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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?

Austria

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

Before the ruling of the European Court of Justice became public, general questions raised to the AT CA whether products made by new genomic techniques would fall under the scope of the EU-GMO regulations and/or the Austrian Gene Technology Act (GTG). Since the GTG excludes only non-directed mutagenesis, all these general questions were answered in the positive, based on Austrian national law.
Additionally, an international consultation on regulatory aspects of citrus products protected against the "Citrus Greening Disease" held in 2015 at the Federal Ministry of Health (BMG, now Federal Ministry of Social Affairs, Health, Care and Consumer Protection, BMSPK).
Representatives of an US company discussed ongoing research & development projects initiated by the company with experts from the Ministry, the Austrian Agency for Health and Food Safety and the Austrian Environmental Agency. The meeting, initiated by the company, aimed to share information on ongoing experimental work in the USA involving GM citrus tristeza virus on the one hand as well as the development of GM citrus trees on the other as independent approaches to induce resistance in citrus trees grown for orange production.
During consultation also regulatory matter were discussed: regulatory status of oranges (juice) produced from GM virus treated trees, specific data requirements for the Risk Assessment of GM trees according to the EFSA guidance framework, product characteristics that would render products not regulated according to Dir 2001/18/EC and labelling issues regarding orange (juice) products.
The company told that they consulted also CAs of other EU member states. The meeting recommended that the company should consult EC as well as EFSA.
GM applications introduced during the consultation are undergoing massive field trials in the USA.
(until 2019 a 400 acre experimental field trial was conducted in Hendry and Polk Counties, FL, a subsequent 513 500 acre trial permit is pending, with an Environmental Impact Statement (April 2019 https://www.aphis.usda.gov/brs/aphisdocs/17_044101r_deis_reopen.pdf) and a preliminary pest risk assessment (https://www.aphis.usda.gov/brs/aphisdocs/17_044101r_ppra_reopen.pdf) being drafted and submitted to public consultation)).

* **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

The Austrian mutation exemption provided in the GTG is more specific as the respective definition according to Dir 2001/18/EC (exempting only products developed by non-directed mutagenesis methods). Thus, the current GTG is fully in line with the 2018 decision taken by the Court of Justice of the European Union (ECJ) on the status of regulation of products developed by methods of genome editing.

As the AT GTG is fully in line with the ECJ decision, there was no specific need for action. EC was made aware of this.
Information was exchanged between the AT CA and EC concerning the wording of the definition of products which are exempted from regulation according to the GTG.

For national information exchange, the AT CA regularly informed its advisory body (Gentechnikkommission, GTK) and its subsidiary scientific bodies on the discussions on regulation of NGT within EU and the proceedings at and decision of the ECJ on the matter.
Therefore, the scientific body of the GTK is aware that applications of NGTs intended for deliberate release or placing on the market according to the GTG and EU regulations need to be notified to the CA and assessed by the competent institutions, including the scientific body of the GTK.
No change in AT policy and assessment regime is necessary. The involved AT bodies are aware of this situation, however no notifications for NGT products were submitted in AT.
The implemented information sharing channels in Austria were appropriate to address the upcoming issues, however no major non-routine issues were encountered and had to be taken care of.
Concerning medical applications, measures from the medicines legislation perspective are adequate.

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

- ○ Yes
- ◉ No

* Please explain why not

See above

* **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

Since robust and validated routine analytic methods for products made by NGT are not available, there was no possibility to adopt changes to the current inspection practices related to NGTs.

There was also no change in the procedure in the seed certification system including enforcement control. No additional measures have been implemented. The storage of seed samples during the variety registration procedure has been and is already in place.
In the application forms, it is mandatory to indicate the GMO status of the variety. A note was added that GMOs are interpreted in the sense of the ECJ judgment C-528/16.
According to the Austrian Seed Act 1997 (§57, §58) the responsible authority may ask for additional information.

For medical applications, no adaptions were needed. Traceability requirements covered by the medicines legislation; therefore, there was no need to build an additional traceability framework for NGT medicinal products.

