhouses or growth chambers and GMO regulation is applied to avoid unintentional dissemination, in particular with regard to pollen or seed dispersal. Plants are destroyed at the end of the experiments and seeds are kept under controlled access. Similarly, field trials are put in place and tightly monitored following GMO regulation. Transport of NGT-products (mainly seeds) is carried out under GMO regulation and the possession of the necessary permits at the receiving facility is assured.

NGT-products (mainly seeds) received from third parties are subject to the same rules as NGT-products obtained by our members. The declaration of the NGT-origin of the material is part of good laboratory practices between collaborating scientists and one has to keep in mind that the NGT-modifications are generally the prime interest of the collaboration.

* 2 bis. Have you encountered any challenges?

- (●) Yes
- ( ) No

* Please provide details

Although the majority of our members did not encounter any technical challenges due to their longstanding experience with GMO regulation, four types of challenges should be mentioned:
(i) Compared to work with non-GMO material, the application of GMO regulation represents an administrative (declarations, permits) and financial (infrastructures with special/additional equipment) burden. The advent of genome editing provoked a boost in the number of plants falling under GMO regulation and thereby amplified this burden and led to space constraints in adequate facilities.
(ii) Despite a strong scientific interest to confirm results obtained in confinement under real world agricultural conditions, EPSO members remain very reluctant to perform field trials. In addition to the enormous administrative and financial burden, the fear of destruction (by GMO-opponents) is a major reason for this auto-censorship.
(iii) A minority of EPSO members, who previously worked only with EMS or transposon-induced mutants, would like to switch to NGT induced mutants. Since they don't have experience with GMO regulation or lack adequate facilities, they are bridled in their ambition and start to lose their scientific competitiveness.
(iv) Although the situation should not be generalized, at least in some countries the decision of the European Court of Justice (ECJ) to apply GMO regulation to NGT-products had a negative impact on funding of public research in the NGT field by the private sector. There is also an indirect effect on public funding, since the marks for the socio-economic impact of otherwise excellent fundamental research projects tend to decrease with the argument "no application in Europe".

* **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

NGT research is booming across the world since the early 2010s: an exponential growth of scientific publications on the topic, calls for proposals worldwide, license agreements between companies, as well as the first releases of plant varieties made with NGTs on the market in the US.

In European academic research, a large part of the project applications in fundamental plant science presently incorporate producing and testing of NGT plants as an essential research tool for studying the function of genes. In addition, a certain number of projects specifically developing or applying NGTs have been funded by dedicated research calls. The most important ones are:

- CHIC, NEWCOTIANA, COSMOS, and other H2020 -funded research projects (AU/EU)
- Sus-Crop-ERA-NET: https://www.suscrop.eu/; e.g. the project Prostrig (https://www.era-learn.eu/network-information/networks/suscrop/1st-transnational-joint-call-on-sustainable-crop-production/delivering-novel-maize-genotypes-with-improved-resilience-and-productivity-through-the-application-of-predictive-breeding-technologies-to-modulate-strigolactone-levels) uses NGT to develop more productive and resilient maize plants
- PlantED COST Action: CA18111 - Genome editing in plants - a technology with transformative potential (https://www.cost.eu/actions/CA18111/#tabs|Name:overview) coordinated by Dennis Erikson
- GENIUS (2012-2020) funded with 6 M€ by the French government established NGTs in 9 crops (wheat, rice, maize, oilseed rape, tomato, potato, apple, poplar, rose) and 3 models (Arabidopsis, Brachypodium, Physcomitrella; Nogué et al, 2019).
- Biotechnologies for Agriculture (BIOTECH): funded by the Ministry of Agriculture (MiPAF, Italy) and run by the Consiglio per la Ricerca in Agricoltura e l'Economia Agraria (CREA). Funding: 6 M€ per year, for three years (started in 2018). Species: horticultural species, cereals, fruit trees, grapevine, olive.
- Swedish Foundation for Strategic Research, SSF, Agenda 2030 Strategic Research Centre: Call directed towards plant biotechnology (including genome editing) funded with 6 M€. Project selection is expected in June with a start 2021.
- "Nutzpflanzen der Zukunft" Federal Ministry of Education and Research (BMBF) (started 2018): 26 projects are funded with up to 500 000 € each for 2 years. Subjects of funded projects are varied, for list (in German) see https://www.pflanzenforschung.de/de/pflanzenwissen/journal/modernste-methoden-fuer-schnelleren-zuechtungserfolg-di-11026

Worldwide hundreds of proof of concepts exist and lists indicating the used species/concerned topics were reviewed recently (Modrzejewski et al., 2019, Ricroch et al., 2017, Jansing et al., 2019). Two random examples in important species for Europe are the following (see also Q17):

- (SE) Per Hofvander and co-workers performed field trials with genome-edited starch potato (2016-2018) in collaboration with the company Lyckeby Stärkelse. For increased amylopectin, transient CRISPR-Cas9 expression in protoplasts was used (Andersson et al., 2017) or alternatively CRISPR-Cas9 ribonucleoprotein delivery was employed (Andersson et al., 2018). Furthermore, reduced enzymatic browning in potato tubers by editing the polyphenol oxidase gene was achieved (González et al., 2020).
- Elimination of coeliac disease epitopes from gluten in wheat (Sánchez-León et al., 2018; Jouanin et al., 2019)

A handful of field trials are ongoing with camelina (UK), maize (BE), tomato and oilseed rape (ES), or are planned for 2021 with potato (NL). See Q9 for more detail. Plant varieties produced with NGTs currently on the market are treated under Q17.

NB: Please see supporting document #1 for list of cited references.

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

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

* Please provide details

As for Q2, we assume that the question concerns both the follow up of the NGT-products produced by the European plant science and breeding sector and the use of (potential) NGT-products provided to the sector by third parties. In the first case, the strict application of GMO legislation declares, identifies, tracks and labels NGT-products. In the second case, incoming material declared as NGT is used under GMO regulation. However, there is no technical safe guard possible to shield against edited material not declared as NGT in cases where there is no obligation for such a declaration in the country of origin.

Although the application of GMO legislation is clearly sufficient to guard against unintentional use of NGT-products produced by the European plant science and breeding sector, the sector believes that less stringent measures would still allow to achieve this objective. For example, a simple declaration of the genome modification(s) would provide the necessary detection tools to third parties worried by unintentional use, as proposed by Bratlie et al., (2019) or AFBV-WGG (2020).
With regard to incoming NGT material, e.g. plant varieties used for further improvement by plant breeding, the sector presently applies GMO legislation in the same way as for its own material, as long as the NGT-origin is declared. However, in numerous countries including the USA, Argentina, Brazil, Columbia, Chile, Israel, Japan and Australia, at least certain NGT-plants are exempted from GMO legislation and not subject to specific legislation (Ishii and Araki, 2017; Dederer and Hamburger 2019). In the absence of methods allowing the attribution of genome modifications to specific techniques (Grohmann et al., 2019), the European sector is faced with a major challenge to know which incoming material has to be used following GMO legislation. The most far reaching solution, i. e. to no longer use any plant varieties from outside of Europe would severely impact the capacity of the sector to provide European farmers with plant varieties adapted to evolving needs.

NB: Please see supporting document #1 for list of cited references.

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

- (●) Yes
- ( ) No

* Please provide details

Present GMO legislation and the tools implemented for its reinforcement are clearly not suited to guard against unintentional use of NGT-products if the nature of the genome modification(s) is not known. Although unknown genome modifications can be detected under certain circumstances, this does not permit the identification of the process that generated it and to decide, whether GMO legislation needs to be applied or not.

Enforcement of GMO legislation is based on event-specific or construct-specific PCR methods that allow the detection of transgenes in the genomes of GMOs. They are costly but rather easy to apply because the inserted sequences are known, the construct building blocks (notably promoter sequences) are rather limited in number, the number of deregulated events remains low. They are rather sensitive with a PCR detection threshold around 0.9%. These methods are still useful for certain NGTs or the rare case where the genome editing tool triggering the genome modification (Cas9 transgene and/or sgRNA unit) are still present in the genome. However, as indicated above, our answers to this questionnaire are limited to the vast majority of

NGT-plants, which are transgene-free. Such NGT-plants-either never had a transgene inserted in their genome (transient expression or RNP technology) or lost the transgene by genetic segregation (null segregants). In such cases, as concluded by European Network of GMO Laboratories (ENGL 2019), the PCR-based screening methods mentioned above cannot be applied nor could novel methods be developed for detection of this type of NGT-plants.

