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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?

Czechia

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

Research organisations enquire about the status of NGT organisms developed in various projects, mostly in contained use. Many questions come from medical sector, e.g. enquires on DNA vaccines.
Breeding companies and seed importers have raised questions related to the legal status of genome edited products either imported or locally developed. These companies have to adopt their breeding programs in compliance with the current legislation. They perceive the future benefit of NGT-products, however, market analysis does not encourage them to start innovation programs with NGTs.
In 2007 and again in 2011, the Czech competent authorities were contacted by US company Cibus regarding the legislative status of the Oligonucleotide Directed Mutagenesis (ODM), called also „Gene Repair Technique“ or by the trademark name of the company Cibus the „Rapid Trait Development System“ (RDTS)". The expert advisory body to the Ministry of the Environment, the Czech Commission for the Use of GMOs and Genetic Products, issued an opinion, that the technique ODM resulted in genetic modification and the resulting organism fell under the scope of the GMO legislation. The company was informed accordingly.

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

- (●) Yes
- ( ) No

* Please describe the measures and, if possible, their effectiveness

NGT-products had been considered GMOs in the Czech Republic even before the EU Court of Justice ruling on mutagenesis in July 2018 was issued. However, the biotechnology research and industry were informed about the ruling immediately. The state grant agencies have been notified as well.

* What best practices can you share?

The expert advisory body to the Ministry of the Environment, the Czech Commission for the Use of GMOs and Genetic Products (CzC GMO), organises every year one meeting open to the public. GMO users, their biosafety officers and contact persons are invited. On this occasion, the CzC GMO and the Ministry present new developments in regulations and risk assessment methodology.

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

- (●) Yes
- ( ) No

* Please describe

The administrative burden is a hindrance for biotechnology research.

* How could these challenges or limitations be overcome?

The limitations can be overcome by fast change of the current regulations – updating of the obsolete legislative framework.

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

- (●) Yes
- ( ) No

* Please describe these practices (e.g. adaptation of multiannual control plans) and, if possible, their effectiveness (including of physical checks)

Relevant supervision bodies and GMO detection laboratories were informed and instructed by the Ministries of the Environment and of Agriculture about the application of the GMO legislation to NGT-products. In case the authorities receive any information on possible presence of NGT-product on the market these bodies and laboratories will be alerted immediately.

* What best practices can you share?

Co-operation among the relevant Authorities.

* Have the adapted inspection practices created additional requirements/burden for operators and/or public authorities?

- (●) Yes
- ( ) No

* Please provide concrete examples/data

According to the Czech National Reference Laboratory for GMO, additional financial resources will be needed to perform the detection of NGT-products (equipment, chemicals, personal cost and access to bioinformatics data).

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

- (●) Yes
- ( ) No

* Please describe

There are very limited possibilities to identify some types of unauthorised NGT-products imported from third countries.

* How could these challenges or limitations be overcome?

Dissemination of information to the supervision authorities is important, as well as the traceability of products like commodities and seeds. Here again, fast change of the current regulations – updating of the obsolete legislative framework is needed.

* **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

Labelling and traceability controls may run according to the plans of supervision authorities in agriculture in a similar way as GMO supervision, provided the analyses (for example PCR detection) can be based on commonly used molecular techniques.
The Czech National Reference Laboratory appointed pursuant to Article 33 of Regulation (EC) No 882/2004 and Article 100 of Regulation (EU) 2017/625 is a member of ENGL (European Network of Reference Laboratories) and is supported by EU RL. NRL representatives are members of working groups focused on establishing standardized procedures. Based on this cooperation, we agree that detection of NGT products in compliance with the current EU legislation is more or less feasible, depending on a type of a NGT-product.

* What best practices can you share?

The Czech competent authorities recommend collaboration within EU and follow the outcomes of EU RL and ENGL.

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

- (●) Yes
- ( ) No

* Please describe

The challenges, limitations and costs depend on the status of the NGT-product whether it is authorised or not.
Within the authorisation procedure for NGT-products in EU, applicants have to provide a detection method and reference material. The method must be (i) verified by the EU RL, (ii) validated in collaboration with NRLs and (iii) workable. The costs corresponding to the accreditation of currently used GMO detection techniques are predicted for each method.
Regarding NGT-products authorised outside EU, probably new approaches have to be developed. Significant increase in personnel and material costs can be expected, especially purchase of new platforms can be demanding. Costs could be estimated to reach 300 - 500 000 EUR. Training of new experts and development / use of new education programmes will be needed. Assistance of EU RL will be required.
Regarding unauthorised NGT-products: new approaches, extensive scientific effort and bioinformatics will be required. Even though detection of a specific plant could be possible (provided a list of all mutations discovered for each locus is available), detection of NGT-products in mixtures (food, feed) is not feasible for routine laboratory controls, based on the current level of knowledge.

