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Member State 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

endorsed in the Joint Working Group of GMO competent authorities on new genomic techniques on 15 January 2020

Introduction

With this questionnaire the Commission is collecting contributions from Member States competent authorities to respond to the Council's request[1] for "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). The scope of the study goes beyond new mutagenesis techniques, as there are other new techniques, for which the Council seeks clarification. Therefore, the study covers all new genomic techniques, which have been developed after 2001.

For the purpose of the study, the following definition for new genomic techniques (NGTs) is used: techniques, which are capable to alter 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-organims and derived food and feed products obtained by NGTs for agri-food, medicinal and industrial applications and for research. GMO competent authorities are invited to seek input from other competent authorities when appropriate.

The questionnaire is meant to provide information primarily, but not exclusively, at national level. 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 a specific NGT, please indicate this in the reply. With regard to agri-food applications, replies may include considerations on specific sectors, such as the organic sector.

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

Instructions

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 30 April 2020 (closure of business) to submit the questionnaire via EUsurvey.

QUESTIONNAIRE

* Which Member State are you representing?

Slovenia

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

* **1. Have you been consulted by companies/organisations/research institutes for regulatory advice or another issue on products developed or to be developed by NGTs ?**

- (●) Yes
- ( ) No

* Please provide details on the request

Ministry of the Environment and Spatial Planning of the Republic of Slovenia (MESP), as a competent authority for the Directive 2009/41/EC, had been consulted by companies/organisations/research institutes for regulatory advice or another issue on products developed or to be developed by NGTs that are destined to be used in the contained use systems.

MESP, as a competent authority for the Directive 2001/18/EC, was not consulted by companies /organisations/research institutes for regulatory advice or another issue on products developed or to be developed by NGTs.

Ministry of Agriculture, Food and Forestry, as a competent authority for the regulation 2002/178/EC, was never consulted or received an application to authorise a NGT product for food/feed use.

* **2. Have you taken specific measures (other than inspection) related to the application of the GMO legislation to NGT-products?**

- ( ) Yes
- (●) No

* Please explain why not

No specific measures had been taken in relation to the application of the GMO legislation to NGT-products, because NGT products are assessed by GMO legislation.

* 2 bis. Have you encountered any challenges or limitations, including administrative burden or costs?

- ( ) Yes
- (●) No

* Please explain why not

NGT products are assessed by GMO legislation.

* **3. Have you adapted your inspection practices to cover all NGT-products and to ensure the enforcement of traceability requirements?**

- ( ) Yes
- (●) No

* Please explain why not

NGT products are covered by GMO legislation, therefore no specific measures had been taken in relation to the inspection practices. Enforcement of traceability legislation should be enabled by providing the required methods and reference materials by the producers. There are also no systematical monitorings for NGT products in food/feed because we do not have any information on such NGT product and, consequently, no detection methods. The documentation checks of the shipments are performed according to the legislation. In the case of RASFF notification SI would act in accordance with existing GMO legislation.

* 3 bis. Have you encountered challenges or limitations, including administrative burden or costs?

- ○ Yes
- ◉ No

* Please explain why not

NGT products are covered by existing GMO legislation

* **4. Do you have experience or information on traceability strategies, which could be used for tracing NGT-products?**

- ◉ Yes
- ○ No

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

We have nominated National institute of biology as Slovene reference laboratory for detection and identification. European Network of GMO Laboratories (ENGL) has prepared a document on »Detection of food and feed plant products obtained by new mutagenesis techniques« (https://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf), where the topic of detection that enable traceability was addressed from the perspective of currently available analytical techniques. As was concluded, products of genome editing can only be readily detected and quantified in commodity products by enforcement laboratories, if prior knowledge on the altered genome sequence, a validated detection method and certified reference materials are available. Otherwise this products can enter the market undetected. In the research sector it is very important to know and preserve the identity of research material, including research material produced with NGTs. In the research sector NGT products are traced through the use of ID numbers or codes. Records are kept in (electronic) lab notebooks. NGT materials that are essential parts of work described in scientific papers are generally deposited in public repositories.
Until today they have not encountered any requests for detection of NGT products, most probably due to limited information available on the products in the pipeline, and due to the fact that such products are already available on the US market, where they are not considered as GMOs and the producers do not need to provide methods for their detection. In the field of food/feed the traceability is checked by the documentation inspection, relying on the producers and importers acting in accord with the legislative provisions.