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

- ○

Yes
No

* Please explain why not

See above

* **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

There is a lot of experience concerning the certification of organic produce or products certified to not contain GM materials (GT-free Label), which might be helpful for tracing some of the NGT-products.
A description of procedures for identity preservation of organic produce or GT-free labelled products according to the AT guidelines for organic or non-GM-production can be found under the following link:

(https://www.verbrauchergesundheit.gv.at/lebensmittel/buch/codex/beschluesse/gentechnikfreie_produkte.html)

Procedures are effective as checked by analytical random testing, which are conducted to ensure the absence of GM material along the production chains. However, with some NGT products, such analytical methods may not be available. Therefore, international information exchange (e.g. via a public registry, database, etc.) for NGT products in development, used for field trials or marketed is highly recommended. In particular, exchange of information on analytical methods for detection would be important.

In addition, the fact that in some third countries NGT and the respective products made with these technologies are not subject to authorization as well as labelling will hinder the traceability. Therefore, mandatory and active information on patents from third countries could be helpful.

However, additional handling costs (to establish proper documentation on products) as well as additional testing costs (for developing test methods, providing appropriate testing routines) are anticipated.

Concerning seed, traceability is granted due to the requirements of the European and Austrian Seed legislation. In the Technical Questionnaire (“Technischer Fragebogen”), information concerning the pedigree (e.g., hybridisation incl. details, mutation incl. the initial varieties, discovery) is required. Please refer also to question three.

The system of seed testing includes a number of steps, laid down in the legislation in detail. It covers at least:
a.) Information on the pedigree
b.) Visual inspection of the crop on the production site, testing of samples, including mandatory laboratory testing on specific pests, diseases and quality properties
c.) Enforcement control including testing of random samples following a risk-based approach.
Documentation of all steps and inspection results is kept by the authority and can be traced via information given on the seed label, e.g. the unique lot number.

From the perspective of the medicines legislation and tissues and cells legislation there is experience on traceability strategies.

* What best practices can you share?

See above

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

- (•) Yes
- ( ) No

* Please describe

See above

* How could these challenges or limitations be overcome?

See above

* **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:**

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

Medicinal sector

In the medicinal sector we share experience on clinical trials, compassionate use and named patient use. As there are no experimental releases in AT in all other applications, there is no experience.

* **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

As of April 29th, 2020, no NGT-derived plant varieties have been registered in the Austrian National Catalogue (GMO according to Directive 2001/18/EC and interpreted in the sense of the ECJ judgment C-528 /16).

During the application process, information on the applied technique is obtained as required in the Technical

Questionnaire. In the Austrian National Catalogue, a GMO is indicated based on this information ("Gentechnisch verändert. Veröffentlichung gemäß Saatgut-Gentechnik-Verordnung BGBl. II Nr. 478/2001 zgd BGBl. II Nr. 76/2011."). As mentioned in question three, to clarify the Austrian definition of a GMO based on the GTG, a note was added to the Technical Questionnaire that GMOs are interpreted in the sense of the ECJ judgment C-528/16.

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

The BMSGPK has commissioned a study on RNAi based techniques, accelerated breeding and CRISPR-Cas in plant breeding:
Hilscher J, Bürstmayr H, Stöger E, 2017. RNAi-based techniques, accelerated breeding and CRISPR-Cas: basics and application in plant breeding. Vienna, Federal Ministry of Health and Women: 1-108.
Executive Summary: https://www.verbrauchergesundheit.gv.at/gentechnik/gruen/techniken_pflanzenzuechtung_summary_20170323.pdf?72a0uv

The Austrian Science Fund (FWF) is supporting NGT-related research projects. Title, duration of the project, abstract and final report, the amount of national funding and the receiving entity can be found following the link:
https://pf.fwf.ac.at/en/research-in-practice/project-finder (To find the respective project search for related keywords such as CRISPR/Cas, genome editing etc.)

