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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?

Belgium

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

1) In June 2016, a research institution asked to the CA for a regulatory advice regarding a field trial with a maize obtained by using CRISPR/Cas. In first instance, it was considered as non GM and not subject to authorization by the Competent Authority. After the ruling of the ECJ in July 2018, the CA asked the research institution to comply with Directive 2001/18 part B, for details see notification number B/BE/18/V2.
2) On 6 July 2016 the Biosafety and Biotechnology Unit (SBB) received a request to advise the Flemish Competent Authority ("Vlaamse overheid, Departement Leefmilieu, Natuur & Energie, Afdeling Milieuvergunningen") about the regulatory status within the meaning of the GMO legislation of certain plants and animals genetically modified using the transient presence of the CRISPR/Cas9 system delivered as purified ribonucleoprotein with or without a homologous repair DNA template. This request was made following a question from a Belgian research institute whether or not the Decree of the Flemish Government of 6 February 2004 (VL, 2004) transposing Directive 2009/41/EC (EC, 2009) should apply to activities under containment involving these CRISPR/Cas9-modified organisms. The SBB concluded that the intended uses under containment of animals and plants genetically modified as described in the request should be considered for exclusion from the scope of the Decree of the Flemish Government of 6 February 2004, according to Annex 15 B of this Decree (Annex II Part A of Directive 2009/41/EC).
3) In December 2017, a research institution asked for a regulatory advice regarding a microorganism obtained by cisgenesis. The question was if the legislation on deliberate release of genetically modified organisms apply to this type of cisgenic strains. The CA considered that cisgenic strains are under the scope of the GMO legislation. The EU Commission and the Regulatory Committee 2001/18/EC were informed on 25 January 2018 of that request.
4) On 25 May 2018 the Service Biosafety and Biotechnology (SBB) received from the Federal Agency for Medicines and Health Products (FAMHP) the information about a request for a clinical trial with CRISPR/Cas9 modified eukaryotic somatic cells. In the meantime (22/06/2018) the applicant was requesting the GMO status of these cells via the STA platform2, namely the regulatory status within the meaning of the GMO legislation of eukaryotic somatic cells genetically modified using the transient presence of the CRISPR/Cas9 system delivered as purified ribonucleoprotein without a homologous repair DNA template. In his advice of 06 July 2018, the SBB considered that the intended uses under containment of cells genetically modified as described in the present request should be considered for exclusion from the scope of the regional Decrees (VL, 2004; Wa, 2002; RB, 2001) on the contained use of GMOs and/or pathogenic organisms (Annex II Part A of Directive 2009/41/EC).
5) In 2019, a notification for a field trial with a maize obtained by CRISPR/Cas9 was introduced in January and authorized in April. For details see notification B/BE/19/V1.

*

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

For NGT products considered as under the scope of the GMO legislation, the legislation is applied without any specific distinction or measures.

In the absence of an analytical detection method available in Europe, it is not possible for the control agency, as part of the official control, to verify the compliance of products obtained through targeted mutagenesis techniques who would not have obtained authorization under Regulation 1829/2003 either as inspection through a document check or through analyses.

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

- ◉ Yes
- ○ No

* Please describe

In the absence of an analytical detection method available in Europe, it is not possible for the control agency, as part of the official control, to verify the compliance of products obtained through targeted mutagenesis techniques who would not have obtained authorization under Regulation 1829/2003 either as inspection through a document check or through analyses

* How could these challenges or limitations be overcome?

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* **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

Documentary monitoring of traceability, i.e. the ability to track GMOs and GMO-based products at all stages of the production and production chain or distribution, in the absence of an analytical tool, can only be based on the confidence that companies only bring authorized products to the market.
This is a big problem for the organic production, as in organic production it is not allowed to have products with GMOs, but it is also not authorized to have products produced by or with GMOs. In the organic regulation a declaration could be an asset, but as there are no traceability properties, it might be worthless.
The control of the truthfulness of the statements obtained as part of a documentary check, about the GMO or non-GMO nature of a product within the meaning of the legislation, is based on the fact that there are analytical detection methods validated in the EU and reference material available.