Gold standard whole genome DNA sequencing has been proposed as an alternative to detect unknown DNA alterations through "variant calling", which is able to reveal single nucleotide polymorphisms (SNPs), deletions and inversions. This is actually the case if (i) an appropriate (ideally the parent) reference genome sequence is available (difficult for incoming material without a pedigree), (ii) high quality de novo genome assembly (for example a combination of long and short reads complemented by an optical map) and not just simple resequencing with short reads is carried out (costly and time consuming) and (iii) the material has a certain homogeneity. However, the detection of a genome modification does by no means permit the identification of the process that generated it (Grohmannn et al., 2019). SNPs, deletions and inversions are known to exist "naturally" between crop varieties of the same species and to be the origin of important agronomic traits (Olsen and Wendel, 2019). For example, when comparing two maize varieties, on average 5% of the genome are either missing in one of the two lines or found in another location (Darracq et al., 2018; Haberer et al., 2019). Therefore, it is impossible to distinguish genome modification that have been obtained by NGTs from genome modifications that have been obtained by conventional breeding or random mutagenesis techniques, which are exempted from GMO regulations (Custers et al., 2019).

Unintentional use of NGT-products should not be confounded with unintended effects of certain NGTs, i. e. modifications at other sites of the genome than the one targeted by the genome editing tool (off-targets). There are two types: (i) modifications at sites with sequence homology to the target site and (ii) modifications at totally unrelated sites. The first type can be handled e.g. by designing guide RNAs to such target sites without very high sequence homology elsewhere in the genome (Tang et al., 2018; Li et al., 2019). For example, the probability of editing at a duplicate site drops to 0.09% (5 out of 5700), if four or more mismatches discriminate the two duplicated sequences (Modrzejewski et al. unpublished). There are also reports that the use of certain types of genome editing tools (Kaya et al., 2016) or transient DNA-free genome editing (Andersson et al., 2018, Liang et al., 2018) can lower off-target effects (Hahn and Nekrasov, 2019). With regard to the second type of unintended effects, there is consensus among plant scientists that there is no evidence for bona fide off-target mutations even in the case of continued expression of Cas9 or Cpf1 (Tang et al., 2018). The nature and frequency of genome modifications at unrelated sites is the same as for spontaneous mutations from one generation to the other (approximately 10 mutations/1 Gbp; Ossowski et al., 2010), which makes it impossible to attribute them to one or the other. Modifications triggered by tissue culture (somaclonal variation) rather than editing tools may occur during NGT production, but are not fundamentally different from deletions, insertions or inversions arising spontaneously (Tang et al., 2018; Li et al., 2019).

NB: Please see supporting document #1 for list of cited references.

* **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

NGTs are less invasive and more precise than classical GM techniques by which one or several transgenes are inserted into the genome in an uncontrolled process at random positions. Consequently, EPSO members consider that the measures foreseen by GMO legislation are more than sufficient for plants obtained by NGTs and no additional or specific measures are needed.

As already mentioned in our answer to Q2, plants obtained by our members by the use of NGTs have been declared to the competent authorities and have obtained the necessary permits. NGT-plants and their products are therefore clearly identified. NGT-plants are cultivated in P2 confinement greenhouses or growth chambers and GMO regulation is applied to avoid unintentional dissemination, in particular with regard to pollen or seed dispersal. Plants are destroyed at the end of the experiments and seeds kept under controlled access. Transport of NGT-products (mainly seeds) is also carried out under GMO regulation and the possession of the necessary permits at the receiving facility is assured.

Similarly, the rare field trials were put in place and tightly monitored following GMO regulation. For example, in the case of tobacco plant lines edited in juvenility/flowering-related traits in Spain, this included the obtainment of permission for open field experiments (deliberate environmental release of GMOs) through the national biosafety/bioethics authority CNB (Resolution B/ES/20/01).

* 5 bis. What challenges have you encountered?

Our members did not encounter any major challenges in the application of GMO legislation to plants obtained by NGTs. Nevertheless, as detailed in our answer to Q2, the application of GMO legislation (i) represents an additional administrative and financial burden compared to work with non-GMO material, (ii) discourages researchers to perform field trials needed to confirm greenhouse results under real world agricultural conditions, (iii) bridles the ambition of a minority of our members not used to or equipped for the constraints of GMO legislation and (iv) negatively impacts public and private funding at least in some member states.

Whenever our members obtain plants by NGTs, they necessarily develop methods that provide evidence for the desired modification in the genome. Applying good laboratory practices, they also keep pedigrees of these plants. Consequently, the detection/traceability of these NGT-plants is not an issue in confined environments or closely monitored field trials.

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

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

* Please describe what type of support and what best practices you can share

It is difficult to answer this question with yes or no. We are not aware of any specific national or European effort, put in place after the Court of Justice's judgment in Case C-528/16, to support research institutes and universities to conform or comply with EU GMO legislation when working with NGTs or NGT-products.

Notwithstanding our disapproval of the Court of Justice's judgment in Case C-528/16, which to our opinion disregards scientific evidence (EPSO 2019), it had the virtue to clarify the regulatory situation for all member states. Scientists previously seduced by less strict opinions of certain national competent authorities but hesitant about their adoption, now have clear guidance.

More generally speaking, after three decades of GMO research under confined conditions, the procedures to obtain the respective permits are well established in most countries and the timelines rather reasonable. However, the limited surfaces available in growth chambers and greenhouses fulfilling GMO requirements start to become a bottle neck, for example in Italy. The situation is more diverse in regard to field trials. Whereas Spanish researchers found the terms and time lines for application of deliberate environmental release reasonable and the authorities supportive, French researchers refrained from applications because the last requests had never been processed.

NB: Please see supporting document #1 for list of cited references.

* **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

Our members involved in the use of NGTs as well as other actors of the sector, namely seed companies with active R&D in biotechnology and service providers specialised in the detection of GMOs have experience in the detection of known genome modifications achieved by NGTs. With regard to the detection of unknown NGT-events, we fully share the conclusion of the European Network of GMO Laboratories (ENGL 2019) that under the current circumstances, market control will fail to detect unknown genome-edited plant products. Finally, a declarative traceability along the entire value chain does not seem credible without the possibility of technical verification.

Known modifications: Technically speaking, NGT-products can be traced, for example by classical polymerase chain reaction (PCR), quantitative PCR (qPCR) or digital droplet PCR (ddPCR), as long as the modification and the genomic sequence of the plant, which carries the modification are known. This detection is easy, as long as the sample is a pure NGT-product, and gets more challenging, when the NGT-product is only present in trace amounts, for example in an otherwise non-NGT sample or in food stuff. Methods based on ddPCR seem particularly suited for the highly sensitive detection of variant alleles in a DNA sample (Mock et al., 2016, Wang et al., 2019a).

Unknown modifications: The PCR-based screening methods mentioned above, which are commonly used to detect conventional GMOs cannot be applied nor could novel methods be developed for detection of NGT plant products. The reason is that the currently used screening methods are targeting common sequences which are not occurring in NGT plants (ENGL 2019). Whole genome DNA sequencing allows under certain conditions to detect unknown DNA alterations in a product. However, this detection of a sequence alteration does not permit the identification of the process that generated it since the same DNA alteration could have been obtained by conventional breeding or random mutagenesis techniques, which are exempted from GMO regulations (Grohmann et al., 2019). The conditions for exhaustive detection by whole genome sequencing include (i) the availability of an appropriate reference genome sequence, (ii) high quality de novo genome assembly (not simple resequencing), e.g. a combination of long and short reads complemented by an optical map and (iii) homogeneity of the sample or at least preponderance of the modified type in heterogeneous samples.

Declarative traceability: Although it is theoretically possible to trace a genome modification from its creation in a laboratory over the numerous generations and crosses of a breeding program to farmers, transport companies, traders, processing industries, distributors and finally the end user, two main reasons argue against such a scenario. (i) Compliance with this type of traceability could not be reinforced due to the technical limitations in detection of NGT-products explained above, (ii) the present policy of non-disclosure of genome modifications in non-EU countries exempting NGT-products from GMO legislation would severely hamper the process on the international level and (iii) the scale of testing would be unprecedented taking into account the current massive use of NGTs in plant breeding that will likely lead to thousands of unknown genome modifications and combinations thereof.

Artificial tags: Our members have no specific experience or knowledge on the voluntary introduction of tags into NGT-products. Such identity preservation systems have been developed in the past for certain types of GMOs. They ensure retention of control over the product from the production phase until end-use sales at consumer level. Tags would be counterproductive to the small changes (i.e. single base pair mutations) equivalent to natural mutagenesis that are possible by NGTs, i.e. tags would be a larger modification than the NGT-caused modification themselves. We are not advocates of such tags (genetic or other) and rather propose that the NGT-products covered by our answers (see above) should be excluded from EU GMO legislation.

NB: Please see supporting document #1 for list of cited references.

* **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

No specific measures for NGT-products were taken, general GMO legislation was respected (see below)

* What best practices can you share?