* What best practices can you share?

No experience with NBT products.

4 bis. Have you encountered any challenges or limitations, including administrative burden or costs?

* (●) Yes
( ) No

* Please describe

Products of genome editing can only be readily detected and quantified in commodity products by enforcement laboratories, if prior knowledge on the altered genome sequence, a validated detection method and certified reference materials are available.

* How could these challenges or limitations be overcome?

The availability of information on the genome editing products in the pipeline and methods for detection as well as validated detection method and certified reference materials are esential to overcame challenges.

* **5. What other experience can you share on the application of the GMO legislation, including experimental releases (such as field trials and clinical trials), concerning NGT-products in the:**

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

Agri-food sector

No experimental releases (field or clinical trials) using NBT products were performed. For the time being all the legislation that is in place for GMOs should also be followed for the NGTs and their products. No experience with food/feed NGT products.

Industrial sector

No experimental releases (field or clinical trials) using NBT products were performed. For the time being all the legislation that is in place for GMOs should also be followed for the NGTs and their products. No experience with food/feed NGT products.

Medicinal sector

No experimental releases (field or clinical trials) using NBT products were performed. For the time being all the legislation that is in place for GMOs should also be followed for the NGTs and their products.

* **6. Have plant varieties obtained by NGTs been registered in national catalogues?**

( ) Yes
(●) No

* **7. Do you require specific information in national catalogue when registering plant varieties obtained by NGTs?**

( ) Yes
(●) No

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

The maximum file size is 1 MB

B - Information on research and innovation

* **8. Have you supported with national funding programmes NGT-related research projects/programs (ongoing or finalised in the last 5 years), including on identification or traceability?**

- (●) Yes
- ( ) No

* Please provide an overview of the project/program including title of project, a brief summary with scope and objectives, the amount of national funding received and possibly specify if the receiving entity is public or private

P4-116 - Microbiology and Biotechnology of food and environment; University of Ljubljana, Biotechnical Faculty (UL_BF) and SME Acies Bio. The main goals of the program is to understand microbial interactions, microbial biofilms, responses to stress in relation to environment and food safety, and to develop novel biologicals/antibiotics/enzymes used in biotechnology and pharma. They apply diverse NGT technology to prepare recombinant strains which are used to address specific scientific questions.
J4-7637 - Investigations of bacterial social interactions in biotechnologically and medically important microbial biofilms; UL-BF and SME Acies Bio. Investigated NGT as potentially faster methods for inactivation of secondary metabolite gene clusters in bacterial species (Streptomyces, Bacillus), tested a large collection of mutants for physiological responses to other species.
J4-8228 - The role of social and genetic kin discrimination on B. subtilis interactions (head Polonca Štefanič) investigated novel approaches to increase horizontal gene transfer though antagonistic sociality of bacteria.
J4-9302 - Investigations of cell-cell communications in multi cellular groups composed of different Bacillus isolates (head I. Mandić-Mulec) applied NGTs (Crisper) to inactivate specific genes and prepare bacterial mutants important for testing the hypotheses.
J4-1775 - Development of microflow systems for bacterial cell analysis, selection and application; UL- FKKT in collaboration with UL-BF and SME Acies Bio. Investigates suitability of NGT for genetic engineering of industrially relevant Bacillus subtilis strains and uses NGTs to manipulate Bacillus subtilis for social interaction studies in microflow systems.
Research group of Petkovič Hrvoje at UL-BF and SME Acies Bio has been supported by Slovene research agency (ARRS), by other ministries, pharma industry in the range of 50-100K per year in addition to EU-funded grants. These grants in part covered genetic manipulation of bacteria which produce medically important primary and secondary metabolites, industrial enzymes. These microbial producers (Streptomyces species) have been modified by NGTs.
Research group of Roman Jerala at Chemical Institute received the public funding of about 1 mio € that was partially related to NGT in the last 5 years.
P4-0165 Biotechnology and plant system biology; National Institute of Biology (NIB). One of the main goals of the program is to gain a better understanding of plant stress responses using a systems biology approach. The NGTs allow them to efficiently study the function of candidate genes potentially involved in plant stress response. Related to detection of GMOs and also NGT NIB is also nominated as national reference laboratory and is cooperating in European network of GMOs laboratories, headed by Joint Research centre being European reference laboratory, where the topics are also discussed and guidance documents prepared.
J4-7636 Spatiotemporal analysis of hypersensitive response to Potato virus Y in potato (2016-2019) and J4-1777 Unravelling mechanisms of effectiveness and specificity in potato immune signalling through innovative