* How could these challenges or limitations be overcome?

The change of current GMO legislation is a key element to overcome the above-mentioned challenges. In addition, reliable funding for building capacity for the effective implementation of updated legislation will be needed in upcoming years – higher requirements for human resources (number of experts and their training), financial resources to cover higher running costs, additional laboratory equipment and also IT support can be expected. In addition, member states shall continue and benefit from international collaboration and harmonization.

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

Agri-food sector

According to the Czech agri-research institutes and breeding companies, the reform of regulations is necessary. Current GMO legislation raises constraints to application of NGTs in new cultivars development as utilisation of GM products by farmers and subsequently by food industry is not accepted. Breeders are forced to use other, less efficient methods.

Medicinal sector

Especially in the medicinal sector, the application of the current GMO legislation is contentious. The definition of a GMO by listing the techniques resulting in GMO reflects the situation in 1990s when the use of GMOs in medicine was far from development. So the formats and requirements of the regulations are mostly tailored to GM crops.

* **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 specify

The information whether the variety is genetically modified is required in the registration process.

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

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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

CRISPR and other NGTs are standard tools in many research projects in the Czech Republic.
Some of the projects in plant research, medicine and genetics are listed in the annex.

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

According to plant scientists, NGT crop breeding projects are not funded by the government agencies, due to the negative perception of GMOs in EU. Because it is practically impossible to bring any gene edited plants to commercialization, development of such plants is not supported.

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

NGTs are rapidly evolving towards ultimate precision and safety (i.e. base to base modification and zero off-targets). Once there, it will quickly prevail over all previous techniques.
Opinion of the plant sector: NGTs are used in basic research, however, due to legal issues in Europe, the testing and commercial use are delayed. In plant research, the leaders will be China and USA with EU lagging behind both in basic and particularly in applied research. Change of regulation could have positive impact on biotechnology and breeding sector in Europe and also could lead to better public perception. Many researchers now do not want to get into NGT-related research because of the negative public and political attitude to GMOs. Why should they waste their energy and intellect if the authorities and consumers do not support it? Because of this situation, funds are mostly directed to projects that manipulate the genetic information using techniques that are not subject to the GMO regulations (Molecular Markers Breeding, Genome-Wide Association Study, Genomic Selection).

Medicinal and genetic sector: NGTs have become a fundamental part of basic research in the areas of molecular biology and medicine and we can expect NGT tools to be even more relevant in foreseeable future. Apart from basic research, we can expect therapeutic applications based on NGTs in close future. There are tremendous resources allocated to NGTs to make them safer, more efficient and versatile. NGTs are less expensive, more precise and efficient compared to the previous methods, and could bring faster development of medicines especially for orphan diseases. However, the potential of NGTs is hampered by obsolete legislation and bureaucratic obstacles.

* **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

NGT methods can be used in many breeding programs, including minor crops, vegetables and industrial plants. In the context of the EU aim to minimalize the use of pesticides, NGTs can help to develop suitable varieties to keep the European agri-food sector competitive. Drought-resistant crops and varieties are needed urgently, due to the climate change and resulting shortage of water in many regions of the Czech Republic.

Example of a specific research: The Institute of Plant Molecular Biology of the Czech Academy of Sciences, together with the Hop Research Institute, Ltd. plan to apply CRISPR/Cas9 technique for functional analysis of various hop genes. It is not possible to conduct such research in a greenhouse because hop plant requires natural sunlight for the induction of flowering. To get an authorization for a field trial is difficult, although only female plants would be grown and thus the risk for the environment would be negligible.

Research and development of medicinal products: there is a need for NGT-specific guidelines for development of medicinal products (non-clinical, clinical, quality guidelines and also long-term efficacy and safety follow-up).

* **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

Certainly yes. CRISPR and other NGTs are currently standard tools in many research projects. Introduction of NGTs (CRISPR/Cas9) has greatly accelerated progress in molecular biology.
In agricultural sector there are ongoing projects to improve disease resistance of crops and stress tolerance, especially to drought stress. Efforts to improve nutrient profiles, especially reduction in toxins and allergens, are also very important. NGT tools enable breeders to reach their goals faster, cheaper and with more precision and with fewer trade-offs. But it is necessary that the future regulation in this area is sound and fit for the purpose. Regulations focused more on the trait novelty and less on the used tools might be more suited for future development. More novel tools will be developed in the future and the legislation based on the list of regulated techniques will always be outdated.