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

See above

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

It is expected that NGT-related research will become more and more important in the field of biotechnology. The number of CRISPR/Cas applications is growing very fast. The techniques will be more precise and easier to use in the future. An important aspect will be that not only applied research but also safety, risk assessment and detection studies have to be conducted.

NGT-related research is an important aspect of basic research, e.g. to elucidate gene functions. It opens up new possibilities to address a lot of questions related to complex plant genomes. By this, research will substantially support breeding activities. NGT is a valuable tool that greatly facilities the gain of new knowledge in any field of biological research.
For a practical example, global climate change could be a driver for research on heat and drought resistant plant varieties.

Based on current information NGT-related research for contained use and the use of NGT-related techniques are available in almost all life-science research institutions in Austria. NGT-related techniques are used for instance in the fields of molecular biology, developmental biology, microbiology, biomedical research, research on genomic population in model organisms and basic research on plant genomics.

In the medicines sector it will probably find extensive application both for production and as medicinal products by themselves. It will be a societal challenge to deal with NGT, in the context of in vitro fertilisation (IVF). Advancing technology will also commit access to NGT to persons who are not themselves expert in the field.

*** 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

As mentioned above, in addition to basic research that is still needed, studies concerning the safety, risk assessment and detection of NGT have to be conducted. It is of utmost importance that for the development of detection methods EU should coordinate, facilitate and finance these studies.

In the past few years CRISPR/Cas applications have rapidly advanced. They are now regularly applied in plant research activities, but also in the development of applications for plant breeding. In the absence of molecular signatures or sequence elements that are common and specific for a larger group of NGT-derived plants, no general screening approach is applicable – as outlined in the ENGL report on detection of food and feed plant products obtained by new mutagenesis techniques (JRC116289 from 26th March 2019). Therefore, it is assumed that the stepwise approach between detection by screening and subsequent identification may not be applicable as for conventional GMOs.

For enforcement laboratories, it will be essential to develop robust laboratory methods to assure that unknown unauthorised NGT products can be prevented from entering the market. This would require a significant level of method optimisation and experience, which is currently not available. None of the techniques described in the available literature to date are able to distinguish whether the small modifications (like Single Nucleotide Polymorphism, SNP) is caused by genome editing, by classical breeding technologies, or by natural mutation.
Focused research activities have to be initiated in the near future, otherwise the analytical confirmation for enforcement of the regulations for NGT remain very challenging.
Competent authorities must be able to detect and identify particular GMOs to facilitate post marketing control and inspection (1). This is feasible if producers of GMOs (including NGT-derived plants and products) provide the detection methodology in compliance with Directive 2001/18/EC foreseen when plants are within the scope of the Directive and in the case of notification for placing on the market. Today it is technically difficult to identify GMOs engineered by NGT if no or insufficient technical information to facilitate detection is disclosed by the developer.

Therefore, the following points were identified:

a.) Development of screening methods for the identification of undisclosed NGT engineered GMOs is necessary but demanding. The establishment of comprehensive sequence databases containing reference genomes of non-genetically modified organisms is necessary.

b.) Development of biostatistical approaches and workflows for sequencing data evaluation and validation to improve the relevance of sequence comparisons of large genomes.

c.) Focus on research and development of techniques for the identification of matrix effects due to transformation stress-induced alterations in the engineered genome to identify so called “scars” or “signatures” in GMOs produced by NGT.

d.) Improvement and streamlining of GMO risk assessment procedures for products produced by NGT to reduce the workload for risk assessors and support competent authorities to focus on relevant risk management options.

e.) Further research on design and criteria for risk assessment of NGT applications with characteristics different to current GMO applications (e.g. insect resistant (IR), or herbicide resistant (HR) products) is required (16-18), including specific considerations for the risk assessment for emerging NGT applications, such as:

f.) Gene Drive Organisms,

g.) RNAi-based approaches (RdDM),

h.) Complex genome-edited products (developed by multiplexed genome editing);

i.) NGT organisms with traits that increase the environmental fitness of crops,

j.) GM virus applications (e.g. GM CTV-applications)

*** 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

To the seed-breeding sector it could be beneficial that up-to-date aims like resistance of plants against drought, heat or pests will be achieved in a shorter period. NGT-related research will help to reduce breeding times and streamline breeding schemes which presumably will reduce costs for commercialization of transgenic organisms (2).