data acquisition and modelling (2019-2022); NIB. During the national project J4-636 they started to optimise and implement the use of CRISPR/Cas9 technology to edit potato plants. Since this technology is in constant development, within the project J4-177 they continue working on the optimisation and improvement of this methodology. CIRSPR/cas9 system is a potent tool that they are using to study the role of potato genes and miRNAs in plant defence response against pathogens. This knowledge that they are gaining represents an important step in understanding plant-virus interactions.
Use of CRISPR in modification of fungal genomes to produce auxotrophic model organisms and subsequent studies of radiotolerance of fungi within the Bilateral cooperation financed by the Slovenian Research Agency (Edible mushrooms and ionizing radiation - fungal survival and post-esxposure fruiting).
V4-1650-GSO Procedures for ensuring safety and social acceptability of new techniques and applications of synthetic biology and modern biotechnology; Agricultural institute(I), UL-BF, NIB and UL-FKKT; financed by ARRS and Ministry of Environment and Spatial Planning (32500€)). The applicability of existing approaches for risk assessment of products of modern biotechnology and synthetic biology has been assessed with a view to ensure high level of biosafety. Appropriate amendments were proposed where needed. In addition, a set of socio-economic factors associated with wide use of new techniques has been defined. Results of the project will be important for deciding on the necessity of adjustment or upgrading the existing biosafety system in Slovenia.
Cumulative public funding over 5 years exceeded 2,5 mil EURO, although only smaller part of this money was channelled directly toward NGTs.

* 8 bis. Please highlight the potential challenges encountered when supporting/funding NGT-related research and any consequences from these challenges.

Several research groups in Slovenia working in the field of Biotechnology were supported by national funding programs to carry out NGT-related research, although few for this purpose only. Instead, research grants have broader aims and NGTs are used as tools to test specific hypothesis.

*** 9. How do you see NGT-related research evolving?**

Many key stakeholders expressed their oppinions and the general conclusion is that NGT-related research is a fast evolving field of science with many valuable applications in various sectors. The use of NGTs has been progressing very fast, because of easier use, enabled higher accuracy and less side effects in genome editing. The pace of development increased enormously since the development of CRISPR-Cas approach for genome editing. CRISPR-Cas is now the most frequently used technique. However, some stakeholders expressed distrust towards NGTs believing the NGTs will not meet the expected benefits and that NGT is only the new name for GMOs. In the agri-food sector, NGT present emerging technologies in the field of plant breeding where they ease and accelerate the process and make it more precise/efficient in meeting the needs of new crop varieties (adaptation to changed environment, tolerance to biotic and abiotic stress, improved nutritional quality, adaptation to low-input agricultural crop production). In the field of wood processing the stakeholders believe that the pace is too slow and wish for an efficient organism to break down lignine. NGTs are developing to enable specific support to genetic/metabolic engineering of diverse microbial species, enabling rapid biotechnological development of strains for which conventional genetic tehniques are less available. Alternative CRISPR-based solutions that does not involve regular Cas9 protein, will have an important role for scientific and technical reasons. NGTs are also developing rapidly to enable specific support to medicinal use eather to enable easire production of medicines or to use NGT products for gene therapy.