No specific measures for NGT-products were taken, general GMO legislation was respected (see below)

* Please explain why not

Since our members currently have no GM or NGT-product on the market, we are not concerned by EC regulation concerning the labelling of GMOs. As mentioned above, our members apply standard GMO regulation for the identification and traceability of NGT-plants in their research facilities.

A specific situation concerns France, where the recent ruling of the State Council (Conseil d'Etat 2020) asked the government to apply stricter rules than the ones suggested by the Court of Justice's judgment in Case C-528/16. This means that plant varieties obtained by certain chemical and irradiation mutagenesis techniques will also fall under GMO legislation. This may oblige public French research institutes to either label certain of their plant varieties as GMO or to withdraw them from the French market.

NB: Please see supporting document #1 for list of cited references.

* 8 bis. What challenges have you encountered?

The main challenge with labelling is that control of compliance is practically much more difficult than with classical GMOs and even impossible in many cases (see answers to Q7 and Q28), so much more effort is needed on track and trace.

* **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:

- ☑ Agri-food sector
- ☐ Industrial sector
- ☐ Medicinal sector

Agri-food sector

GMO legislation has a strong negative impact on the number of field trials involving NGT-plants carried out by our members, which is approximately 50-fold lower than the number of research projects in confined environments. This is fundamentally different from research with mutants obtained by techniques with a safe history of use, which are frequently analysed under field conditions, or research in conventional breeding, which is essentially carried out under field conditions.

With regard to field trials by our members, it is not surprising that they are concentrated in countries that either authorize the culture of GMOs or are very open to field trials for GMO R&D:

- GB: Camelina with high oleic acid content (Rothamsted Research, B/GB/19/R08/01)
- BE: Maize with altered DNA damage repair, a research tool to assess environmental stress (VIB Ghent, B/BE/19/V1)
- ES: Tobacco with longer vegetative phase with a delay in flowering time (CTAEX, B/ES/20/01)
- SW: Potato with modified starch (SLU in collaboration with Lyckeby Starch AB, B/SE/19/5614)
- SW: Potato with mutations aiming at late blight and early blight resistance (SLU, B/SE/20/1726)
- NL: Potato with genome editing in different genes (WUR, upcoming in 2021)
- ES: Tobacco with modified nicotine pathway (CTAEX, upcoming in 2020)
- ES: Tomato with improved protection against pathogens and pests (CBGP)
- ES: Oilseed rape for enhanced tolerance to environmental changes such as heat and drought (CBGP)

Compared to non-GMO trials, these field trials were clearly a lot more expensive. High cost was noted for application, containment and/or protection.

In other countries, researchers frequently refrained from field trials despite promising results under confined conditions. The reasons include fear of destruction, additional cost, doubt on a timely reply to permit requests and inexperience with the administrative procedures. A minority is also worried about the negative impact NGT-field trials may have on public perception of their institute and the possible negative consequences for their non-NGT research.

NB: Please see supporting document #1 for list of cited references.

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

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B - Information on research on NGTs/NGT-products

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

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

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

Almost all EPSO scientists use existing NGTs as tools in fundamental research to decipher and alter

biological processes and in applied research to develop crop varieties with improved agricultural performance or leading to products with improved quality (Blanvillain-Baufumes et al., 2017; Nieves-Cordones et al., 2017; Modrzejewski et al., 2019). Furthermore, EPSO members perform research to develop new NGTs, to enhance their efficiency and specificity and broaden their field of application. So in principle NGTs have become routinely used tools in the plant research community which is represented by EPSO (see also Q16).

Quite a few EPSO members are involved in two European research programs funded by EU H2020 grants No 760331 (NEWCOTIANA, 7 EU member states, 7.2 M€) and No 760891, (CHIC, 10 EU member states, 7.3 M€). In NEWCOTIANA the subject is replacement of nicotine in tobacco by added value substances. The consortium focuses on Nicotiana benthamiana, aiming for transgene-free editing and gene targeting to produce and evaluate new metabolites for medicine and cosmetics (https://newcotiana.org/). The CHIC-project aims at the improvement and exploitation of chicory as a multi-usable crop. The consortium develops and implements new NGTs to modify the chicory genome by directed mutagenesis. The final goal is to produce inulin for dietary purposes and several bioactive terpenes for a bio-based economy (http://chicproject.eu/).

Other major funding initiatives are not focused on a single species. For example, in the Netherlands gene editing counts as focal technology providing a total public funding of 5.8 M € plus 4.4 M € from breeding companies, mostly SMEs. In Italy the three-year "BIOTECH" program was awarded 6 M€ from MIPAAF for NGT research on grapevine, olive, apple, citrus fruit, apricot, peach, cherry, strawberry, kiwifruit, eggplant, tomato, basil, artichoke, wheat, rice, and poplar trees (https://www.crea.gov.it/-/biotech). In France the GENIUS project (2012-2020) funded with 6 M€ established NGTs in 9 crops (wheat, rice, maize, oilseed rape, tomato, potato, apple, poplar, rose) and 3 model plants (Arabidopsis, Brachypodium, Physcomitrella) (Nogué et al, 2019).

Several smaller scaled research programs (0.5 to 1M €) have been started in most countries across the EU, a lot of them before the EU court decision. EPSO received input from all major EU countries but could not go into detail for all projects (see example list).

The plants and subjects addressed in these projects are highly diverse. For example, a recent unpublished survey in France listed 38 species of microalgae and higher plants. Although herbicide tolerance may appear in some abstracts, it is only used as a research tool to optimize the still delicate SDN2 technique and does not present a breeding objective of academia (Danilo et al., 2019). The main applied research subjects of our members are improved agronomic value characteristics, enhanced food and feed quality, resilience against biotic and abiotic stress and production of new beneficial components in plants (for review see Modrzejewski et al., 2019; Metje-Sprink et al., 2019; Ricroch et al., 2017).

A non-exhaustive example list of agronomic relevant research subjects and plants in the EU until end of 2019 is itemized below. EPSO wants to emphasize that basic research issues are uncountable as daily new ones are published and therefore only projects or publications dealing with agronomic relevant traits are listed.

- Agronomic value characteristics: Improved biomass production and better grain quality in sorghum (INRA) and wheat (Wang et al., 2018), root biomass in rubber (Wieghaus et al., 2019), increased shatter resistance in canola (Braatz et al., 2017), early flowering and fruit ripening in tomato (Soyk et al., 2017; Jiang et al., 2018; Wang et al., 2019b), waxy rice (Perez et al., 2019), altered fruit shape in wild tomatoes (Zsögön et al., 2018).
- Biotic stress resilience: Bacterial blight and speck resistance (Blanvillain-Bafume et al., 2017; Oliva et al., and Eom et al., 2019; Ortigosa et al., 2019), potato virus Y resistance (Zhan et al., 2019), wheat dwarf virus resistance in barley (Kis et al., 2018), powdery mildew resistance in tomato (Nekrasov et al., 2017).
- Abiotic stress resilience: Drought resistance in maize (Njuguna et al., 2018, Belgium).

• Food and feed quality: Improved oil composition in Camelina (Aznar-Moreno et al., 2017; Morineau et al., 2017, Rothamstead Research, 2018), low caesium rice (Nieves-Cordones et al., 2017, INRA), low gluten wheat (Sanchez-Leon et al., 2017), altered carotenoid composition in tomato (not published, Milano-Italy).
• New beneficial components: Improved starch quality in potato (Andersson et al., 2017; Veillet et al., 2019; France, UK, Sweden). Modified starch in cassava (Bull et al., 2018, Belgium, Switzerland).

NB: Please see supporting document #1 for references

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

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

* Please specify

Since their development in the last 10-15 years, NGTs, especially considering site directed nucleases (SDN), spread very quickly in all fields of plant research and they are nowadays routinely used tools in 45 plant genera belonging to 24 botanical families for plant researchers worldwide (Shan et al., 2020). Ricroch published a review in 2017, summarizing the worldwide plant research using CRISPR/Cas9 for basic and applied research (Ricroch et al., 2017). Modrzejewski et al. published in 2019 a more comprehensive report due to the more recent database search. The systematic map research shows that especially CRISPR/Cas9 based applications in plant science grew exponentially between their discovery (in 2012) and June 2019 (the date of the database search). The evaluation of this map showed that 555 publications containing primary data about SDN applications existed in the plant field (Modrzejewski et al., 2019). These 555 publications contained more than 1300 evaluable studies. The data were analyzed for different topics like the used plants, the performing countries worldwide, the addressed genes or even traits and if basic or applied research was performed. One result was that the majority of the 1328 studies were using CRISPR/Cas9 (1032) and only a minority was using TALEN, ZFN and meganucleases (227 altogether). In most of the studies, point mutations were induced and in total the genome of 51 different plant species was modified by the SDN technique. The majority of worldwide research happened in Asia (784 studies) followed by the USA (508 studies) and Europe (198 studies). Rice was the plant most often used (465 studies), followed by Arabidopsis (218 studies, see Modrzejewski et al., 2019).