Moreover NGT-related research in general could bring benefits to human and veterinary medicine, agriculture, aquaculture as well as the environment.

In the medicinal sector addressing unmet medical needs and providing approaches for single treatments where currently only chronic or symptomatic therapy is possible.
NGT-related research will also improve and speed up the production of vaccines and their administration (3), drug discovery, development and therapy (4) and will open new opportunities in in vitro diagnostics leading to improved cancer staging and therapy (5).

*** 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

As mentioned above questions of safety, risk assessment and detection concerning products developed by NGT are still not addressed sufficiently. Therefore, society has just little information for a detailed and informed risk/benefit discussion.

In addition, ethical questions have to be considered. Therefore, the BMSGPK has commissioned a study concerning ethical questions on NGT (Dürnberger C. 2019. Ethical Delphi: Neue Pflanzenzüchtungsverfahren in Österreich. Dissens verstehen. Nach Konsens fragen. Messerli Forschungsinstitut Abteilung Ethik der Mensch-Tier-Beziehung Vetmeduni Vienna, Medizinische Universität Wien, Universität Wien Professor Herwig Grimm, Institut für Philosophie Lehrstuhl für Angewandte Ethik Universität Wien Professor Angela Kallhoff (in press)).

A challenge for science and society will be to facilitate these discussions based on objective data and information. Therefore, the Austrian Agency for Health and Food Safety published the so called "Risikobarometer".
https://www.ages.at/wissen-aktuell/publikationen/risikobarometer-umwelt-gesundheit-2019/

The sceptical position of politics and society on "conventional" GMO, in particular concerning genetically modified plants, led to restrictions also for research (for example research on sharka-resistant apricot in the 1990s). This critical position of society eventually led to destruction of field trials in some MS.

Furthermore, the following technical aspects linked to NGT products should be considered in particular:
a.) Identification of off-target effects (8)
b.) PAM dependencies (8)
c.) gRNA production is difficult due to extensive posttranscriptional processing and modification of mRNA produced by RNA polymerase II (8)
d.) Necessity to develop robust robust methods to deliver effector molecules. DNA and RNA injection-based techniques are used for CRISPR/Cas9 delivery, such as injection of plasmids expressing Cas9 and gRNA and injection of CRISPR components as RNA. The efficiencies of delivery methods depend on the types of target cells and tissues. More attentions should be paid to develop novel robust delivery methods for CRISPR/Cas9 (8)
e.) Sufficient molecular as well as phenotypical characterization of newly developed NGT applications, given the increased speed of development for some NGT approaches (incl. accelerated breeding, multiplex genome editing, etc.) (16,17)
f.) Need to develop analytical methods for enforcement purposes (routine analytical detection and identification) (20)

In addition, there are societal challenges like:
a.) General challenges to develop an overall approach ensuring the biosafety of plant and animal breeding applications (16,19)
b.) Challenges to further develop and improve the current regulatory system for GMOs (17, 19)
c.) Need to conduct a societal discussion regarding various aspects (biosafety, ethical considerations, socio-economic considerations, policy development) associated with the newly developed NGT products
d.) Ensuring enforcement requirements: coexistence, freedom of choice (protection of GM-free production), labelling (GM labelling, non-GM labels)

In the field of Agri-Food, the following challenges are anticipated:
a.) Addressing the two-way challenge on the one hand support of emerging, relevant R&D while on the other hand ensuring safety and sustainability of developed products
b.) Ensuring proportional regulation of all agro-food developments focusing on relevant issues of concern
c.) Ensuring appropriate monitoring of environmental effects of NGT applications (for imported products as well as product for cultivation / release)

In the medicines field NGT will bring challenges/concerns to science and to society but the given framework should be able to deal with them.