*** 10. Have you identified any NGT-related research needs from private or public entities?**

- (●) Yes

No

* Please specify which needs and how they could be addressed

There was no official survery to assess any needs of NGT-related research organised by the competent ministry in SI. However, many researchers stress the need in their public relation statements. On the occasion of collecting answers to the EC Questionnarie on NGTs some needs were expressed by the key stakeholders.The need was expressed is in agri-foof, medical, biotechnological & pharmaceutical, industrial and chemical sector. Pharmaceutical, chemical and biotech companies are seeking new ways to speed up the turnaround time of design-build-test-learn cycle, shorten the time to the market and have identified CRISPR as a suitable tool. However, comprehensive methodologies dealing with genome engineering of specific non-conventional microorganisms are still in development. In the field of wood processing the stakeholders wish for an efficient organism to break down lignine. Research is going on in collaboration with pharmaceutical companies on improving biopharmaceutical production where gene editing to study factors that affect cell line productivity and stability is used. Potato breeding and medical cannabis-producing companies on also collaborate on a research project that would include identification of and modification of genes for improved stress resilience and secondary metabolite production. In the current situation in other parts of the world where certain applications of NGTs are treated the same way as the conventional crops, the farmers, operators and consumers are likely to benefit much more from NGTs than farmers, operators and consumers in SI/Europe. Generally the market place (the needs of farmers, producers, consumers and society in general) will direct what type of crop-trait combinations will be developed and which NGT products will be placed on the market. It is important that knowledge about these needs is assessed to prevent a gap between what is developed and what is most desired.

* **11. Could NGT-related research bring opportunities/benefits to science, to society and to the agri-food, medicinal or industrial sector?**

Yes
No

* Please provide concrete examples/data

The main conclusion from the stakeholder answers is that NGT-related research has an enormous opportunity potential for many areas, including science, to society and to the agri-food, medicinal or industrial sector.
These approaches, especially CRISPR-Cas-based ones, have transformative potentials for science, as they enable opportunities to investigate biological systems on the genetic / molecular level. Genome editing enables unprecedented accuracy of genetic modifications, which is of an enormous importance for genetics. CRISPR-Cas-based screening approaches, on the other hand, provide accuracy in identifying e.g. disease-causing genes or gene targets for biotechnological development. Areas where science was not able to obtain fast and convenient results now are more accessible. For example, specific modifications in certain gene in organism’s genome was few months long project when old genetic techniques were used. Nowadays, NGTs allow genome modifications practically within a few days.
In agriculture, NGT-technologies are developed in order to edit genes, involved in the ripening of vegetables, multiplying copies for pathogenesis-related proteins that activate self-defense of plants against pathogens, etc. On the one hand, this research could be a solution to food shortage, the scarcity of environmental resourcesand weeds and pests infestations.,
In medicine NGTs enable easier diagnosing disease condition development of gene therapy products and biological drugs, therefore enabling wider population an access to these treatments. Besides medical treatment improvement, NGTs enable control of some infectious animal diseases of economic importance, as well as production of vaccines.

In agriculture, NGTs have enabled the introduction of genetic variation in crops in a much more targeted and efficient way, which accelerated the plant related research. It is an essential improvement in crops breeding because of large genomes of crop plants. It is now for instance much easier to make knockouts. This helps to perform basic research in a more efficient way and will contribute to deciphering the genetic and molecular mechanisms that determine how plants develop and grow under normal circumstances, and circumstances of stress, and how the interaction of plants with its environment is regulated. In this way important scientific knowledge is generated that may contribute to help achieve the sustainable development goals.It is now also possible to target all copies of a certain gene to introduce a desired edit in all copies of that gene at the same time. This has for instance been done in wheat where all six copies of the MLO gene were mutated in one go, thereby achieving wheat that is fully resistant to mildew. With conventional breeding and transgenic technology this is almost impossible to achieve.NGTs have made it possible to introduce genetic changes in multiple genes simultaneously through a process that is called multiplexing. NGT-technologies are developed in order to edit genes, involved in the ripening of vegetables, multiplying copies for pathogenesis-related proteins that activate self-defense of plants against pathogens, etc. This opens the door to achieving relevant alterations in properties that are determined by more than one gene or to introduce different beneficial properties at the same time. NGTs have enabled the possibility of 'fast domestication', which has made it possible to simultaneously introduce important domestication traits into land races and other older varieties that possess important properties that have been lost in more modern varieties.
This research could be also a solution to food shortage, the scarcity of environmental resourcesa nd weeds and pests infestations.
In the field of socio economic aspects a qualitative expert evaluation was carried out using method of obtaining group compromise estimates with the Delphi two-cycle participatory process. Among the results the most positive effects of the use of new applications can be expected in the field of economic impacts, while the most negative effects of the use are expected for a content section of regulatory and policy frameworks. There will also be great influence on social aspects, yet the results were rather inconclusive in comparison with previous research on this topic.
On the other hand some stakeholders from organisector believe that NGT related research bruings opportunities only for science – employment possibility for researchers and money given to research institutions, perhaps for medicinal sector – but medicine is used only in the case of illness and for short time, contrary food is something else – used every day, more times per day; and definitely NOT for the agrifood sector, society, environment.