According to the systematic map, the modified traits in crop plants consist of three main groups: Agronomic value (36 applications), food and feed quality (28) and biotic stress tolerance (16) and three smaller groups of applications: Herbicide tolerance and industrial use (6 each) and abiotic stress tolerance (5 applications, see Modrzejewski et al., 2019).

A more detailed listing of published NGT approaches follows under Question 13.
Regarding applied research with field release of NGT crop plants Metje-Sprink (2019) showed that only two out of 27 published field trials were placed in Europe (see Q9 for additional unpublished field trials in Europe), whereas 24 happened in China, Japan or the USA. Again here the most often used plant in the field was rice (18 of 27 field releases) followed by tomato (three). In total eight different plant species modified by NGTs occurred in published field trials until 2019 (see table 1 in Metje-Sprink et al., 2019). In these field trials NGT-rice, tomato and Camelina were investigated regarding biotic (pathogens) and abiotic (salt, drought) stress resistance, improved agronomic values (early flowering, shelf life) and food and feed quality (altered oil composition, low Cd-accumulation).

NB: Please see supporting document #1 for list of cited references.

* **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

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

* Please describe

A substantial number of EPSO members reported direct or indirect negative impact on the funding of research involving NGT or NGT products.

A main impact of the EU ruling on mutagenesis consists in demotivation of researchers throughout the EU (reported from most EPSO members) and a decline of funding programs dedicated to NGTs after 2018. Basic research is possible in principle but regarding the socio-economic future of NGT products, applied research is almost impossible to realize in the EU. This includes field trials of NGT-plants, which are rarely performed in the EU similar to field trials for GMOs. Only two out of 27 published field trials involving NGT plants worldwide were performed in the EU until 2019 (Metje-Sprink et al., 2019; see Q9 for additional unpublished field trials in Europe). Five international consortia were declared ineligible by the Austrian ministry because of planned NGT work (e.g. SUSCROP consortia with EPSO members). Austria, France, Germany, Spain and Italy reported either direct funding restrictions due to planned NGT-work (ERAnet) or indirect funding restrictions by demotivation of industrial and academic partners after the court decision. EPSO members from EU states tend to avoid participation in big collaborative applied projects involving the use of NGTs that will request intentional release for proof of concept in the field as this is almost impossible in most EU member states. Researchers participating in larger collaborations transfer their field trials and generated expertise to somewhere outside of the EU.
Indirect funding restrictions of partnerships between academia and enterprises are also a consequence of the EU-ruling as companies are not interested to invest in projects without the later possibility to use the product in the EU. Altogether, this is a huge disadvantage for applied research using NGTs in the EU compared to other countries in Asia and South- and North-America that handle NGTs more flexibly.

NB: Please see supporting document #1 for list of cited references.

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

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

* Please provide concrete examples/data

As already mentioned in the answers to Q10 and Q11, worldwide a large number of plants have been modified using NGTs to result in better products. The direct benefit for research is the ability to modify interesting traits much more easily in virtually any plant species (see Ricroch et al., 2017; Modrzejewski et al., 2019; Nogue et al., 2019; Sedeek et al., 2019). Besides the already published examples of trait modification in more than 50 different plant species, NGT will also speed up the breeding in polyploid crops, which are not easily amenable to mutation breeding (e.g. wheat, oilseed rape, potato, rose, leek, kiwi, banana, cotton). Furthermore, the production of improved food products by eliminating allergens e.g. breeding wheat with a low-gluten content is now possible (Sanchez-Leon et al., 2018). This application underlines the opportunities of simultaneous modification of dozen of genes in gene families. Additionally, NGTs offer the ability to knockout plant specific glycosylation in order to produce proteins in plants that are better suited for pharmaceutical/medical application (Jansing et al., 2019).

Precise genome editing by NGTs is used to establish plants resistant against various pathogens like bacteria e.g. Xanthomonas oryzae (Wang et al., 2016; Blanvillain-Baufume et al., 2017; Oliva et al., 2019; Tian et al., 2019; Xu et al., 2019), fungi (Zhang et al., 2020) and viruses (Macovei et al., 2018; Kis et al., 2019). NGT approaches can accelerate the use of mosses as green cell factories for the production of proteins, lipids and fine chemicals thereby avoiding environmental pollution (Reski et al., 2018).

Many more applications with agronomical and consumer benefits are published or in the research pipeline worldwide (Modrzejewski et al., 2019). Different EPSO members reported a number of funded research projects dealing with tomato resistance against bacterial and fungal diseases, improved yield, flavour and colour, drought tolerance in rice as well as virus resistance in melon and cucumber. In summary, such applications of NGTs will decrease the burden on the environment in the long run as less pesticides or fungicides have to be used and in case of drought tolerance water use efficiency is increased.

An additional aspect is the neo-domestication of new crops and the accelerated breeding of orphan crops; this will eventually lead to a larger crop diversification available for crop rotation in agriculture (Lemmon et al., 2018; Li et al., 2018c; Zsögön et al., 2018).

NB: Please see supporting document #1 for list of cited references.

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

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

* Please provide concrete examples/data

Since the ECJ-ruling of 2018, NGT-related research faces the same challenges as GMO-research in the EU. This is particular challenging for applied research with emphasis of developing better products for agriculture, as these are almost impossible to place on the market in the EU for small and medium companies. The bureaucratic efforts and costs combined with a substantial risk of destruction of fields by GMO opponents has led to a very limited amount of performed field trials in the EU (see Q9). Field trials are essential to test new plant varieties under real life conditions and so companies and research facilities either do not work with NGTs in the EU or if they do so, they go overseas for field trials. The final products cannot be commercialized in the EU. This is of course a large handicap for applied research in the EU because the development chain from research to market is severed. As a consequence, this leads to demotivation of researchers and companies and to brain drain of young enthusiastic scientists to outside Europe. Thereby, Europe is losing its competitiveness with the rest of the world.

Another big challenge is the enforcement of the regulation of NGTs in accordance to the existing EU law. Despite the claims of some stakeholders that NGT plants containing only small mutations are easily traceable, the fact is that they are not. Small genome alterations occur during each propagation of a plant and can mimic the intended (or unintended) mutation by the breeder. Almost every mutation can be found in a given plant but it cannot be assigned to a certain method. This has been clearly stated and discussed by Grohmann et al., (2019) and the report of the European Network of GMO Laboratories (ENGL 2019). It is a huge challenge for the national controlling authorities, which have to screen imports routinely for approved and unapproved GMOs. If the authorities do not know for which unapproved NGT they are looking for, the only chance to find something is whole genome sequencing. Some parties claim that this will detect any mutation in the respective plant. The truth of this claim depends on additional information such as knowledge of the ancestors of the plant, a reference sequence and a gold standard coverage of the genome (Grohmann et al., 2019). Nevertheless, this time and money consuming procedure will only detect mutations but not assign them to a specific cause. The detected mutation can be produced either by an NGT, by mutation breeding (which is exempted), by somaclonal variation or by natural mutation and there is no way to discriminate what the causative procedure was. Furthermore, this is an unsolvable challenge for any contamination of imported goods with a natural or exempted mutation because this would appear like an unapproved GMO (see also answer to Q7).

NB: Please see supporting document #1 for list of cited references.

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

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

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

EPSO identified a number of research needs and gaps regarding NGT-related research.

One urgent need is to increase the efficiency of the transformation and regeneration in many crop species and subspecies (Altpeter et al., 2016; Das Bhowmik et al., 2019). The range of genotypes in which NGTs can be applied has to be increased i.e. by improving the cell/tissue culture procedures for certain species (Kausch et al., 2019). An increase of addressable sequence loci in genomes is needed, this can be achieved by exploitation of Cas-enzymes that possess different binding and/or cutting features (i.e. different PAM sequences, Chen et al., 2019).

There is also a large need to improve research and society interactions, so that research can take on board society's expectations and fears, both from technical and ethical point of views. For this, it is necessary to establish more as well as more regular forums for meeting and dialogue, than those that currently exist. Civil society should be an intrinsically part of the research steering process to enhance transparency.

Besides these research needs, one identified research gap is a comparison of NGTs to older techniques with a history of safe use (e.g. chemical mutagenesis, in vitro propagation, conventional breeding) with regard to large deletions, inversions and other genome modifications. Recurrently different stakeholders argue that NGTs unintentionally provoke large deletions or even inversions in genomes and that this is a) special for the technique and b) dangerous. This is contrary to scientific knowledge since it is known for a long time that any DNA break in a genome can provoke large insertions, deletions or inversions of DNA and that this phenomenon is occurring during natural propagation of a plant (Salomon and Puchta 1998; Puchta 2005; Grohmann et al., 2019). Therefore, a direct comparison of NGT mediated genome alterations to natural occurring ones or such alterations provoked by somaclonal variation or chemical mutagenesis would undoubtedly prove or disapprove the safety of NGTs.