Medicinal sector and genetic research:
NGTs are the crucial technology in molecular biology research that enables rapid and efficient preparation of various animal and cellular models that allow us to study human diseases and to develop NGT based therapies.
NGT-related research will certainly bring new opportunities and benefits to medical sciences. NGTs can provide less expensive, more targeted and efficient therapies. Newly developed vectors will carry human genes coding specific proteins or enzymes. Using these vectors, the correct genes could be introduced in recipients having defects (for instance metabolic) and so the defects could be compensated. Relatively successful attempts to correct genes responding for thalassemia, haemophilia or cystic fibrosis have already been made. The modification of genes and their transfer to immunocompetent cells open possibilities of specifically targeted immunological response to selected antigens, which brings very promising possibilities for treatment of various tumors.

* **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

Yes, as every new method, NGTs must be applied with caution and the consequences must be carefully examined. NGTs allow researchers and companies to modify genomes in a targeted way. In these terms, it is safer and more efficient than the previous genome-modifying techniques. But NGTs do not solve any of the ethical or biological challenge that a genome modification raises. Example is the generation of CRISPR edited babies carrying mutation in CCR5 (in China). Some of the applications needs to be carefully evaluated, e.g. gene-drive applications, which introduce a mutator locus into a wild population and can, for example, rapidly induce population-wide sterility of a pest or vector species.
Another dimension is the democratization of science. Today the genomic information of most important plant species as well as other organisms is freely available on the Internet. Molecular biology reagents including Cas9 can be brewed cheaply in DIY settings, DNA parts can be either relatively inexpensively either custom synthesized or ordered from depositories such as Addgene. So the enabling tools and technologies to create custom made life forms are at the disposal not only for smaller laboratories and SMEs but also to enthusiasts and hobbyists. Society should find the balance between freedom to use these tools and responsibility.

Research and development of medicinal products: NGT-related research already brings many challenges and concerns, especially on ethical aspects. To industry, it can bring new view on intellectual property (in the field of medicines the typical approach is market protection of the new active substance, however in case of the use of NGT it is not clear, what will be under protection of intellectual property?).

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

* Please describe briefly the content, methodology and conclusions

The Czech Republic participated in the ORION Open Science project (funded by EU Horizon 2020) focused on dialog and public education on gene editing (https://www.orion-openscience.eu/tags/genome-editing). The aim of the public dialogue is to better understand public opinion on technologies such as CRISPR/Cas9 and also advise the research institutions how to communicate the new technologies with the public, in calls for funding and in the policy advice process. The scientists-public discussions on gene editing in medicine and agriculture were organized by the Czech branch of the international market research company IPSOS in cooperation with the scientific center CEITEC. About 30 randomly selected participants and 3 scientists-moderators were discussing 2 times (total about 8 hours) various aspects of gene editing technology. At the beginning the public-participants were completely unaware that such technology exists. According to a scientist-moderator, at the end of the session most of the public-participants supported the sensible use of

gene editing both in medicine and in agriculture, provided that the goals (especially in agriculture) will benefit both society as a whole and the environment. Participants were more skeptical regarding traits bringing benefits only to the producers (e.g. herbicide resistance).

The expert advisory body to the Ministry of the Environment, the Czech Commission for the Use of GMOs and Genetic Products, organizes every year one meeting open for the public. The aim of this event is to inform the public about the activities of the Commission and about new developments in biotechnology. The application of NGTs was discussed during last two or three public meetings.

The NGO Biotrin, together with the University of Chemistry and Technology in Prague, organized an international conference called "New Breeding Techniques (NBT) - Hope for Agriculture and Food Chain" in September 2018. The conference was open to the public (no registration fee) and there was enough time for discussions. See the website https://www.biotrin.cz/nbt-conference/

Institute of Molecular Genetics of the Czech Academy of Sciences held a public discussion (~200 attendees) concerning the attempt to modify humans China in 2019.

Crop Research Institute in Prague has organized seminars on new breeding techniques for specialists in agri-food sectors.

* **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

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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

Discussions that include ethical aspects take place in media (TV, newspapers, journals) and in social media as well. Some Czech experts are very good at popularization of life sciences.
According to plant research specialists, it is important to shift the focus of the discussions from the tools used by breeders (NBT/NGTs, transgenesis etc.) to goals pursued by breeders. Novel tools enable breeders to reach their goals faster, cheaper and with more precision and with fewer trade-offs. But while the society keeps discussing the tools, which leads to inevitable simplification and polarization (e.g. artificial vs. natural, or natural vs. GMO), the more important and relevant social discussion on what goals are worth pursuing is missing. If something should be scrutinized from ethical perspective, it should be specific breeding goals (e. g. breeding for herbicide tolerance vs. hypoallergenic crop).