*** 12. Could NGT-related research bring challenges/concerns to science, to society and to the agri-food, medicinal or industrial sector?**

- (●) Yes
- ( ) No

* Please provide concrete examples/data

Most of the stakeholders identified also the concerns. As with any new technology, there are a lot of challenges and risks also with NGT-related research. However, the relatively high accessibility of these technologies resulted in their widespread use and consequently protocols for their applications have been developed and tested independently in many laboratories, thus solving faster some of the common challenges of new technologies. Risks and safety of NGT products for medical treatment of genetic diseases are assessed in preclinical and clinical studies also involving oppinions of ethical committees. Other concern is their influence on naturally present balance in the nature. However, strict regulatory procedures are already in place in the agri-food, pharmaceutical and medicinal sectors to avoid most safety-related concerns in using engineered microbes. Another layer of challenge for science and society is traceability of the changes introduced. As it is beneficial not to leave traces of the change for the technology effect to be

better on one hand, on the other hand it does not allow to distinguish some of these artificial changes from natural occurring ones (e.g. SNPs). Therefore, there should still be case-by-case assessment. From the society point of vew, lagging behind in development of NGT is also a challenge. Namely, reduced access to this core technology could have a big negtive impact on competitiveness of European/Slovenian biotechnology sector. There is uncertainty among young plant scientists whether it is a good idea to go for a career in plant science in Slovenia/Europe because of the lack of perspective to use NGTs for sustainable agriculture and food production in Europe. The recent experience with (technologically related) GMO techniques vividly shows that public concerns, or even sharp opposition may go beyond the regulative boundaries, adding social and economic concerns to the process of (non-)acceptance of novel products. It is important to effectively address socio-economic issues in the process of developing applications in the field of synthetic biology and genome editing. Globally it is a big ecological concern, for example devastating development in Amazon River area, in big part a result of growing plants, resulting from gene techiques applications.

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

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C - Information on public dialogues and national surveys

* **13. Have you or other institutions/bodies/entities organised national dialogues concerning NGTs?**

- ○ Yes
- ◉ No

* **14. Have you or other institutions/bodies/entities organised national surveys, which assessed public opinion on NGTs?**

- ○ Yes
- ◉ No

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

D Information on ethical aspects

* **15. Have any national bodies or expert groups discussed or issued opinion on the ethical aspects of NGTs?**

- ◉ Yes
- ○ No

* Please describe briefly the content, methodology and conclusions

The research project entitled ‘Procedures for ensuring safety and social acceptability of new techniques and applications of synthetic biology and modern biotechnology' briefly touched ethical aspects and presented them on different forums, but no opinion on the ethical aspects of NGTs was issued in Slovenia. However, the stakeholders point out that the use of NGTs as a part of gene therapies should be thoroughly discussed and a clear statement should be issued.

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

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E - Information on opportunities and benefits from the use of NGTs and NGT-products

* **16. Could the use of NGTs and NGT-products bring opportunities/benefits to the agri-food, medicinal or industrial sector?**