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

- (•) Yes
- ( ) No

* Please describe

See question 3

* How could these challenges or limitations be overcome?

There's need for developing detection methods for NGT's.

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

- (•) Yes
- ( ) No

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

We here refer to the opinion of the Belgian NRL-GMO already submitted to the EU Commission on 19 December 2018 :
As the type of products being the results of the use of Site Directed Nuclease mutagenesis type 1 (SDN), from the genetic/molecular point of view are very divers, we will describe only the most simple case and its impact on the activities of the official testing and the work of the National Reference Laboratories (i.e. the GMO analysis in the context of enforcement). This means that we will focus on addressing the question to products that are obtained by an SDN technology and resulting in one mutation in a gene in one locus of the genome. In this case we consider a small indel (basepair change, small insertion or small deletion), being the result of NHEJ repair.
Further in the text we describe other types of changes in the genome being as well the result of NHEJ, but are from the analytical point of view at least more complex, such as mutation in all genes of a gene family at different loci in the genome. In such case also more fundamental questions need to be addressed : e.g. what is the «event» in this case. Are multiple mutations in different loci to be dealt with in a similar way as stacked events, as we know them today in the context of the "conventional GMO's"?

Difficulties (including the impact on resources for analytical methods of detection during official controls) :
Detection of GMO is currently based on the amplification of GMO specific DNA fragments. These fragments can be either fragments for screening such as fragments of promotors, terminators that are often used for the development of GMO or DNA fragments that comprise the junction of the inserted fragment and the locus where the insertion took place (event-specific detection). Typically fragments of a length between 100 to 200 bp are amplified in the PCR. PCR methods can be either qualitative or quantitative. An integrated approach of different steps in the analysis is used, which is in line with the legislation (starting with a screening, followed by identification and quantification). The quantitative result has an output in % GMO per species.
The official control laboratories are accredited, according to ISO17025, for the overall procedure and the individual analysis.
For the detection of mutants the currently three step approach will not be possible to be used for several reasons:

• We will need dedicated methods for each individual mutant, because there are no general screening elements in this case.
• Secondly the currently applied PCR methods will not be suitable, as one needs to identify only a one base pair difference.
• Thirdly in the current approach we make use of endogenous gene to determine the quantity. It needs to be evaluated whether this approach will work for the mutants. Of course alternatives could be thought on, but need to be developed. One could potentially find inspiration how this mutant detection is done in the clinical context. However, one needs to realize that the analysis is less complex as the sample is only coming from one individual. In the case of plants or food/feed samples the situation will be much more complicated. Products will at least contain more than one individual of a particular species, but most likely even more species. This means that specificity of the locus to be analyzed needs to be studied in detail in a broad range of species that are likely to be present in the product to be analyzed.
• Finally, if a method allows to detect a mutant, it cannot be excluded that exactly the same mutant already exists in nature or is obtained by applying mutagenesis tools of which the products are excluded from the application of the legislation. Of course, if other type of information (traceability) is available the legal value could be stronger in this case.
The current approach to monitor the presence of non-authorized GMO is not applicable for the detection of non-authorized SDN mutants, such as CRISPR-Cas9 mutant, as they will not contain common elements that can be tested for in a screening approach. This means that a direct detection method needs to be developed, which is impossible if no information is available on what to look for.

* What best practices can you share?

nothing to mention

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

- (●) Yes
- ( ) No

* Please describe

Enforcement in function of the detection of unauthorized SDN mutants will be highly problematic or even impossible. First, because products that are developed and commercialized outside Europe are developed and commercialized in a different legal context. As a consequence, in most cases molecular information on the mutation (genetic changes) will not be available. Secondly, because this SDN technology (e.g. CRISPR-Cas9) is rather easy to apply and as a consequence one can expect a fast growing number of plant varieties developed by applying it. Moreover the application of the technology will not be restricted to the major commodity crops, but is applicable in all plant species. For enforcement, this means that more plant species need to be monitored.
There is also a scientific and technical issue, which makes detection of unknown mutants impossible even in the simplest case where the target of the monitoring is a pure variety. To demonstrate the dimension of the complexity, we consider a variety in which all plants have the same genotype (e.g. hybrid maize).
A maize genome consist of approximately 2,3 Giga base pairs. The question will be : Where and how to look for a one base pair change? But if one wants to demonstrate a change, being the result of a mutagenesis approach (in this case SDN) one need to be able to compare the “suspect” locus and the mutation in that locus, to a reference sequence. What will be the reference sequence , knowing that genomes in plants and all organisms are dynamic? Genome changes occur naturally, as they are the basis of variation, essential in the process of survival of the fittest. In other words a universal comparator for a species does not exist.
As stated above an analysis of a pure hybrid or a vegetative propagated crop would be the most simple case. Of course in real live most products, and especially commodities, will consist of a mixture of varieties.