NB: Please see supporting document #1 for list of cited references.

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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

Almost all EPSO scientists use existing NGTs as tools in fundamental research to decipher and alter biological processes and in applied research to develop crop varieties with improved agricultural performance or leading to products with improved quality (Blanvillain-Baufumes et al., 2017; Nieves-Cordones et al., 2017; Modrzejewski et al., 2019). Furthermore, EPSO members perform research to develop new NGTs, to enhance their efficiency and specificity and broaden their field of application. In principle NGTs have become routinely used tools in the plant research community which is represented by EPSO.

As already mentioned in the answer to Q13, worldwide a large number of plants have been modified using NGTs to result in better products. The direct benefit for research is the ability to modify much more easily interesting traits in virtually any plant species (see Ricroch et al., 2017; Modrzejewski et al., 2019; Nogue et al., 2019; Sedeek et al., 2019; Shan et al., 2020).

Besides the already published examples of trait modification in more than 50 different plant species, NGT will also speed up the breeding in polyploid crops, which are not easily amenable to mutation breeding (e.g. wheat, oilseed rape, potato, rose, leek, kiwi, banana, cotton). Furthermore, the production of improved food products by eliminating allergens e.g. breeding wheat with a low-gluten content is now possible (Sanchez-Leon et al., 2018). This application underlines the opportunities of the simultaneous modification of dozens of genes in gene families. Additionally, NGTs offer the ability to knockout plant specific glycosylation in order to produce proteins in plants that are better suited for pharmaceutical/medical application (Jansing et al., 2019).

Precise genome editing by NGTs is used to establish plants resistant against various pathogens like bacteria e.g. Xanthomonas oryzae (Wang et al., 2016; Blanvillain-Baufume et al., 2017; Oliva et al., 2019; Tian et al., 2019; Xu et al., 2019), fungi (Zhang et al., 2020) and viruses (Macovei et al., 2018; Kis et al., 2019). NGT approaches can accelerate the use of mosses as green cell factories for the production of proteins, lipids and fine chemicals thereby avoiding environmental pollution (Reski et al., 2018).

Many more applications with agronomical and consumer benefits are published or in the research pipeline worldwide (Modrzejewski et al., 2019). Different EPSO members reported a number of funded research projects dealing with tomato resistance against bacterial and fungal diseases, improved yield, flavour and colour, drought tolerance in rice as well as virus resistance in melon and cucumber. In summary, such applications of NGTs will decrease the burden on the environment in the long run as less pesticides or fungicides have to be used and in case of drought tolerance water use efficiency is increased.

An additional aspect is the neo-domestication of new crops and the accelerated breeding of orphan crops; this will eventually lead to a larger crop diversification available for crop rotation in agriculture (Lemmon et al., 2018; Li et al., 2018c; Zsögön et al., 2018).

NB: Please see supporting document #1 for list of cited references.

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

- (●) Yes
- ( ) No

* Please explain

One major advantage of NGTs is to open up new avenues for the modification of specific genes in a very fast way. This is used for instance to accelerate forest or fruit tree breeding to shorten the long generation times, as some traits are only visible at maturity (e.g.: the timelines of a single cycle of genetic improvement in South-Eastern United States pine species).

Some of the most revolutionary progresses in agriculture are based on natural mutations that impacted on crop development, productivity and enhanced resistance to biotic and abiotic stresses. Such known point mutations can now be introduced precisely and very quickly into existing crop varieties.

NGTs also strongly improve vegetatively propagated varieties, which are less or not amenable to conventional breeding, e.g. by making potato disease-resistant by activating disease resistance genes that are present in the variety but silent.

In some cases, these benefits can only be obtained by NGT: For instance, when the desired useful variation does not exist in the natural variation of a given crop e.g.: a) nucleotide change providing viral resistance in tomato can be copied from capsicum to fight the same disease that also affects tomato b) for some plants (e. g. banana), trait improvement through classical breeding including crossing has proven to be very difficult c) modifying the domains of a transporter to alter its affinity to toxic metals d) acceleration of domestication of new crops (or improvement of domestication process). NGT-aided induced variation in domestication genes can help gaining a lot of generations and come up with a product that can used by breeders and farmers (Lemmon et al., 2018; Li et al., 2018c; Zsögön et al., 2018).

In other cases, the benefits are not exclusive for NGTs but NGT makes the breeding process more swift and precise. For instance, combination of favorable alleles at multiple loci can be achieved using markers linked to these multiple genes through pyramidal crosses but applying NGT with multiplexed targets could considerably fasten the generation of such a rare combination. Point modifications can be done at these loci without dragging linkage to unfavorable genes. The same holds true for introduction of presence/absence variations (PAV): PAV genes generally reside in polymorphic regions with structural variation that hamper recombination in these regions. NGT will allow to add the missing genes (e.g. adaptation genes) at their exact syntenic positions in elite materials.

NB: Please see supporting document #1 for list of cited references.

* **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?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

NGTs are a lever to address challenges to agriculture in Europe and worldwide (reviewed in e.g. Modrzejewski et al., 2019, Ricroch et al., 2017, Jansing et al., 2019). For example, reduction of pesticide use can be achieved by introducing novel disease resistance genes into crop varieties using cisgenesis, i.e. modifying a genome to copy a gene existing naturally in another variety of the same species (e.g. against potato late blight, Haverkort et al., 2016). Additional opportunities by NGTs are the activation of endogenous but silent disease resistant genes by precise promoter editing, and by knocking out susceptibility genes or some of their promotor elements by gene editing (for examples see below). Disease-resistant varieties fit well in agroecology, as the role of predators and biological control agents can become more central than in

conventional systems based on pesticides (Lotz et al., 2020). Some examples of disease-resistant crops are:

- MLO knockout in wheat and tomato confers resistance to powdery mildew (Nekrasov et al., 2017; Wang et al., 2014).
- Modification of eIF4G to confer virus resistance in rice (Macovei et al., 2018).
- Rice resistant to bacterial blight (Oliva et al., 2019; Eom et al., 2019). These authors mutated the SWEET genes targeted by the pathogen and produced a comprehensive package of plant varieties and tools enabling integrated pest management (IPM), prohibiting pathogen adaptation under local/regional conditions across worldwide important rice cultivation areas.
- A disease-resistant crop package was also developed for cisgenic late blight-resistant potato that is aimed to prohibit pathogen adaptation (Haverkort et al., 2016).

NGTs can help to mitigate climate change impact by adapted life cycles (phenology) and improved abiotic stress tolerance of crops (Miao et al., 2018). Furthermore, improving nutrient use efficiency in existing crops (Li et al., 2018) and accelerated domestication of forgotten crops or crop-wild relatives to combine their stress tolerance with elite traits are addressed by NGTs (e.g. tomato Solanum pimpinellifolium, Zsögön et al., 2018; groundcherry, Lemmon et al., 2018).

Crops with higher yields achieved by knocking out genes with negative effects on grain number, size, weight, panicle size, tiller number (e.g. in rice: Li et al., 2016; Li et al., 2018) can contribute to global food security. Improving consumer or processing quality of crops is also achieved by NGTs. Examples are:

- Creation of low-gluten wheat (Sanchez-Leon et al., 2018; Jouanin et al., 2019) for improved human health in coeliac disease patients.
- Crops with reduced absorption of toxic heavy metals, e.g. rice with low levels of cadmium (Tang et al., 2017 Sci. Rep. 7:14438), contributing to animal and human health
- High amylose/resistant starch with improved dietary fibre by targeted mutagenesis (e.g. rice, Sun et al., 2017). A high amylopectin (waxy) maize with higher starch quality is in the pipeline of product development of Pioneer (US). For potato, see Andersson et al., (2018).
- High oleic Crambe with improved oil composition (higher in monounsaturated fatty acids). High oleic soybean is already commercialized in US as Calyno oil by Calyxt since 2019.

New crops for farmers to increase crop diversity and extend the rotation. Example: High oleic Crambe oil crop can be developed into a dual-use crop by reducing glucosinolates so that the crushed seeds can be used as animal feed. Camelina high in oleic acid and low in sinapine is currently in field trials in Rothamsted, UK (https://www.rothamsted.ac.uk/news/gm-field-trials-approved).