- (●) Yes
- ( ) No

* Please provide concrete examples/data

Most of the stakeholders experience and recognise important opportunities and benefits of NGTs and NGT-products. Examples are in cell therapy, metabolic engineering, new bio(nano)materials, drought and frost-resistant plants. NGTs and especially CRISPR-Cas-related technologies and products have a transforming potential for all the above-mentioned sectors. In the agri-food sector, these technologies enable development of new breeds and varieties with more predictable desired traits and with much less genetic alterations (compared e.g. to traditional breeding approaches), thus minimizing safety concerns. In medicine, NGTs enable manufacturing of advanced therapy medicinal products ie. gene therapy and cell therapy to treat and increase quality of life for specific groups of people with diseases disabling them to lead normal life. Moreover, precise tool for gene therapy can be designed only by using NGTs. The use of NGTs in research also accelerates identification of hitherto unidentified targets for gene therapies of additional diseases.In the industrial sector, NGTs enable design of novel and improved cell factories for biotechnology. Moreover, NGTs have the potential to significantly expand use of microbial cell factories for efficient production of exisiting biochemicals/biologicals as well as accelerate the discovery and development of new compounds with improved biological activity. In addition, industrial strains could be rapidly engineered to consume alternative feedstocks with smaller environmental impact for production of bulk and speciality chemicals. By applying efficient genetic engineering methods in industrial biotech we can significantly reduce the time needed to produce novel production strains. NGTs and products obtained by NGTs that are research tools bring important benefits to the research sector and stimulate the research, enabling new discoveries that could be important for the society and to the agri-food, medicinal or industrial sector.
On the other hand, NGTs may introduce new risks to food security, the environment and human health such as loss of biodiversity; the emergence of superweeds and superpests; the increase of antibiotic resistance, food allergies and other unintended effects. Some NGT for example are very unstable and are degraded by cell machinery in a few hours (RdDM, Zinc finger proteins).

*

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

- (●) Yes
- ( ) No

* Please provide concrete examples/data

Genetically engineered microorganisms have shown potential for bioremediation applications in soil, groundwater, and activated sludge environments. The increasing amount of organic pollutants (i.e. PCBs, PAH, pesticides) with hazardous effects that are resistant to degradation represent toxological threat. Bioremediation is the most promising strategy where microorganisms are harnessed to degrade the organic and inorganic pollutants. Currently various metabolic techniques are employed to produce genetically engineered microorganisms with better bioremediation efficiency. We see a great potential for new genomic techniques such as rational designing and directed evolution that have been developed to genetically modify microorganisms and their enzymes for the degradation of persistent organic pollutants. Several developments in the field of recombinant DNA technologies are carried out to achieve safe and efficient bioremediation of contaminated sites. Foods and food products could be produced with less problems of contamination with pesticides and with longer shelf life. The development of animals resistant to specific infectious agent would enable avoidance of drastic measures to control certain infectious diseases that have a major impact on animal welfare, environment as well as economy. NGTs-products could be a solution to food shortage, the scarcity of environmental resources, weeds and pests infestations, diagnosing disease condition, medical treatment improvement, improvement of the quality of life with longer life span, as well as production of vaccines and other useful drugs. Climate changes present an important challenge that could be counteracted by transforming the technology by greater application of biomimetic principles and application of NGT could advance sequestration of carbon in biological systems and in general for the promotion of carbon-neutral economy. Definitely the availability of new products with improved quality and/or other properties could present smaller footprint to the environment, what would bring benefits to society in general. This is a technology that is closest to the proceses in nature and has the potentials to benefit the humankind. However, the path to wider availability of such products is still long.
On the other hand, NGTs may introduce new risks to food security, the environment and human health such as loss of biodiversity; the emergence of superweeds and superpests; the increase of antibiotic resistance, food allergies and other unintended effects. Some NGT for example are very unstable and are degraded by cell machinery in a few hours (RdDM, Zinc finger proteins).

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

It is important that we also monitor the acceptance by the public of NGT techniques and their products. In the view of the fast development of NGTs and from the perspective of comprehensive consideration of the benefits and risks, it is important that on a case by case basis environmental and human health risk assessment would also be accompanied by an assessment of the socio-economic aspects.