This means that one can expect a lot of polymorphisms between these varieties and as consequence “dilution” of the signal coming from the mutant, resulted from applying the SDN technology. Testing for the presence of this kind of mutants in real life food and feed end products will be completely impossible because of the background noise signal.

In summary detection of unknown mutants is not possible today for several reasons:
1. A universal comparator genome does not exist. This means that, if differences between genomes (maize 2,3 Giga base pairs) are found, it is impossible to identify a candidate that could be the result of SDN.
2. In theory, it would be possible to demonstrate the presence of a mutation in a genome that is not existing in a wide range of varieties. This could be an indication that this mutant is obtained by SDN mutagenesis. However, not a proof, because the owner, responsible for the development of the product can always claim, that this genotype has been found in nature or is obtained by classical mutagenesis. One can argue that this indication can be sufficient to start a court case, but this would result in a long procedure, which is far away from the time that is currently given to the laboratories (2 weeks) to report result allowing the enforcement body to take legal and undisputable actions.
3. In contrast with the detection of transgenic plants, the detection of a mutant does not give any information on the process that has been used to obtain this mutant. In transgenic plants the junction fragment is not only identifying the genotype, but provides also a direct proof that the process of transgenesis that has been used to obtain this genotype. (statistically the occurrence of the inserted fragment, joint to that specific plant sequence is not existing in nature). It can only be explained by the fact that it is obtained via gene transfer (Agrobacterium mediated or direct gene transfer)
To conclude, the EU member states are not in a position to enforce the implementation of the legislation as it is interpreted by the ECJ.

* How could these challenges or limitations be overcome?

A lot of research is going on to improve detection methods such as droplet digital PCR, which might be more suitable for detection of known mutants. This could be a potential solution in the case a mutant is authorized within Europe and information on the mutant is available.

Comment on data collection and data management :
New analytical tools are currently available and/or are under development. They open new prospective. However, it will always be necessary to make a scientific evaluation, whether they will able to generate data that are useful to answer the specific question, addressed (in this case do they allow to detect a mutant obtained via SDN). High Resolution Mass Spectrometry and Next Generation Sequencing (NGS) are examples of these new tools.
It should be realized that these methods generate a huge number of data that need to be interpreted. Currently, also in this domain a lot of progress is being done. This makes possible to evolve from a targeted analytical approach towards looking for correlations within and between datasets and in this way to identify potential problems in the food chain. There is a huge potential for exploring these possibilities and they may be integrated in concepts such as data sharing and block chain.
This new methods may lead to new strategies in food safety control. This will need investment in equipment and expertise. Case by case, we will have to evaluate the possibilities whether this new technologies will also effectively may lead to solving the problems. In the case of detection of mutants obtained via SDN, these tools will not allow to prove whether a mutant is the result of the use of SDN or not. This fact is not due to the limitations of the technology as such, but are explained by the nature of the origin of this difference. Mutations as such do not differ on the basis of the way they are obtained. However, finding the mutant as such may be of importance to trigger further investigation.
NGS analysis will need to be combined with bioinformatics analysis, data searching, database comparisons. In order to implement these new methods and strategies in the context of enforcement, substantial

investments in infrastructure and expertise will need to be made.

Good strategic choices that are balanced and are in the benefit of society and support food and feed safety will have to be made and are of utmost importance.