Other beneficial applications are: fragrant rice, improved pharmaceutical production by glycosylation knockout. Improved production and reduced impact or conversion steps, e.g. simpler and breakable lignocellulosic material from trees and crops for the pulp and paper industry, thus avoiding the highly pollutant technology of hydrolysis. For examples, reduction of lignin level by editing genes in the biosynthesis pathway (poplar: Zhou et al., 2015; switchgrass: Park et al., 2017). Avoiding mineral losses in the chain. Feed from low phytate grains or oilseed cakes enables better phosphorus (P) use by monogastric animals, thus avoiding high P losses from manure into the environment (e.g. Sashidhar et al., 2020 in oilseed rape; Holme et al., 2017 in barley). Dow Agrosciences (US) produced a low phytate maize variety and queried USDA about (exemption of) regulatory oversight (US).

NB: Please see supporting document #1 for list of cited references.

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

Most non-European breeding companies are already using this technology for the generation of new crop varieties, and products are on their way to the market (see US examples above).

European breeding companies participate in research projects on NGT, some carry out NGT programs in house, but only for research purposes. Successful prototypes made with the use of NGT must subsequently be phenocopied, e.g. by screening random mutagenized populations for similar mutations. This duplication benefits neither the European companies (as they have double costs) nor the European society (as the resulting varieties are less precisely developed).

Thus it is time for a fair and adequate EU regulation, (proportionate to risk without additional burdens) so that such benefits and opportunities of the use of NGTs can be provided to society.

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

- (●) Yes
- ( ) No

* Please explain

All crop breeding programs will benefit of NGTs, as it is an additional tool that will contribute to make breeding faster and more efficient, which will help addressing the challenges of making agriculture sustainable in the 21st century while mitigating climate change.

Specific advantages exist for crops in which breeding is currently slow (polyploid crops such as potato) and for traits that are too complex for traditional breeding and random mutagenesis methods (such as lowering gluten in wheat, which involves modifying over 100 genes of five gene families in polyploid wheat) but are amendable by gene editing (CRISPR).

The availability of NGTs in the breeder's toolbox to speed up breeding and to make new traits available for plant breeding, can also be a supporting force for a broad societal discussion in search of novel orientations for a sustainable agriculture. The traits required in our crop varieties should be discussed considering the needs of all actors, based on current dynamics in an open and respectful dialogue.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

The short history of NGTs in general, and CRISPR/Cas9 technology in particular, has been marked by a strong involvement of public research and startup companies. SMEs are also very present in the development of NGT-products, but this potential is threatened by the cost of licence fees to access the technology and the cost of regulatory approval in the countries where NGT-products fall under GMO legislation (see also answer to Q22).

The involvement of numerous SMEs in the NGT sector, especially in the medical but also in the agricultural sector (for example Calyxt, INARI, Caribou or PlantEdit in the USA or IAGE in Europe) is closer to the situation in conventional breeding with hundreds of small scale operators in Europe than the one in GMO breeding. This was confirmed by a recent study comparing the cases of NGT-products that have been presented to the regulatory system in Argentina, against the cases of GMOs that have been deregulated in the country. Whereas 90% of the applications for GMO-products stemmed from multinational companies, this percentage dropped to 9% for NGT-products (Whelan et al., 2020). The fact that 59% of the applications for NGT-products came from local companies and public research and 32% from foreign SMEs, demonstrates the potential for SMEs in a country where NGTs and NGT-products have been exempted from GMO legislation.

The present inclusion of NGTs and NGT-products in GMO legislation in Europe will likely stop the emergence of other startup companies and incite the existing ones to stop their investment on the old continent and displace their activities (including brainpower) to more favourable skies. Another challenge is the cost of license fees to access patents on NGTs, although there is some room for hope of reasonable arrangements looking at the history of licensing patents on earlier foundational technologies such as recombinant DNA, small interfering RNA (siRNA) and PCR (Sherkow, 2015).

SMEs are agile actors that are able to react rapidly to emerging consumers' demands or opportunities in bio-sourced industries, in particular in niche markets neglected by large companies. Present GMO legislation of NGT-products therefore deprives such consumers and bio-industries from the benefits of NGT-products.

NB: Please see supporting document #1 for list of cited references.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

NGTs are patented and access to this type of technology is vital for our members for both basic and applied research. For continued translation of knowledge into innovation it is indispensable to obtain appropriate NGT-licences for research and development as well as commercialisation at reasonable conditions. With regard to patents on traits present in NGT-products, our members prefer other means of protection, i. e. plant variety rights, without excluding patents in certain cases. Increased homogeneity of patent laws and NGT legislation on the international level would be very helpful for sane competition both in academia and commercial breeding (see also answer to Q23).

According to the website of the Broad Institute, the US Patent and Trademark Office has issued more than 300 patents with claims to CRISPR and/or Cas9 from nearly 100 applicant organizations and the European Patent Office (EPO) has issued more than 100 such patents from about 60 applicant institutions (Broad Institute 2019). A recent analysis of the 2072 patent families showed that the leading countries in the number of applications are the USA (42.1%) and China (41.4%), Europe lagging far behind (9.4%, Martin-Laffon et al., 2019). A licensing deal between the Broad Institute and DuPont Pioneer clarified the access to CRISPR technology in the plant science and plant breeding field (Broad Institute, 2017). Not only private seed companies but also public research institutes have recently been approached by Corteva (successor of DuPont Pioneer) to negotiate appropriate licenses for research and development, service and commercialization. Therefore, the benefits and opportunities of European NGT-related research and products mentioned in Q13, Q14, Q16 and Q17, depend on access to patented NGTs at reasonable conditions (see also answer to Q23).

Plant varieties cannot be patented in Europe. However, protection of biotechnological inventions can be obtained by patent if the invention is new, has an inventive step and industrial applicability, knowing that protection conferred by a patent to a biotechnological invention also applies to varieties in which it is inserted (Le Buanec and Ricroch, 2014). In other words: A plant variety can contain a patented NGT-trait. The second way to protect innovation and ensure investment in research and development is to protect a new NGT-variety on the basis of global guidelines (UPOV, International Union for the Protection of New Varieties of Plants). This protection is attested by a PVP (Plant Variety Certificate). It prohibits anyone from producing and marketing seeds of the variety without the express consent of the owner. Whereas the license fees for varieties containing patented traits are freely negotiated between the patent holder and user and may exclude certain users (exclusive license), return on plant varieties rights are generally fixed percentages and the varieties are accessible to any user. The plant variety protection system also differs from the patent system in that it allows protected varieties to be used for experimentation and for breeding in order to create new ones, without the need for the owner's agreement. This helps to prevent possible monopoly situations and, above all, the slowing down of genetic breeding progress, by allowing access to genetic diversity for the creation of new varieties. In the case of a plant variety containing a patented trait, the variety without the trait can be freely used for further breeding, whereas the use of the patented trait requires a license from the patent holder (see also answer to Q23).

Up to the advent of NGTs, protection by plant variety rights was generally chosen for new varieties obtained by conventional breeding or mutagenesis breeding, whereas protection by patents was almost systematically the choice for GMO breeding. With regard to NGT breeding, our members agree that systematic patenting, especially in minor crops, would likely be counterproductive to rapid and widespread use of the benefits of NGT-products. Whereas the movement towards open science incites a minority of our members to take a clear stand against any patenting of NGT plants (INRA 2018), the majority remains open to parsimonious use of patenting, keeping in mind the widespread use of patenting in other parts of the world.

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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
- ( ) No

* Please describe and provide concrete examples/data

It is difficult to answer this question with yes or no. On one hand our members identify certain challenges, on the other hand they do not share concerns of other stakeholders. We finally chose the "yes" section to present both types of arguments.

As mentioned earlier (see Q7), it is in most cases of small mutations impossible to trace that the variation is synthetic and generated by NGT and not induced/selected in natural variation. It will clearly become a challenge in the next decades for our breeding activities if NGTs are implemented in some countries and not others. As we expect quite a large number of traits which will be mutated by NGTs without the necessity to trace them back (according to the regulation in other countries like China, the US or South and Latin America) the enforcement of the EU regulation will be a big challenge (see also Grohmann et al., 2019; ENGL report 2019).
Also depending on the interpretation of the national jurisdictions of the ECJ ruling, other materials (e.g. conventional mutants, tissue-culture derived plants) may fall under the regulation: in this case all our past and current breeding activities will be negatively impacted. This would be a dramatic challenge for breeding and research as a considerable number of the plants used there have undergone some kind of mutagenesis like irradiation or tissue culture in their past.

Regarding the safety of NGT plants it has been shown that plants produced by induced mutagenesis (e.g. irradiation) possess a lot of more modifications (at transcriptomic and proteomic level) than GM plants, without going through the same regulatory framework (Batista et. al, 2008). Therefore, we do not think that NGT plants pose a larger risk for humans or the environment than plants produced by induced mutagenesis.

NB: Please see supporting document #1 for list of cited references.

* Are these challenges/concerns specific to NGTs/NGT-products?