Another dimension of ethical issues are the impacts of EU regulation on international trade and non-European countries, particularly on the developing world. While non-adoption of more effective breeding methods in EU might lead only to higher production prices, brain drain and/or unnecessary environmental damage, non-adoption in less developed countries might lead to crops failures, endemic malnutrition and eventually even to migration pressure and wars.

Ethical aspects of NGTs in medical applications are even more complex. Also this discussion is ongoing, including the religious points of view.

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

Certainly yes. In agri-food crop sector, products resistant to plant disease and resilient to climate change will be most important and easily achievable. Also reduced allergen and toxins traits might be of importance. NGTs can be used similarly to other (conventional, unregulated) breeding methods, but depending on the crop species, NGTs might be faster and cheaper. Today, when the EU public is deeply concerned about the overuse of agricultural chemicals, particularly plant protection products, NGTs have the potential to dramatically reduce the PPP applications.
Also in veterinary research, precise genome editing can be used to develop animals resistant to various diseases. A good example was described in one of the projects mentioned in Q8 above - chickens resistant to the subtype J of Avian leukosis virus have been developed. This disease causes problems mainly in Asia, however, on the background of ongoing global pandemic, much more effort should be made to limit spread of any potential pathogen.

Medicinal sector: See also the response to Q11. NGTs can bring cheaper and affordable medicines, especially for orphan diseases and inborn genetic diseases. NGTs may be a better alternative for gene therapy strategies. NGTs have huge potential in developing animal models that mimic human diseases. This will significantly speed up our research and brings us closer to finding potential treatments.

*** 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

Certainly yes. See also the responses above. NGTs could bring benefits like reduction in plant protection products, improved nutrition profiles of crops, allergens elimination.
An example of NGTs benefit in plant breeding is incorporation of genes from a wild relative to a modern fine-tuned cultivar using targeted gene transfer within the same species. Crop wild relatives are sources of many beneficial alleles of biotic and abiotic resistance genes. By traditional breeding it is not possible to add or replace specific alleles of a gene without untuning the genetic background of a modern cultivar.
Another example can be targeted gene duplication or modification of the transcription level. Both within one species, one line, one genotype. To find a suitable natural mutation would be a long process, if it is ever found. With NGTs the aim could be achieved in months or weeks.

Medicines: NGT-products bring opportunities/benefits for medical sciences (see above), which imply also social and economic benefits even in the short, but mostly in medium and long terms. NGTs can be used for production of recombinant viral vectors that will serve as vaccines for animals and humans. The benefit in oncology is evident and certainly will have a big impact on treatment possibilities.

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

On condition the regulation in this area is sound and adapted to the scientific progress.

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

- (●) Yes
- ( ) No

* Please explain under which conditions

From the technical point of view, NGT are suitable for SMEs, thanks to relatively low price and availability of the necessary equipment and reagents. It should be specifically up to SMEs to develop new varieties of minor crops or special traits of plants and animals. However, the hindrance is the current complicated GMO regulatory regime. Because of the legislation, only multinational corporations possess sufficient financial and personal means to commercialize NGT-products. And even for these corporations it is possible to develop and commercialize just handful of traits of few most important crops. SMEs in the Czech Republic almost stopped research on GM and NGT crops because there is not chance for their commercial use.

Medicinal sector, research: SMEs will certainly take part in the research and development of NTGs (this already works), and consequently they will take part in the finalization of NTG-products. Development of gene therapy could be less expensive thanks to NGTs.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes, as with any other technology. The issue of patenting is sensitive. Historically plant varieties were excluded from patenting and were protected by different instruments in the EU. Among the reasons for this was that the precise genetic makeup of the variety was unknown and thus it could not be described in the patent application, nor easily duplicated. With the gene editing and other modern technologies, some

important traits will be much more precisely described and characterized. Copying of the traits into other varieties will be easier as well. We believe that at some point the legislative will need an update to better balance the rights between the party that originally identifies an important trait and those who would like to use it in their breeding efforts.
While patenting of gene edited crops developed by commercial entities might be necessary, enforcement of the patent rights might be as complicated as will be the traceability of NGT-crops.

Medicinal products: NGTs can bring a new view on intellectual property to the pharmaceutical industry (in the field of medicines, the typical approach is the market protection of the new active substance, however in case of NGTs it is not clear, what will be under the protection of intellectual property).