* **5. What other experience can you share on the application of the GMO legislation, including experimental releases (such as field trials and clinical trials), concerning NGT-products in the:**
  - [x] **Agri-food sector?**
  - [x] **Industrial sector?**
  - [ ] **Medicinal sector?**

Agri-food sector

Only three field trials with such GM plants have been (positively) assessed so far: a first one (in 2011) involving cisgenic potato lines (reduced susceptibility to late blight); two others (in 2018 and 2019) involving maize lines genetically modified using the CRISPR/Cas9 technique (impaired DNA-repair mechanism and modified growth characteristics).
In both cases the GMO legislation was applied. From the risk assessment viewpoint, these NGT-products were evaluated in the same way as any other GMO.

In 2016, a first request for a field trial involving maize genetically modified using the CRISPR/Cas9 technique was submitted to the Belgian authorities (thus before the ECJ ruling on genome editing).
At that time, the authorities considered that these NGT-products fell outside the scope of the GMO legislation, based on the following scientific grounds:
- the genetic modifications achieved in the plants are similar in type and extent to those that can be obtained via natural or induced (using chemical or physical agents) mutagenesis.
- these NGT-products do not raise additional safety concerns as compared to products developed through conventional mutagenesis techniques.
It was considered that these scientific considerations could apply to all cases where the CRISPR/Cas9 system is used according to the so-called SDN-1 approach, i.e. to generate site-specific mutations (small nucleotide deletions and/or insertions - indels – at one target site, or deletions, duplications or inversions of DNA sequences between two target sites) without the simultaneous delivery of exogenous DNA (DNA template or full gene).
After the publication of the ECJ ruling in 2018, the field trial was re-notified under the GMO legislation.

There are monitoring issues in case of field trials with organisms obtained by new mutagenesis techniques :
• Method must be available for the detection of GMO targeting single nucleotide modification (ex qPCR or digital PCR or target PCR amplification followed by sequencing. In case of field trial it might be possible to monitor the presence of this particular mutant as the applicant knows the mutation and for instance qPCR method could be developed.
• A priori knowledge of the frequency of the mutation in the nature is needed, especially in the tested non-GM cultivars. If this information is unknow, a pre-monotoring must be done in the tested non-GM cultivars to determine this natural frequency of mutation.
• Monitoring during the field trial to determine the frequency of mutation: Preliminary statistical study needs to be done to determine the number of samples to take during the field study in order to be able to test for significant deviation of the frequency of the mutation (due to GM) in comparison with the frequency of the natural mutation via statistical analysis.

Industrial sector

For contained use applications, the traceability of NGT's products could be based on the register of contained use activities. This register has to be updated annually by the authorization holders in order to evaluate if changes/new knowledge could induce a need for reviewing their containment measures.
The contained use legislation applied to NGT's is in line with the precautionary principle.

* **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 inscription of varieties to the national list, the catalogue, is not the solution for a kind of "notification" of the varieties obtained by new breeding techniques.
There is no legal obligation for the applicant to declare the GM character of a variety listed in the catalogue. The only obligation comes from the GMO legislation. However, it's common practice to always ask the applicant whether the variety had been obtained by gmo-techniques and to add the required authorizations. As organisms obtained by new mutagenesis techniques are considered as GMOs, and are not exempted, there's no need and no legal obligation to change something at the current situation.
If the variety is GM, it's mentioned. It's also good to note that the catalogue legislation concerns only a list (large but finite) of agricultural or vegetable species. A large number of cultivated species escape this legislation, including ornamental species.

They are considered as GM in application of the court ruling and no GM varieties have been registered in Belgium. As far as the past is involved, it seems that it would be a good solution that the Commission addresses the question 6 to the seed companies, a demand to declare any variety obtained by a new technique. It's not efficient to oblige each MS to make the same approach with the same companies (Monsanto, Limagrain, Syngenta and others...). The Commission could also reiterate to these companies the requirement of prior authorisation of any new variety obtained by new mutagenesis techniques.