- ( ) Yes
- (●) No

* Please explain why not

As explained in more detail above and also in Q7, the challenge to identify and trace a small mutation is specific for NGTs as we discuss them here. All plants showing only small genomic alterations and contain no foreign DNA from the NGT process can exist in nature just by chance (see Puchta, 2005). This is in contrast to most of the older GMOs, which usually possess traceable sequences like promoter, terminator or antibiotic resistance genes inserted in their genome. Using these foreign sequences, a detection and identification procedure is on one hand possible and on the other hand requested as a mandatory prerequisite for approval of GMOs in the EU.

NB: Please see supporting document #1 for list of cited references.

* **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 describe and provide concrete examples/data

It is difficult to answer this question with yes or no. We finally chose the "yes" section to present both types of arguments.

As we have discussed in Q17 there are many benefits for the society that can result from the application of NGTs (less pesticide and fungicide use for disease-resistant plants, less use of watering for climate resilient plants, allergen reduction, better flavours etc.). Nevertheless, if NGTs or NGT-products are regulated like GMOs, the framing in the public will automatically adopt them as negative and artificial food or feed. A negative framing combined with the high regulatory burden and costs will hinder SMEs to develop and market such products in the EU.

Regarding the environment, human and animal health, consumers and animal welfare: the number of benefits easily outweigh the proposed challenges that are raised recurrently by other stakeholders for NGTs and are present in a similar way in conventional or mutation-induced breeding procedures (e.g. off-target effects or unintentionally arising harmful plants). If properly and intentionally used, there is no intrinsic risk for the safety of the environment, humans or animals in NGTs. Misuse is possible for every technique, including conventional or mutation-induced breeding.

An economic and societal challenge is rather the non-use of NGTs. As we have pointed out in other questions, if the EU does not allow the marketing of NGTs (or poses too high a bureaucratic burden with consequential costs on it, as is the case now) this will lead to a number of disadvantages for the research community as well as for public private partnerships, breeders and the industry.

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

Please see previous answer to Q21.

* Are these challenges/concerns specific to NGTs/products obtained by NGTs?

- ( ) Yes
- (●) No

* Please explain why not

NGTs that we discuss here produce the same result (plant) as conventional breeding or mutation-induced breeding that means if there are concerns, they should be similar to the ones we have for conventional breeding methods. In contrary, if the traits developed by NGTs are beneficial for the environment, human or animal health they might raise interest and demand for this technology rather than concerns. This is what happens with good conventional or organic breeding products and NGT-products can produce the same in a shorter time.

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

- (•) Yes
- ( ) No

* Please explain and provide concrete examples and data

Public research institutes and SMEs have played an important role in the discovery, development and use of NGTs. However, regulatory approval of GMOs is a costly process and SMEs/small scale operators are less likely to have the necessary capital and to take the risk involved in such an investment, in particular if their product is aiming at markets with low return. Another important cost difficult to bear for SMEs are the license fees to be able to use patented NGTs (see also answer to Q18).

The total cost to develop a genetically modified crop and to bring it to market is estimated at 100 M$ for classical GMO-products (Mumm, 2013). In this total the cost to meet the initial requirements for government approvals to support commercial release of a GMO-crop represents approximately 15 M$ (Kalaitzandonakes et al., 2007). Under GMO legislation, the costs for a NGT-product are of the same magnitude (SBA, 2018). This high cost presents an almost insurmountable financial effort for SMEs/small scale operators. Obligatory labelling of GMO products is an additional burden for efficient marketing. Although SMEs have been shown to quickly surpass multinational companies in the number of applications for NGT development in Argentina, where NGTs and NGT-products are exempted from GMO legislation (Whelan et al., 2020), the scenario in Europe is likely to be the opposite.

NB: Please see supporting document #1 for list of cited references.

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

- (•) Yes
- ( ) No

* Please describe and provide concrete examples/data

NGTs are patented and access to the technology at reasonable conditions is a challenge for our members, especially when translating academic research into new plant varieties. After a clarification of the patent landscape in 2017, the arrival of new variants of genome editing technology further complicates the situation. With regard to patents on traits present in NGT-products, the coexistence with plant variety rights may be difficult to handle at a large scale and the infringement difficult to prove. Strong heterogeneity of patent laws and NGT legislation on the international level biases competition both in fundamental and applied research (see also answer to Q19).

Despite early involvement of European actors such as Vilnius University (US Patent Application No. 61/613,

373), patents on genome editing technologies are largely in American and Chinese hands (Martin-Laffon et al., 2019). While purely academic NGT-research is presently carried out without a licence under a rather generous interpretation of the research exemption, the licence issue becomes more critical as soon as our members either are solicited as service providers due to their technical know-how in NGTs, or wish to translate their academic knowledge into new plant varieties with improved agricultural performance. The general benefits for society resulting from NGT use need to be considered by patent holders in such licence negotiations.

The complexity and rapid evolution of the patenting landscape around genome editing technology is another challenge for our members. After a court battle between the Broad Institute and University of Berkeley (Cohen 2017) and a licensing deal between the Broad Institute and DuPont/Pioneer (Broad Institute, 2017), the license presently offered by Corteva is supposed to cover access to CRISPR/Cas9 technology. However, the European patent EP 2771468 of the Broad Institute was revoked by the European Patent Office (EPO) earlier this year, alternative systems such as Cpf1/Cas12a require different licenses (Ledford, 2017), and the situation around upcoming alternatives such as base or prime editing still needs to be clarified. This remaining uncertainty of the genome editing patent landscape clearly has a negative impact on long term technical choices and breeding efforts.

The coexistence of the patent and plant variety protection systems was facilitated up to now by the low number of GMO traits, which were often stacked in a limited number of genomic positions. To benefit from the breeder's exemption, it is relatively easy to either remove a GMO trait from a plant variety by genetic segregation or to negotiate a license if the trait is indispensable for further breeding. Assuming a massive arrival of NGT-traits, in particular if NGT-products were to be exempted from GMO legislation, the high number and diverse origin of modifications spread over the genome would present a change in scale difficult to cope with if all NGT-traits were patented. To avoid an erosion of the breeder's exemption, it seems therefore preferable to limit patenting of NGT-traits.

As explained in more detail under Q4, there is no technical means to determine whether a discrete modification in a plant genome was provoked by NGTs or arose spontaneously (Grohmann et al., 2019). Consequently, infringements concerning patented NGT-traits are difficult to prove, since a comparable modification could have been found or arisen in the natural variation of the species. This difficulty may be an additional motivation to refrain from patenting.
While patents on NGT-traits do not patent the plant variety itself, they generally patent the use of particular alleles for specific traits. What at first glance is a justified compensation of innovative research, may pose a problem if the patented allele exists in the natural variation of a species. For example, it allows theoretically to claim a license fee from a farmer who uses unknowingly the very same allele present in one of his ancient varieties. Another example is benefit sharing under the Nagoya protocol. Indeed, it is now possible to introduce a rare favorable adaptation allele existing in a landrace, which has been selected through the millennial effort of farmers, by genome editing without access to the actual biological resource. For such cases, certain of our members consider that some sort of return on the benefits of digital sequence information (DSI) may be envisaged similar to what is in place for biological resources.

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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**

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

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

Thus, it has been concluded that genetically and phenotypically similar products deriving from the use of different techniques are not expected to present significantly different risks different techniques. (SAM 2017, Schiemann et al., 2019).

Defining the range of changes that can be introduced using techniques that are considered safe would be important to classify changes introduced by NGTs, distinguishing those that can be obtained also using breeding methods with an history of safe use from the ones that can only be introduced using NGTs (Custers et al., 2019).

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

- ○ Yes
- ◉ No

* Please explain why not

NGTs comprise several different techniques that can be used to introduce changes in the sequence of plant genomes. Any safety assessment should take into consideration, rather than the technique employed, the type and detailed characteristics of the changes introduced into the genome. In this framework, NGT products do not present more concerns than plant materials derived from other biotechnological or conventional methods, as long as a safety assessment is conducted on a product basis.

It should be also considered that the technique is rapidly evolving, and that any consideration concerning a specific technique may quickly loose relevance, while considerations concerning the type of modification are not influenced by technical evolution.

Off-target effects are frequently cited as an argument to question the safety of NGTs/NGT-products. Off-target events can easily be avoided by state-of-the art design of genome editing tools if the genome sequence to be modified is available, either by excluding such sites from the design or by checking for absence of modifications at the expected off-target sites. For example, the probability of editing at a duplicate site drops to 0.09% (5 out of 5700), if four or more mismatches discriminate the two duplicated sequences (Modrzejewski et al. unpublished). Thus, off-target events can be drastically reduced to a level

similar to that of spontaneous mutations occurring during natural plant reproduction on the basis of a) a deep knowledge of the genome to be modified; b) an accurate design of genome editing tools; c) introduction of novel/refined NGTs (Kim 2018; Xu et al., 2020).