One of the main functions of the patent system is to foster technological innovation by providing an incentive for research and development. The patent system also works to disseminate technical information and promote technology transfer. Taking into account the NGTs, major benefits could be seen in patenting inventions primarily concerned with improving gene editing methods, which have or could have potential use in justified cases, e.g. in solving crisis situations, such as pandemics, long-term drought, etc. in the future. Subsequently, the patenting of inventions relating to methods for determining/distinguishing NGT-products from products obtained without use of NGTs. There are currently no published national patent applications in the Czech Republic dealing with this issue.

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

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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

Yes, in agri-food sector, it could raise challenges especially regarding evaluation (as a GMO or a new food product), traceability and labelling.
Much depends on the development of the market and how benefits of specific NGT-products will affect the market and whether NGTs won't result in monopoly in some of those sectors.
In industry, NGTs methods and products can bring big advantage for an institution which can successfully implement them but it will be big competitive disadvantage for someone who does not start to use it.
Medicines: Yes, concerns could be e.g. long-term safety, potential off-target toxicity, missing information on off-target effect in genomic regions with unknown functions.

* **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

Yes, like anything else. NGTs methods are only tools that can be used for various purposes.
The use of NGTs can represent a competitive advantage for non-European countries in the medium and long terms.
Medicines: Yes, concerns could be e.g. long-term safety, potential off-target toxicity, missing information on off-target effect in genomic regions with unknown functions.

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

General public does not see any difference between NGT-products and “traditional” GMOs even though NGT-products are indistinguishable from classical breeding outcomes. To reduce these concerns, the society in general should be better informed about GM techniques and NGTs.

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

◉ Yes
○ No

* Please explain under which conditions

From the technical point of view, NGTs are suitable for SMEs, thanks to relatively low price and availability of the necessary equipment and reagents. However, the hindrance is the current complicated GMO regulatory regime. SMEs do not possess sufficient financial and personal means to commercialize NGT-products. SMEs in the Czech Republic almost stopped research on GM and NGT crops because there is not chance for their commercial use.

Medicines: Development of gene therapy could be less expensive thanks to NGTs, the research and development of medicines can be more open for SMEs.

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

◉ Yes
○ No

* Please describe and provide concrete examples/data

Patenting of NGTs should follow the rules and principles set out by the Directive 98/44/EC on the legal protection of the biotechnological inventions. This Directive harmonises national law on the patentability of inventions relating to biological material and is fully implemented into the Czech legal framework (the Biotech Act No 206/2000 Coll.).

With respect to the patenting, there are no concerns, if the invention is described in the patent application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, including the original sequence which was genetically modified, if it represents a reproducible technical solution (is industrially applicable) and if the invention fulfils all other criteria of patentability (novelty, inventive step) in line with the Patent Act No 527/1990 Coll. and Biotech Act No 206/2000 Coll. However, the public should be informed that the grant of a patent does not automatically mean that the invention is safe in all respects. The nature of the patenting process, where each invention must be novel and include the inventive step, implies

that it is either a completely new method or the use of a known method, but in a new unexpected/surprising context. Therefore, at the time the patent is granted there is usually no sufficient information available to assess the impact on the environment, human health, etc.

Research and development of medicinal products: There are especially ethical aspects, to industry it can bring a new view on intellectual property (in the field of medicines, the typical approach is market protection of the new active substance, however in case of NGT, it is not clear what will be under the protection of intellectual property).

As for the access to NGT-products, it is important that it is clearly indicated which products are concerned and that methods are available to distinguish these products from non-NGT products. All potential users should be able to choose NGT-products or not and should have access to the latest information on these techniques, their benefits and possible risks.

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

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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

Technical comment: In the introductory part to this questionnaire, on page 1, footnote 2, it is written: “Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs.” This statement doesn´t fully correspond to reality. The “conventional development” of GMO plants leads to random inclusion of the gene of interest into the genome, whereas in NGTs products, the genome is changed in a specific locus. However, Agrobacterium or other methods are still used to deliver the new sequence into the genome.

Final note: We believe that the current EU GMO legislation might have been appropriate application of the precautionary principle at the time of its conception. Now, more than two decades later, we have generated substantial knowledge on GMOs. So far, we have not found any evidence that methods based on recombinant DNA technology constitute any novel or unique risks other than that related to the novel trait. EU has set quite ambitious goals to become the most competitive knowledge-based economy and at the same time to reduce the carbon footprint and environmental damage (New Green Deal). It will be very demanding to reach these goals even with the most advanced technologies available and nearly impossible with the legislation that creates unnecessary roadblocks to new technologies. If there is an opportunity to change the GMO related legislation and make it in line with the last two decades of scientific knowledge, it is now.

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Contact

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EU Survey on New Genomic Techniques

Czech Republic

Annex to Q 8

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?

CRISPR and other NGTs are standard tools in many research projects in the Czech Republic.