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

A project starting at fall 2020 is funded by the federal public services public health, food chain safety and environment :
RF 20/6342 GenEdit - Development and evaluation of approaches for detection of organisms modified by new genome editing techniques
Budget : 300.000 euros Duration : 3 years
Research questions:
The proposed research wants to address several scientific questions.
The first one is that we need a state of the art of the situation. We need to know which are the genome-edited organisms with the new breeding techniques (NBT) commercially available or close to the commercialization and what are the main modifications performed. We know that these technologies are already used to modify animals and plants but an overview of the situation is not available. This will help to decide where to set the priorities.
The second question concerns the possibilities of detection of NBT. A difference must be made between what could be authorized (inexistent now) and what is unauthorized. If we know the exact localization of the changes within the genome, some technologies could help. All the potential solutions presently discussed by panel groups are merely theoretical. It is also necessary to distinguish between the different types of mutants that are obtained. Finally, we need to know if these technologies are able to detect the modifications in typical food and feed products received for analysis (processed samples and/or complex matrixes). The question of the genetic diversity of an organism must also be addressed, as it could hinder the development of untargeted approaches.
The third question concerns the differentiation through the production of metabolites. We need to know if the analytical strategies based on metabolomics and peptidomics are able to detect modifications that will permit to distinguish modified organisms from non-modified ones.

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

nothing to mention

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

The publication of Jaganathan et al. (2018) shows an exponential augmentation of the number of publications using the CRISPR technology for crop Improvement. This show the interest of the scientific community and private companies for Genome Editing.

Three types of NGT-related research can be identified:
(1) Research on the further development and optimization of NGT technologies, including research on molecular characterization of organisms developed through NGTs.
(2) Research making use of NGT technologies as a tool to help answer relevant research questions.
(3) Research & Development activities that have the goal to develop products and services based upon NGT technologies.

The first type of research should expand in the coming years until the moment a plateau is reached where it will probably be difficult to achieve further progress. Currently a lot of work is done on the improvement of the specificity of editing technology, the improvement of homology-directed repair approaches, or the improvement of DNA-free methods. The latter has sparked renewed interest in setting up well-functioning

platforms for the regeneration of plants from protoplasts.

The second type of research should continue indefinitely. One can expect that the use of NGTs will become even more commonplace than it is already today. NGTs are and will remain an important tool to help answer important biological questions. The type of research that bridges basic research and the development of NGT-based products is however likely to be negatively affected by the fact that regulating NGT products as GMOs will complicate their market introduction and practical applications.

For R&D activities aiming at developing products and services based on NGTs, a distinction needs to be made between different fields of application:
- In the biomedical field NGTs will become more and more commonplace, and live NGT engineered organisms should be more and more developed. For instance, immune therapies, cell therapies, vaccines and biologicals produced by means of an NGT organism.
- In the industrial field of biotechnologies where large scale fermentation is used to produce different types of products with a broad range of applications, NGTs will most probably be used (normally in contained format) in addition to the use of other genome engineering techniques. In certain applications residual fermenter sludge is used as feed. If NGT engineered organisms are regulated as GMOs, this sludge will not be marketable in Europe because it would have to go through the GM food & feed legislation.
- In the agricultural field there is a risk that R&D to develop NGT engineered crops and foods in Belgium could slow down, as observed in recent years with R&D to develop transgenic plants.

Several seed producers announce that they will invest in this technology. If their seeds cannot be sown in Europe, they will be used in other countries allowing the use of this genome edited as crops. Some laboratories see in GE crops a way to adapt plants to global warming (e.g wine, ISVV, Bordeaux, France). Numerous GE animals are also developed for different purposes : human consumption, companion animals, production of industrial compounds, medical and pharmaceutical, disease control or research.

Concerning detection methods, the EURL-GMFF has created an ENGL Working sub-group for the detection of GE organisms. At this stage, most of the considerations are theoretical.

*** 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

In the document provided on 19 December 2018, you can read :

There is enormous progress in the domain of DNA sequencing e.g. Next Generation Sequencing and linked to this the bioinformatics tools to interpret the obtained data. By doing this there is in the long run, a shift possible from dedicated searching for a particular target towards collecting large datasets and looking for correlations between parameters within these datasets. But this will not bring solutions for the enforcement laboratories at this moment. The major bottlenecks will always be: 1/ What will be the reference to compare with and 2/ finding a mutant is not a proof that SDN approach has been the process used to obtain this mutant.