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 BMSGPK organised the following meetings and discussion on national and international level:
• Special event on risk assessment of new plant breeding techniques for EU RA experts and authorities, on 17th October 2017, Vienna
• Diskussionsveranstaltung zu den neuen Züchtungstechniken (nat. Stakeholder Meeting on issues related to NGT application), 4th September 2018, Vienna
• 1. Behörden-Workshop Neue Züchtungstechniken (1st Workshop on NGT issues for representatives of Austrian authorities), 23rd January 2019; Vienna
• 2. Behörden-Workshop Neue Züchtungstechniken (2nd Workshop on NGT issues for representatives of Austrian authorities), 25th March 2019; Vienna

Additionally dialogue circles were organised: Discussions with various stakeholders, from industry to NGOs, throughout Austria (https://www.zukunft-pflanzenbau.at/home/), respecting, inter alia, the following principles: It is a mechanism to discuss and network ecological, economic and social concerns in Austria. Periodic "Round Tables" are held to discuss current issues in plant cultivation. The dialogue platform is based on a partnership-based relationship of trust between the parties involved, or round tables are intended to promote such a relationship. The joint work should be consensus-oriented and characterised by continuity. The participants accept and respect the positions and interests of the other dialogue partners. The dialogue includes all relevant sectors and organisations and can - if desired and agreed with the stakeholders - be supplemented or extended. The dialogue is intended to create the basis for the development of solutions by mutual agreement. Financing the implementation of the proposals for action is the responsibility of the respective actors within the scope of their possibilities.

In addition, the University of Natural Resources and Life Sciences, Vienna has established an ethic platform to stimulate a systematic and participative discourse for ethical questions concerning NGT (https://boku.ac.at/en/ethikplattform/genome-editing).
The platform aims to initiate University-wide discussions (open to the public) addressing relevant topics connected to ongoing university research and general ethical issues in science & society. The platform chair organized a series of lectures providing input for further public discussion:
• Potenzial und Risiken von Genome Editing bei Nutzpflanzen (Scientific inputs and public discussion addressing opportunities and risks associated with the use of NGTs in crop development), 22rd October 2019; BOKU, Vienna

• Biolandbau und Gene Editing - eine (un-)mögliche Kombination? (Organic farming and genome editing – a potential/impossible match), 15th January 2019; Vienna https://boku.ac.at/ethikplattform/genome-editing/biolandbau-und-gene-editing-eine-un-moegliche-kombination

* **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 BMSGPK has commissioned a study concerning ethical questions on NGT (Dürnberger C. 2019. Ethical Delphi: Neue Pflanzenzüchtungsverfahren in Österreich. Dissens verstehen. Nach Konsens fragen. Messerli Forschungsinstitut Abteilung Ethik der Mensch-Tier-Beziehung Vetmeduni Vienna, Medizinische Universität Wien, Universität Wien Professor Herwig Grimm, Institut für Philosophie Lehrstuhl für Angewandte Ethik Universität Wien Professor Angela Kallhoff (in press)). Participants of this study were stakeholders and NGOs.

The National Bioethics Commission at the Federal Chancellery has ongoing discussions on ethical aspects of NGT (https://www.bundeskanzleramt.gv.at/themen/bioethikkommission.html).
The Bioethics Commission also organized a meeting with national ethic commissions from AT, DE, CH: Bioethik-Kommission diskutiert zu Gen-Chirurgie, Treffen der deutschsprachigen nationalen Ethikkommissionen (DE, CH, AT) zum Themenbereich "gene editing" in Wien, 18th Nov. 2016 https://www.bundeskanzleramt.gv.at/themen/bioethikkommission/pressemitteilungen-bioethik/bioethik-kommission-diskutiert-zu-gen-chirurgie.html

In addition, other discussions were held, however no published opinion papers are available except documentation of events and a press release on the symposium Fighting Malaria with CRISPR/Cas9 – see below)