*** 18. Do you see particular opportunities for SMEs on the market access to NGTs?**

- (●) Yes
- ( ) No

* Please explain under which conditions

NGTs are particularly appropriate for innovations that could be the foundation of SMEs and enabling them to bring a new products to the market in many cases medicines or gene therapy products. They enable

significantly shorter development times and costs from the initial idea to the proof-of -concept stage. Therefore, future entrepreneurs could engage in commercial biotechnology research with reduced risk and less funding requirement resulting in a bigger number of biotech start-ups. SMEs using NGTs could find their niche easier. There are many SMEs in Slovenia that develop NGTs and also some that only use NGTs as a key tool in the development. However, excessive regulation could limit access of SMEs to the market only alowing the large companies to overcome and finance the burden. As long as NGT products are considered to be subject to the EU GMO legislation small scale operators (SMEs) will not be able to market their NGT products, simply because having to comply with the EU GMO legislation creates safety testing and administrative requirements that are too complex, too cumbersome and too expensive to cope with for such SMEs. Thus, simplified regulatory procedures are needed for the approval and placing NGT-products on the market to prevent moving the development and production facilities out of Europe, where environments are more favourable for new technologies. Another obstruction is license accessibility for patented techniques. Usually, the prices for these licenses are very high and make them inaccessible for most SMEs.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Due to work invested and relatively low barriers for copying patenting of new solutions is essential for the biotech industry to protect the intelectual rights. Newly developed NGTs for industrially relevant species can provide SMEs with competitive advantage in terms of faster generation of production strains and proof of concept technologies. However, extremely broad patent claims and high-royalty models even in the R&D stage, such as the one implemented for the Cas9 protein, can also have a negative impact on future development. Patenting could exclude many from the potential advantages and restrict the number of beneficial development. Therefore patents should enable wide accessible licensing to spread the technology rather than limit it to the first-comers. The procedure for granting patents for NGTs NGT-products is also problematic, since it remains the same as it is valid for old techniques for genetic modification invented before the year 2001. In Slovenia the legislation regarding genomic techniques are Industrial Property Act (Official Gazette of the Republic of Slovenia, nos. 51/06 - officially consolidated text, 100/13 and 23/20; hereinafter: IPA) and Regulation for legal protection of biotechnological inventions (Official Gazette of the Republic of Slovenia, no. 81/2003; hereinafter: Regulation). The Regulation transposes the Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnical inventions (Official Journal L 213/13, dated 30. 7. 1998, pg. 13). Benefits /opportunities in patenting or accessing patented NGTs or NGT-products are similar to other techniques and products.

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F - Information on potential challenges and concerns of NGT products

* **20. Could the use of NGTs and NGT-products raise challenges/concerns for the agri-food, medicinal or industrial sector?**

- (●) Yes
- ( ) No

* Please provide concrete examples/data

Most of the stakeholders identified also the concerns, but pointed out that we have not enough experinces and it is difficult to answer. As with any new technology, there are a lot of challenges and risks also with NGT-products. NGT-related research can bring concerns for the agri-food, medicinal or industrial sector. These include safety risks due to unintended mutation or unpredicted side effects, gene flow, ecological consequences on biodiversity and environment. Additional, long term studies will enable us to determine the possible safety and environmental issues. Therefore, case-by-case assessment is still crucial. Difficult or impossible identification of NGT products is one of the biggest concerns. If anything, safety concerns are smaller with NGTs because of their better accuracy and lesser effect on the modified genomes. Fast development of new technologies brings risk in management of the impact of the technology on the society. However, strict regulatory procedures are already in place in the agri-food and medicinal sectors to avoid most safety-related concerns in using engineered microbes. One of the concerns is also that the technology would only benefit a handful of large multinational corporations and the consumers would have a lack of choice in the end. Yet, another concern expresses is a high risk for contamination of non-NGT crops and that organic farming would not be possible. For organic and non-organic GMO-free feed and food producers costs for testing and certification make products more expensive and “polluter pays” principle is not used. In the case of NGTs products compared to the GMOs the problem is even bigger. For several NGT detection techniques are not developed or possible. Detection technology and analytical methods for newly created strains should be readily accessible to all parties who need it. Therefore, the obligation to disclose the used breeding techniques is a prerequisite to avoid that certain strains enter the organic system and to guarantee freedom of choice for farmers and consumers.” (from source https://www.ifoam-eu.org/sites/default/files /ifoameu_policy_npbts_position_final_20151210.pdf