In addition to this previous communication, the following NGT-related research needs are identified (non-exhaustive list):
- To improve the efficiency of homology-directed repair approaches in plant gene editing;

- To improve the efficiency of DNA-free methods of gene editing;
- To improve the specificity of methods of gene editing in human and animal cells;
- To improve the public knowledge and better understand attitudes towards NGTs.

Based on the dossiers that were evaluated up to now by the Belgian Biosafety Council, a need for specific research in support of the risk evaluation procedure of NGT-events were not identified.
Concerning the targeted approach for known GE organisms, it will be important to define the minimum performance criteria for the considered technologies as the modification of a single nucleotide could affect the specificity and the sensitivity of a PCR-based test.

Besides the scope of developing detection methods in function of enforcement, huge investments are made within public as well as private to develop tools to characterize mutants obtained via NGT. Of course the context is more controlled, as in this case one deals with a species or even one genotype with which comparison is needed. And of course a lot of research is going to use this technology in order to obtain the genotype (mutant) resulting in the desired phenotype with no off target effects.

* **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

Where NGTs are used as a basic research tool that helps answering important biological questions, the answers to these questions may result in new types of prophylactics, vaccines, therapeutics or for the development of novel crops and crop species in the interest of agriculture, food industry and society (e.g. maize with higher yields, crops with reduced allergen content, drought-tolerant plants, disease resistant plants…).

The application of NGTs, together with other technologies, speeds up our knowledge development and that will again lead to faster development of new beneficial products.

The fact that this technology is easy to apply will make it accessible and usable to many more players including SME's, which will result in increased innovation capacities and investment initiatives in response to local needs (e.g. improvement of Belgian local varieties such as Conference pear, ornamentals…).

GE techniques are of interest for the agro-food sector. Some examples are plants and animals more resistant to disease, allergy free-foods, better conservation of food products, higher production of fatty acids in plants (for food or fuels), pest control, resistance to global warming,…

For the medical field, GE are also useful in the development of therapies.
Advantages of each modification must be evaluated as a case-by-case study.

* **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

NGT-related research can bring a number of societal challenges, for instance on how to make sure that the public has a correct perception on how food crops are being developed and which role technology plays in the development of that food. It is a challenge that society stays connected with technology development in agriculture and food sectors.
To a lesser extent these considerations may also apply to industrial and medicinal sector if public opinion is not properly informed.

The organic sector fears that when it comes to the funding of breeding-related research activities, NGT-related applications could be funded in an overproportionate manner. This leading to the marginalization of non-NGT related breeding concepts that also have the potential to deliver a wide range of benefits for agriculture and society.
For them, research into unintended modifications at the target site (on-target modifications) and in proximity to the target site (off-target modifications) is needed to get a better understanding of the potential side-effects of applying the technology. With an improved understanding of the technology, the plant genome and metabolic pathways, the technology could potentially be used for the benefit of society.
Also, research on detection methods/strategies for NGTs will be crucial to enable traceability for the benefit of the agri-food chain and consumer choice.

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

Not considered as a national dialogue but a symposium on Genome editing for crop improvement was jointly organized by ALLEA and the Royal Flemish Academy of Belgium for Science and the Arts (KVAB) on 7/8 November in Brussels.

Also not considered as a national dialogue but the Belgian NRL-GMO is involved in the ENGL Working group with regular discussions concerning the possibilities of detection of GE organisms.
At national level, the members of the NRL-GMO (Sciensano, ILVO and CRA-W) have submitted a proposal of project (GenEdit project, proposal RF 20/6342) to evaluate the possibilities of detection of GE organisms.

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

- ( ) Yes
- (●) No

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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

The Belgian Advisory Committee on Bioethics works exclusively on humans and will not consider questions about plants or animals.

He decided at the plenary meeting of 18 november 2019 to work on ethical aspects of somatic and germinal genome editing (CRISPR, etc) in Humans. The work is not yet started.