- UNESCO Lehrstuhl für Bioethik (https://www.meduniwien.ac.at/web/internationales/unesco-lehrstuhl-fuer-bioethik/), Christiane Druml:
  Vector borne diseases, the nature and genome editing: an ethical consultation, 8th – 9th January 2020, Van Swieten Saal, Medical University of Vienna https://www.meduniwien.ac.at/web/internationales/unesco-lehrstuhl-fuer-bioethik/aktivitaeten-auswahl/2020-konferenz-vector-borne-diseases-the-nature-and-genome-editing-an-ethical-consultation/

Fighting Malaria with CRISPR/Cas9: Ethical Implications, 7th September 2016, Josephinum, Vienna https://www.meduniwien.ac.at/web/internationales/unesco-lehrstuhl-fuer-bioethik/aktivitaeten-auswahl/2016-konferenz-die-bekaempfung-von-malaria-mit-hilfe-von-crisprcas9/

- The University of Vienna (Research Platform Responsible Research and Innovation in Academic Practice) organised a symposium “Editing genomes with CRISPR” in Vienna (19-20 October 2017, https://rri.univie.ac.at/workshops-events/crispr-symposium/) with the following aims:
- to host an open dialogue between the scientific community (ranging from life scientists, to social scientists, and beyond) and civil society, discussing ongoing applications of the CRISPR technology, expected and envisioned developments, and the benefits, caveats and consequences of this technology’s applications
- to provide a platform for public engagement on this topic, enabling researchers involved in the CRISPR field to interact with citizens, regulators, and stakeholders
- raise these issues in a European context, in order to facilitate the development of a European engagement with this revolution.

Of note, in the medicinal product field, a dedicated vote by an ethics committee is a prerequisite of clinical trial conduct.

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

To the seed-breeding sector it could be beneficial that up-to-date aims like resistance of plants against drought, heat or pests will be achieved in a shorter period. Also alteration of substances produced by the plants (like wheat gluten, potential allergens, fatty acids) could bring benefits.
In the medicinal sector, addressing unmet medical and providing approaches for single treatments where currently only chronic or symptomatic therapy is possible could bring great opportunities and benefits.

* **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

Additional to the answers to question 16:
Developments on global level show that there is a market for products obtained by NGTs, e.g. in the USA there is a soybean variety with improved fatty acid content that may have positive effects for human health.

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

See above

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

- (●) Yes
- ( ) No

* Please explain under which conditions

SMEs see opportunities as suppliers of raw/starting materials in the production process. Supply can be for all sectors by the same company.

To conduct a reliable evaluation of the potential opportunities, a number of questions concerning the possibility of investments, available in-house know-how, and the size of a possible research and development department have to be considered.

However, if applicants have to conform to the entire range of requirements foreseen in the current approval procedure for GMOs costly approval procedures are given.

In AT seed industry is comprised mainly of SME. There is a major interest in the development of varieties with specific properties particularly for cultivation under specific regional conditions. Contrary to “conventional” GMO, the potential effort (development, production, authorization procedure) using NGT in the field of plant breeding is considerably lower. Therefore, the use of NGT could be of interest for SME. In what extent SME use NGT in the future will depend on the fact, if NGT products have to fulfil all the authorization requirements like “conventional” GMO or not. If applicants have to conform to the entire range of requirements foreseen in the current approval procedure for GMOs costly approval procedures are given.

In particular, an impact on the competitiveness of applied research at the universities is anticipated.

In the medicines sector academic groups/SMEs tend to be involved in early development, but usually commercialization is achieved by larger entities due to the organizational requirements of managing a licensing procedure and the post-marketing life cycle.

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

- ( ) Yes
- (●) No

* Please explain why not

Patents in the field of plant breeding are judged critical in general. The problem is that patents on plant breeding techniques and patents for technical equipment (e.g. electronics) are treated equally. For plant breeders patents are a disadvantage because of excludability and possible licences costs. Therefore, the

tool of plant variety right protection is preferred. Patents could lead to competitive disadvantages of Austrian plant breeders.