Projects in plant research:

1. Plants as a tool for sustainable global development, Palacký University Olomouc, (2018-2022), project financed by the European structural funds, call Excellent Research, CZ.02.1.01/0.0/0.0/ 16_019/0000827, budget 360 mil. CZK
The objective of the project is to acquire new knowledge about growth regulation, phenotype formation and stress adaptation of plants. Novel multidisciplinary approaches will be applied which use the newest technologies and take advantage of international network of cooperating top-class research institutions. The basic plant research will enable further development of targeted projects.

2. Projects of the Institute of Experimental Botany of the Czech Academy of Sciences, funding comes mostly from public sources:
- CRISPR-Cas barley genome editing: prospective tool for modern breeding (2017-2019),
- Gibberellin biosynthesis and signal transduction – identification of novel targets for plant growth regulation (2018-2020),
- Distinct transcription factor families controlling meristem activity and organogenesis in Arabidopsis (2017-2019),
- Genetic and cell biology approaches to study regulation of YODA (MAP3K4) signaling by HSP90 proteins in Arabidopsis (2017-2019),
- Impact of humanised glycosylation pathway on protein accumulation and traficking in plant seeds. The CRISPR/Cas 9 technique is used for blocking the plant glycosylation pathway. The aim of the research is to produce human proteins (antibodies, vaccines),
- Impact of the climate change on resistance of plants to pathogens. In this project, interactions of plant immune system with pathogens will be studied. The CRISPR/Cas 9 technique will be used to identify genes that could improve the resistance to pathogens. In the long term, gene editing could enable breeding of resistant crops.
- Basic research on flowering of Chenopodium plants. The CRISPR/Cas 9 technique is used for knock-out of various genes.

The projects exploit new genome editing techniques TALEN and CRISPR to get new knowledge that can be applied for breeding of economically important crops with higher yields, with resistance to biotic and abiotic stresses, improvement of technological parameters of production processes and increase of minerals contents. Through this new technologies plants hormonal regulations of important synthetic pathways are studied.
CRISPR is used in to study gene function and regulation of hormonal pathways, pollen development, and general cell biology. Similarly, virus induced RNAi, virus induced gene editing and transient gene expression are used in most molecular biology and physiology projects to identify gene function plants and to create recombinant proteins in plants.
The Institute of Experimental Botany also noted some negative experience: One project proposal of the Institute has been dismissed by the authorities in spite of the fact that the CRISPR/Cas 9 technique was planned to be used only in a preparatory phase for identification of target genes. For breeding, EMS (chemically induced) mutants were to be used.

3. Development of biofortified pea breeding lines with low phytic acid content, Company Agritec Ltd., 2018-2020, QK 1810072, financed by the Czech Ministry of Agriculture, budget 14 mil CZK.
The project is focused on development of biofortified pea breeding lines with low phytic acid content and/or higher phytase content and lines with increased content of bioavailable mineral elements (P, Ca, Mg, Fe, Zn, Se) for cultivars with improved nutrition value. CRISPR techniques are used in the project.

Projects in medicine and genetics:
4. Genome editing to treat Stargardt disease – Generation and phenotyping of a porcine model and development of a treatment approach, Institute of Animal Physiology and Genetics of the Czech Academy of Sciences, project number: 19-09628J, 2019 – 2021, international project, budget in CZ 12 mil. CZK, pubic funding.
Summary and aims: Stargardt disease, caused by mutations in the ABCA4 gene, is the most common juvenile maculopathy. The disease manifests most often within the macular area with RPE and cone photoreceptor degeneration, succeeded by generalized cone and rod degeneration at later stages. The unique, biomedical model for this disease is GM minipig, thanks to its size and comparable physiological parameters with men, as well as its retinal morphology with a cone enriched region. Scientists at the institute aim at generating a porcine model of Stargardt disease containing the human pathologic V1973X null mutation, to study the pathology and to develop therapeutic genome editing as treatment approach. They will generate piglets by CRISPR-Cas9 mediated genome editing in oocytes. Data from this project will enable scientists to continue optimizing the treatment approach in subsequent studies, as well as studying other treatment approaches such as cell transplantation. The interdisciplinary project will

develop an efficient and safe therapeutic application in a relevant large animal model that will pave the way towards clinical application in future.

5. Project name: Gene targeting in chicken and the resistance to newly emerging retroviruses, BIOPHARM, Research Institute of Biopharmacy and Veterinary Drugs, Institute of Molecular Genetics of the Czech Academy of Sciences, 2015-2018, code GA15-23993S, budget 7 mil. CZK, pubic funding.