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

- (●) Yes
- ( ) No

* Please provide concrete examples/data

NGT-related research can bring concerns to the society. Arguments against genome editing are similar to arguments already risen for earlier technologies of genetic engineering and they range from ethical issues to lack of knowledge on the effects it may have, since once an altered gene is produced in an organism, the process cannot be reversed. Current applications of genome editing include some with potential impact on the security of the world food supply and on clinical therapies. Modifying the human genome raises ethical and social concerns, especially inheritable germline gene editing (e.g. designer babies). Gene editing of plants and animals intended for food raises questions of safety, traceability and public perception of modified foods. The use of gene editing in animals for research or agriculture raises animal welfare concerns. Development and release of organisms engineered with gene drives for exterminating insects that carry pathogens (e.g. zika) or for controlling invasive species can have unintended ecological consequences on biodiversity and the environment. Economic concerns encompass distrust in corporations with possible appropriation of intellectual rights and in agriculture fear of disrupting local industries dependent on heirloom varieties of animals and plants. They also encompass fear of unintended ecological consequences. There is also an emotional attachment to a particular conception of nature and of genetics. This uncertainty about downstream effects means that risk defined both in terms of known hazards and unknown possibilities is

difficult to determine. Since technical advances are necessary before decisions about NGTs and NGT-products are taken, research on genome editing should proceed under strict guidelines, but over-regulation should be avoided because it could inhibit orderly progression towards legitimate uses of the technology.

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

This would be the case if legislative framework will not be supported with on a case by case basis comprehensive environmental and human health risk assessment which is accompanied by an assessment of the socio-economic aspects.

*** 22. Do you see particular challenges for SMEs on market access to NGTs?**

- (●) Yes
- ( ) No

* Please explain under which conditions

The stakeholder noted similar limitations as for GMOs. In this respect ruling of the EJC that CRISPR-based modifications are the same as GMOs with inserted foreign material has no foundation in science and could in a long term proove to be harmful for the achieving benefits in SI/EU. SMEs are unlikely to market their NGT products under current legal status of NGTs and NGT products. As long as NGT products are considered to be subject to the EU GMO legislation small scale operators (SMEs) will not be able to market their NGT products, simply because having to comply with the EU GMO legislation creates safety testing and administrative requirements that are too complex, too cumbersome and too expensive to cope with for SMEs. On the top of that in the past two decades it has proved impossible to get a GMO approved for cultivation in Europe. While the price for establishing NGTs is typically comparable to other technologies, current uncertainty regarding the IP of some NGTs (especially CRISPR-Cas technology) is a challenge for smaller enterprises.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

From the legal point of view there are no significant hindrances for patenting the NGTs or NGT products as follows from the IPA the patent is granted without providing the search of the state of the art and the substantive examination. That means that the patent is granted without being examined on novelty, inventive step and industrial applicability. Some stakeholders don't have concerns for patenting of NGTs, but have concerns in accessing of patented NGTs when their price is too high. Problem may be also widely granted patents. In that respect a large social responsibility lies with those parties that control these patents. The other stakeholders believe patenting is troublesome, costly and time consuming. Patenting could be tricky for those NGT products that cannot be traced or distinguished from potentially naturally occurring genomic changes

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G - Final question

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

- (●) Yes
- ( ) No

Please provide your comments here

Some observations from the stakeholders involved into answering the questions:
- the questionnaire is too long, with questions that are repeating.
- one of the stackeholders believe, that NGT is going to be most useful in biomedical field. Efficasy and safety in medical applications is today still an issue. However, with time, technology will be optimised. Simmilarly as every new technology, it will take some time (decade or two), to optimise new gene tools and learn how to use it the safe and efficient way.
- one of the stackeholders consider using GM plants and other products (ie. microorganisms,…) based on old or new GT are threat for agrobiodiversity and could be a high risk of contamination with GMOs and there is a threat to farmers abandon growing organic crops (and other traditional crops in non organic sector) and thus lost a potential income opportunity. This was a case in some regions in Spain in organic maize production. In EU (and in several other countries) is increasing consumers demand for organic food which is much higher ad supply. Introducing plants and other organisms from NGTs is in contrary to ideas from EU » Green deal« from the point of view biodiversity which is an important issue mentioned several times and also from the point of view of strategy “From farm to fork” where increasing organic farming - see https://ec.europa.eu/food/farm2fork_en .

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