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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**

Questions related to food production have a profound ethical basis related to the right to food as an essential component to the right to life and dignity enshrined in the Human Rights Declaration. The European Group of Ethics considers the goals of food security, food safety and sustainability as first priorities and guiding principles to which any technology in agriculture must adhere (EGESNT, 2008). NGTs, as any other technology, may be useful to increase food production towards "Zero hunger" and other Sustainable Development Goals of the Unites Nations. In this sense the ethical question of a proportionate risk assessment may be balanced by the risk of refusing to apply promising new development.

The Danish Council on Ethics replies to the question of whether it is ethical to withhold the benefits of a technology from the European farmer, consumer and citizen, which can contribute to reduce the environmental footprint of agricultural production, to provide healthier and more balanced nutrition and to establish a circular, bio-sourced economy by the recommendation that it would be ethically problematic to reject NGTs with beneficial traits provided they are not assessed as posing a higher risk to humans or the environment than similar varieties developed by conventional methods(DCE 2019).

NGTs are not the only lever to face these present challenges of European agriculture. There are complementary genetic tools and additional agronomic, economic and societal levers (Rogowsky 2019). A responsible attitude would call upon all these available tools and it would be irresponsible to neglect any of them unless proven unsafe (see Q24/Q25). Similarly, the Ethics Committee INRA-CIRAD-IFREMER recommends that research organisations should provide all the means to know and evaluate NGTs (CCCE, 2018).

Five sets of ethical concerns have been raised about GM crops (Weale 2010) and the same concerns are presently put forward against NGTs:

- Potential harm to human health: From a product-based point of view, NGT-plants are indistinguishable from mutants obtained by methods considered to have a safe history of use and therefore should not be treated differently. From a process-based point of view, NGTs are less invasive than classical transgenesis, which was shown by recent work not to have a negative impact on mammalian health (Coumoul et al., 2018, Steinberg et al., 2019).
- Potential damage to the environment: As for the previous point, from a product-based point of view, NGT-plants are indistinguishable from "natural" mutants and therefore should not be subject to specific

evaluations beyond the UPOV certification of conventional varieties. With regard to the process, there is no evidence for an intrinsic harm of NGT-plants to the environment.

• Negative impact on traditional farming practice: There is no technical reason that would prevent NGT-crops to be cultured in non-conventional farming systems. As stated by Urs Niggli (2016), director of the Swiss research institute for organic farming, it would be unsightly if a conventional potato farmer grew NGT potato varieties without any pesticides, whereas an organic farmer would continue to grow present potato varieties with environmentally harmful copper treatment.

• Excessive corporate dominance: The rapid worldwide spread of NGTs in public laboratories demonstrates that there is no technical barrier hindering the democratisation of NGTs. The high number of SMEs in the NGT sector is closer to the situation in conventional breeding than in GMO breeding. As demonstrated in Argentina over the last 4 years, under non-GMO legislation SMEs and public actors are major contributors to the application of NGTs in agriculture (Whelan et al., 2020). This may be even more the case for the dozens of minor crop species neglected by multinational seed companies.

• Unnaturalness: Beyond the fact that the genomes of present "natural" crop varieties are nothing else than an instant photography of a longstanding and ongoing evolutionary process implying major rearrangements of these genomes (Pont et al., 2019), there is growing evidence that modifications considered as unnatural actually do occur in nature. Since 2001, it has become clear that not only sequence polymorphisms but also structural differences (large deletions, insertions and inversions) exist naturally between crop varieties of the same species. For example, between two maize varieties, on average 5% of the genome are either missing in one of them or found in another location (Darracq et al., 2018; Haberer et al., 2019). Similarly, there are more and more examples for naturally occurring horizontal gene transfer between species, leading to the presence of DNA from other kingdoms in "natural" crop varieties (Mateeva and Otten, 2019, Quispe-Huamanquispe et al., 2019, Wang et al., 2020). In consequence, the alleged unnaturalness of NGT-crops sharply contrasts with scientific data.

Please see suppl doc for references.

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

- ○ Yes
- ◉ No

* Please explain why not

Ethics generally relate more to the application of a technology rather than to its nature (Swierstra 2017). The real question is not whether genome editing as such is acceptable, but whether the use we make of it supports commonly admitted values and avoids harm to humans and the environment. The reduction of harmful pesticides or non-renewable agricultural inputs, the increase of resilience to climatic accidents and global climatic changes or the reduction of components (allergens, anti-nutrients) with negative impact on human health are desirable uses, whereas the eradication of species, the tolerance to harmful molecules or the appropriation of life are non-desirable uses. However, these considerations on uses are not specific to NGTs but shared with any means to generate novel genetic combinations, including classical GMOs and conventional breeding.

Another important consideration is that many of the products (plant varieties) obtained by NGTs are not different from identical products obtained by non-regulated techniques with a history of safe use. Whereas there are ideological arguments to reject them due to their origin, there is no factual basis allowing specific regulations to discriminate between them.

A last consideration concerns sustainable benefit sharing. Presently only physical genetic resources are

protected by the Nagoya Protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization to the Convention on Biological Diversity (CBD). However, under certain conditions digital sequence information (DSI) is sufficient for modern plant breeding, marking a fundamental change due to the dematerialization of biological resources. This raises issues such as the link between information and biological material, the equity of access to both components as well as to technical platforms. Again, NGTs are not the only techniques allowing dematerialized plant breeding and the present considerations around benefit sharing of DSI needs to include all concerned techniques including classical GMOs and conventional marker assisted breeding.

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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**

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

Our opposition to obligatory labelling is based on the following considerations:
(i) Harm: Obligatory labelling may give the wrongful impression that public authorities consider NGT-products as such to be harmful or problematic in one way or other (Hanssen, 2019). Consumers have the right to know that risk assessment of NGTs should be proportionate and based on scientific analysis carried out on a case-by-case basis adapted to each genetic modification, the recipient organism, and purpose and scope of the application (Casacuberta and Puigdomenech, 2018).
(ii) Traceability: Obligatory labelling is only possible if traceability exists. This is relatively easy for GMO-products since the construct elements are known and not so diverse. Traceability will prove impossible for NGT-products as long as the modifier construct has been removed and is no longer present in the final product (see answer to Q4), unless a specific molecular signature is imposed on NGT-products (difficult to implement).
(iii) International trade: Obligatory labelling is delicate in the present international context where NGT-products fall under GMO regulation and labelling in Europe but are not subject to specific regulation and labelling in other parts of the world. Consumers would have difficulties to understand that cookies made with NGT wheat are labelled as GM if the NGT wheat was cultivated in Europe and not at all labelled if the NGT wheat was imported from the USA or certain Southern American countries.
(iv) Equal treatment: Obligatory labelling of NGT-products must not be considered since similar or even identical products that have been obtained with technologies with a history of safe use can be marketed without labelling. As long as products obtained by NGTs are not different from products obtained by non-regulated techniques, there is no scientific justification of labelling only NGT-products.

Voluntary labelling has the advantage to give voice to different types of values, to maintain information levels equal to all actors and to take into account various lifestyle choices. It allows to mention not only the possibility to exit (for example NGT free) but also to underpin proven benefits (for example produced without pesticides). In fact, in order to offer a true choice to consumers, the information content of a potential NGT label has to exceed the fact of the mere use of the technology in the production process. It should indicate to which end the technique was used as well as give supplementary information concerning practices and challenges in agriculture and food production, without tipping over into information overload (Bechtold 2018).

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H - Final question

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

- (●) Yes
- ( ) No

Please provide your comments here

With regard to the future regulation of NGTs, Europe is facing a monumental strategic challenge that will impact (positively or negatively) on the economy and food-dependency. This should be considered by the regulators since sustainable food production is strategic for European society. Implementation of NGTs is also strategic for European R&D competitiveness. Essentially it is the choice whether the EU wants to become a niche player in this strategic area or whether the EU wants to remain at the forefront in the strategic food and feed production area.

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

A last consideration concerns the precautionary principle. According to the European Commission, this principle should be applied "when there are reasonable grounds for concern that potential hazards may affect the environment or human, animal or plant health, and when at the same time the available data preclude a detailed risk evaluation." (EC 2000). In other words, the precautionary principle is a preventive action based on weak but valid scientific evidence of danger, but it does not recommend action based on hunches, suppositions, or fears that have no support in science (Hansson 2018). To be worth considering, an argument for doing so will have to show that there is a higher degree of plausibility than the mere possibility of some unknown danger, which applies to all cultivated crop varieties (Hansson 2019). Most importantly, the definition of the EC implies that decisions based on the precautionary principle are temporary measures that need to revised regularly on the basis of additional scientific evidence. It may be

timely to revisit Directive 2001/18/EC.

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