Summary and aims: Subgroup J avian leukosis virus (ALV-J) is a newly emerging retrovirus, which induces myeloid leukosis and a broad spectrum of tumors in domestic chickens. It seriously threatens the poultry industry in Asia and the spread into Europe and America cannot be excluded. Therefore, the resistance to ALV-J and development of ALV-J-specific antiviral drugs are big concerns. It has been demonstrated that W38 in the chicken Na+/H+ exchanger type 1 (chNHE1) is necessary for the virus entry into the cells of susceptible species (chicken and turkey) and deletions or substitutions of W38 are present in the NHE1 gene of resistant species (quail, pheasant, chukar and other galliforms). Using the CRISPR/Cas9n–mediated homologous recombination, permanent chicken cell line was derived with the deletion of W38. The same genome editing technique was applied in chicken primordial germ cells with the aim to create inbred chicken line bearing deletion of W38. The ALV-J-resistant cells and chickens will be used for studies on virus-receptor interactions and virus escape mutations.

6. Project name: Advancement of chicken transgenic technology and its biotechnological application Institute of Molecular Genetics of the Czech Academy of Sciences, BIOPHARM, Research Institute of Biopharmacy and Veterinary Drugs, 2018 - 2021, code QK1810344, budget 6 mil. CZK, pubic funding

Summary and aims: The aim of this project is modification of the chicken genome using NGT allowing production of selected recombinant protein in the egg albumen. Further aims are modifications of the Tva gene in the chicken primordial gonocytes. Tva protein serves as a critical host cell receptor for the avian leukosis virus subtype A. The new derived chicken lines with Tva gene modification will be resistant to ALV-A infection and will be convenient e.g. for the vaccine production without danger of leukosis virus contamination.

7. Project name: Antiviral action of avian tetherin/BST2 Institute of Molecular Genetics of the Czech Academy of Sciences, BIOPHARM, Research Institute of Biopharmacy and Veterinary Drugs, 2020- 2022, code 20-22063S, budget 10 mil. CZK, pubic funding

Summary and aims: Interaction of viruses with host factors, and particularly the characterization of direct antiviral restriction factors, constitutes one of the main directions in recent virological research. The project will investigate the orthologue of the key mammalian restriction factor tetherin/BST2, which had been identified in the chicken genome. The antiviral mechanism of chicken BST2 against avian sarcoma and leukosis virus (ASLV) will be described and the in vivo BST2 knockout in chicken will be generated and characterized. The effects of chicken BST2 on two important avian pathogens: Marek's disease virus (MDV) and avian influenza virus (AIV) will be described.

8. Project name: Upgrade of the Czech Centre for Phenogenomics: developing towards translation research, Czech Centre for Phenogenomics, Institute of Molecular Biology of the Czech Academy of Sciences, 2017-2020, CZ.02.1.01/0.0/0.0/16_013/0001789, EU Operational Programme Research, Development and Education (OP RDE), 64 mil. CZK
Czech Centre for Phenogenomics (CCP) is a partner in the collective global network INFRAFRONTIER and the International Mouse Phenotype Consortium (IMPC, http://www.mousephenotype.org/), that aims to analyze the functions of genes in mice. The goal is to discover functional insight for every gene by generating and systematically phenotyping 20,000 knockout mouse strains – this should result in an 'Encyclopaedia of mammalian gene function', representing a very ambitious goal with huge impact in future biomedicine. To achieve the goal, IMPC relies on mouse models, the most important tools at our scientific disposal in understanding mammalian gene function. The fundamental genetic similarity between mice and humans allows researchers to infer a human gene's function based on studies with laboratory mice. One powerful technique is to turn off, or "knockout", the activity of a mouse gene to assess which biological systems are impacted. This gives insights to how a similar gene in humans may contribute to disease when its activity is altered. The CCP now generates knockout mouse strains using CRISPR/Cas9 or TALEN technology, which is very cost-effective and opens also other possibilities, e.g. to simultaneously produce point mutants relevant for human diseases. The strains are made available to the research community via public repositories. Over 250 mutant mouse models have been generated in IMG-CCP in the past 3 years using NGTs.
Research projects supported by EU Horizon 2020:

- IMGENE (Improving Genome Editing Efficiency) ID: 765269, H2020-EU.1.3.1., 2017-2021
- Infrafrontier 2020, Towards enduring mouse resources and services advancing research into human health and disease, 2017-2020, ID: 730879, H2020-EU.1.4.1.1.,
- Other projects in CCP that use NGTs are supported by the Czech Grant Agency and the Czech Ministry of Education Youth and Sports.

Consultation on new genomic techniques – additional replies of the Czech Republic

EC: In **Question 8**, you submitted an annex with information on research projects using NGTs. For the projects of the Institute of Experimental Botany of the Czech Academy of Sciences however, no budget figures are mentioned. Could you kindly provide us with the budget of these projects?