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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

General potential challenges and concerns:
As mentioned above general questions of safety, risk assessment and detection concerning products developed by NGT have not been sufficiently addressed so far. Therefore, society has no basis for a detailed and informed risk/benefit discussion. In addition, ethical questions have to be addressed, too.

Specific challenges and concerns:
a.) Undisclosed GMOs produced by NGT may contain vector backbone sequences of the plasmids used for transforming eukaryotic cells including antibiotic resistance genes which may spread in the gut of the transgenic animals or in the guts of consumers (9).
b.) Separation of GMO/non-GMO product pipelines becomes increasingly difficult due to uncontrolled introduction of NGT products into commercialization (10).
c.) Need to develop improved regulatory risk assessment approaches for complex NGT applications which are or may be released into the environment; e.g. for experimental testing, by accidental spillage and further spread, for agricultural purposes/cultivation and spread into non-agricultural habitats, biocontrol, etc. (16,17).
Examples: Gene Drive organisms, HEGAAs (horizontal environmental genetic alteration agents such as GM virus agents, paratransgenic microorganisms, etc.); de-novo-domesticated wild crop relatives.
d.) Need to develop robust approaches for socio-economic assessment for decision-making (21).
e.) Need to develop analytical methods for enforcement purposes (routine analytical detection and identification) (20).
f.) Ensuring proportional regulation on relevant issues of concern (19).
g.) Ensuring appropriate monitoring of environmental effects of NGT applications (for imported products as well as product for cultivation/release).
h.) Ensuring enforcement requirements: coexistence, freedom of choice (protection of organic and GM-free production), labelling (GM labelling, non-GM labels) (21).

Challenges for the medicinal sector:
The framework for medicinal products is capable of dealing with the challenges and concerns on a product level. However, additional challenges/concerns are seen in the interplay between GMO- and medicines legislative frameworks on a classification and procedural level (e.g. is the therapeutic agent a GMO or not, the currently, on a legal level, not yet harmonized requirements during clinical trials).

* **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

In addition to the points raised at question 20 we see the following challenges/concerns:
There are several issues to be mentioned with respect to potential challenges/ concerns for the environment, human, animal and plant health caused by the application of NGT:

a.) NGTs have different individual characteristics:
The methods of NGTs comprise various techniques with very different individual characteristics. This can lead to different hazards associated with the application of individual techniques. Additionally, for each technique (e.g. CRISPR/Cas) many different variations exist, depending on the aim and the purpose of the invention. Therefore, it is obviously difficult to categorise NGTs in groups, and even more difficult to differentiate them into two groups of which one group will not raise challenges/concerns for environment, human, animal and plant health and the other one does.
This high diversity of genetic engineering techniques and their molecular and technical background is reflected in Directive 2001/18/EC, Annex I A (Part 1), which rather describes the characteristics of techniques that are considered to result in genetic modification than a simple list of techniques. If some NGTs are to be exempt from GMO regulation, this decision has to be based on scientific evidence concluding that a comprehensive risk assessment as for GMOs is unjustified.

b.) Use of recombinant nucleic acids:
Some NGT may use recombinant nucleic acid molecules, i.e. new combinations of in vitro-derived genetic material, which act as a template to direct sequence changes in organisms. This process is different to the sole introduction of DNA double strand breaks (DSB) by NGT which are repaired by the cell's own natural mechanism leading to equal DNA changes as through the repair of naturally occurring DSB. In contrast, NGT that use such recombinant nucleic acid molecules (SDN-2, ODM) cause potential modifications beyond the range of natural mutations and pose novel risks in some types of organisms (11).

c.) Insufficient knowledge:
There are existing uncertainties due to insufficient knowledge about new applications of NGT, e.g. base editing (11). Such lack of information and knowledge makes it difficult to predict risks for the environment, human, animal and plant health in relation to these techniques.
There are also indications for systematic unintended effects for some methods of NGT (12). These should be carefully evaluated in relation to potential challenges/concerns for the environment, human, animal and plant health.
Because of such knowledge gaps, it is important that groups of NGT are not altogether exempt from the EU legislation on GMO. It should be instead analysed and specified why a comprehensive risk assessment as for GMOs is scientifically unjustified for a distinct group/approach of NGT prior to their exemption.