CZ: **Completed and corrected information on projects in plant research – part of the annex to Q8**

Plant research:

1. Plants as a tool for sustainable global development, Palacký University Olomouc, 2018 - 2022, project financed by the European structural funds, call Excellent Research, CZ.02.1.01/0.0/0.0/ 16_019/0000827, budget 360 mil. CZK

The objective of the project is to acquire new knowledge about growth regulation, phenotype formation and stress adaptation of plants. Novel multidisciplinary approaches will be applied which use the newest technologies and take advantage of international network of cooperating top-class research institutions. The basic plant research will enable further development of targeted projects.

2. CRISPR-Cas barley genome editing: prospective tool for modern breeding, Palacký University in Olomouc, 2017-2019, code GA17-07805S, budget 7 mil. CZK, public funding,

3. Gibberellin biosynthesis and signal transduction – identification of novel targets for plant growth regulation, Institute of Experimental Botany of the Czech Academy of Sciences and Palacký University in Olomouc, 2018 - 2020, code GA18-10349S, budget 8.5 mil. CZK, public funding,
4. Distinct transcription factor families controlling meristem activity and organogenesis in *Arabidopsis*, Institute of Experimental Botany of the Czech Academy of Sciences, 2017 - 2019, code GA17-23702S, budget 6.4 mil. CZK, public funding,
5. Genetic and cell biology approaches to study regulation of YODA (MAP3K4) signaling by HSP90 proteins in *Arabidopsis*, Institute of Experimental Botany of the Czech Academy of Sciences and Palacký University in Olomouc, 2017 - 2021, code GA17-24500S, budget 5.9 mil. CZK, public funding,
6. Basic research on flowering of *Chenopodium* plants, Institute of Experimental Botany of the Czech Academy of Sciences, 2019 – 2021, code 19-01639S, budget 8.9 mil. CZK. The CRISPR/Cas 9 technique is used for knock-out of various genes in this project.

The projects exploit new genome editing techniques TALEN and CRISPR to get new knowledge that can be applied for breeding of economically important crops with higher yields, with resistance to biotic and abiotic stresses, improvement of technological parameters of production processes and increase of minerals contents. Through this new technologies plants hormonal regulations of important synthetic pathways are studied.
CRISPR is used in to study gene function and regulation of hormonal pathways, pollen development, and general cell biology. Similarly, virus induced RNAi, virus induced gene editing and transient gene expression are used in most molecular biology and physiology projects to identify gene function and to create recombinant proteins in plants.

7. Development of biofortified pea breeding lines with low phytic acid content, Company Agritec Ltd., 2018-2020, QK 1810072, financed by the Czech Ministry of Agriculture, budget 14 mil CZK.

The project is focused on development of biofortified pea breeding lines with low phytic acid content and/or higher phytase content and lines with increased content of bioavailable mineral elements (P, Ca, Mg, Fe, Zn, Se) for cultivars with improved nutrition value. CRISPR techniques are used in the project.

EC : In **Question 18**, you mention that '*SMEs in the Czech Republic almost stopped research on GM and NGT crops because there is not chance for their commercial use'*. We would be interested in receiving further information on this claim, e.g. which SMEs had to stop research, and which were the projects that were stopped?

CZ : Projects of research institutes and SMEs that have been terminated and where breeding of the GM crops has not continued

Potatoes: Two research and breeding projects concerning SMEs were carried on 10 years ago - GM potatoes resistant to late blight and GM potatoes with modified sugar content in tubers. These projects were notified by Crops Research Institute, Prague, and Vesa Ltd., Velhartice. Field trials were terminated 2011 – 2013 and no similar project has been realized nor planned.

Flax: Various modifications of flax (improved resistance to fungal diseases and pests; increased ability of heavy metals accumulation, increased production of oleic acid) were developed and tested in 2007 – 2018 by a SME Agritec Ltd. Field trials were terminated in 2018 and the projects finished.

Pea: Various modifications of pea (increased resistance to fungal pathogens, selected viruses or insect pests, enhanced accumulation of seed proteins, earlier development of seed embryo) were developed by a SME Agritec and field tests began in 2010. After two years, the field trials were suspended, although the authorisation is valid up to the end of 2020.

Barley: GM barley producing enzyme phytase and GM barley producing additional cytokinin dehydrogenase in roots (for drouhgt tolerance) were notified by the Palacky University in Olomouc. Field trials with the phytase barley were suspended in 2018, although the authorisation is valid up to the end of 2020. The project with the cytokinin dehydrogenase barley finished in 2018.