d.) Unwanted genetic elements:
There are many examples of current NGT applications where transgenes have subsequently been removed by segregation processes (13). Therefore, remaining genetic elements (e.g. plasmid, transgene, repair template) in NGT organisms are not an unrealistic scenario and could be a safety issue. This problem also shows how important it is that regulators check data on NGT products (14).
In general, it is important that there is a consequent data exchange between users of NGT (e.g. plant

breeders) and regulators. In particular, it needs to be ensured that no unwanted transgenic elements remain in NGT products in case these products would not be risk assessed according to GMO regulation standards.

e.) Substantial modification:
NGT may be used to produce food and feed that is substantially modified in composition. It has to be ensured that such food and feed products are safe for human and animal consumption. Clarification is further needed if food produced by some NGT procedures exempt from GMO regulation will fall under Novel Food Regulation conditions.

f.) Spread of antibiotic resistance due to ARGs of transformation vector backbone in the genome of NGT modified mammals (9).

g.) Exclusion from GMO risk assessment procedure would increase the risk for unwanted changes in the modified genome (15)

h.) General challenges to develop an overall approach ensuring biosafety of plant and animal breeding applications

i.) Challenges to further develop the current regulatory system for GMOs

j.) Need to conduct a societal discussion regarding various aspects (biosafety, ethical considerations, socio-economic considerations, policy development)
In the medicinal sector germline modification will be possible in the future and hereditary diseases could probably be cured, however impact on the germline is prohibited at the moment.

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

See above

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

- (●) Yes
- ( ) No

* Please explain under which conditions

In AT seed industry is comprised mainly of SME. There is a major interest in the development of cultivars with specific properties particularly for cultivation under specific regional conditions. Contrary to “conventional” GMO, the potential effort (development, production, authorization procedure) using NGT in the field of plant breeding is considerably lower. Therefore, the use of NGT could be of interest for SME. In what extent, SME use NGT in the future will depend on the fact, if NGT products have to fulfil all the authorization requirements like “conventional” GMO or not.

In particular, an impact on the competitiveness of applied research at the universities is anticipated.

In the medicines sector academic groups/SMEs tend to be involved in early development, but usually commercialization is achieved by larger entities due to the organizational requirements of managing a licensing procedure and the post-marketing life cycle.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Patents in the field of plant breeding are judged critical in general. The problem is, that patents on plant breeding techniques and patents for technical equipment (e.g. electronics) are treated equally. For plant breeders patents are a disadvantage because of excludability and possible licences costs. Therefore, the tool of plant variety right protection is preferred. Patents could lead to competitive disadvantages of Austrian plant breeders. Please note in this context the current discussion on the patentability of plants going on at the European Patent Office.

In general the following challenges were identified:
a.) Challenges exist for SMEs to navigate the maze of the current patent landscape for NGTs, specifically with a view to the contested patents for genome editing tools and approaches, to obtain appropriate licenses for their development.
b.) Challenges exist to grant patents on developments resulting in living organisms.
c.) Challenges exist to maintain plant breeder´s rights according to the convention by the International Union for the Protection of New Varieties of Plants (UPOV) for patented developments.

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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

As mentioned several times in this survey, it is crucial to develop detection methods for NGT products to ensure enforcement of the GMO regulations. In addition, it is important to facilitate and fund research concerning the safety of products made by NGT. Such work has to be done in a collaborative way between all MS and the EC. It is of utmost importance that for the development of detection methods the EU should coordinate, facilitate and fund these studies.

In the medicinal sector the dialogue is already taking place, but just to emphasize the need for intensive dialogue on interface issues with the medicines field and the need for harmonization of requirements in order to facilitate medicines development in Europe.
Certain concerns about the new techniques are already covered in the regulatory framework for medical products and caution should be exercised not to duplicate requirements. In addition, international harmonization should be taken into account

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Contact

SANTE-NGT-STUDY@ec.europa.eu