A related opinion was pubished in 2005 about gene therapy, eugenics, somatic and germinal gene modifications. The opinion is available on https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/opinion_33_web.pdf

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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

Products that have been altered or modified using NGTs can bring clear opportunities/benefits to the agri-food, medicinal or industrial sector.
Some examples:
- NGT engineered micro-organisms that have improved fermentation capacities, making fermentation more efficient, leading to less waste, and lower GHG emissions per unit of production.
- NGT engineered micro-organisms that have improved quality characteristics such as improved freeze tolerance, leading to higher quality bakery products.

- NGT engineered autologous cells for treatment of malignancies.
- NGT engineered trees that are much easier to convert to specialty chemicals for the biobased industries, have improved pulp qualities (for the paper industries), can be much more efficiently converted into biofuels.
- NGT engineered crops with improved biotic and abiotic stress tolerance, with improved quality features, improved agronomic characteristics such as higher yields, higher harvest certainty.

Plant breeding is a continuously running process that aims to improve the quality of agricultural products, to adapt crops in function of the needs of consumer and society in general and to improve efficiency and sustainability of crop production. This last point includes improve environmentally friendly production with as less as possible negative impact on climate change. Crops with higher disease resistance that are adapted to higher temperatures and drought could be examples.

With the NGT, society has now tools and capacity available that allow to improve the efficiency and precision of this breeding process resulting for farmers and food producers to have access to the genotypes and products of interest in a faster way. The efficiency gain that is feasible today is not only the result of having access to tools that allow to modify genetic information in a precise way but it is also the result of huge knowledge gain of the function of genes and their relation with the expressed phenotype.

We suggests that the EU Commission consults relevant stakeholders (e.g. food/feed industry, seed companies and pharmaceutical associations) to collect concrete examples.

* **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

See questions 11 and 16

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

See questions 11 and 16

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

- (●) Yes
- ( ) No

* Please explain under which conditions

Id as for 16, especially because the use of this technology will not be limited to big compagnies.

The fact that this technology is easy to apply will make it accessible and usable to many more players including SME's, which will result in increased innovation capacities and investment initiatives in response to local needs (e.g. improvement of Belgian local varieties such as Conference pear, ornamentals…).

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Access to information's on patented NGTs is crucial in order to adapt inspection systems and prevent, when possible, the presence of unauthorized NGT's on the EU market.

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

The challenge for EU will be to find a good balance in applying the precautionary principle (as it is in the legislation and interpreted today) and on the other hand stimulate innovations in function of tackling problems in society and allow economic development. EU policy should also take care that legal security is guaranteed for all stakeholders active in the whole agri-food sector and should pay attention that farmers, companies and entrepreneurs in general in the EU can compete with equal means, in comparison with the non-EU farmers, companies and entrepreneurs
We suggest that the Commission consult relevant stakeholders (e.g. food/feed industry and pharmaceutical associations) to collect concrete examples.

The organic sector in particular has concerns about the enforcement of traceability requirements :

- The benefits of a solid traceability system for NGTs are economically significant as traceability gives actors in the food chain legal certainty regarding the contents of their (intermediate) product. Especially for the production of organic products it is necessary that all the products that are coming from for instance GMO seed, are known as products produced by/with GMOs, so the harvest has to be notified as a GMO product, and traced back, and the products produced with this harvest need to be labelled as 'by / with GMOs.
- Organic products, for example, lose the organic certificate (& premium) if they contain GMOs (EC 834 /2007) or if they are produced by or with GMOs. This means in practice that they could no longer be sold on the EU market as organic food, which implies a major economic loss. Organic producers need to be sure that for instance the maize they buy is not produced with GMO maize seed. Or the operator has to be sure that the 'maizepowder' he uses in his preparation is not coming from maize produced from GMO maize seed.
- Practical problems regarding traceability could be overcome by requesting (detection) protocols from producers of the genome-edited products that are currently on the market, including a rapeseed grown in the USA and Canada and a soybean grown in the USA. These products are detectable if "prior knowledge on the altered genome sequence, a validated detection method … and certified reference materials are available ", according to the ENGL report of 26 March 2019.

*

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

The use of NGTs and NGT-products will not raise specific challenges that are not already addressed by the current environmental and other types of legislation.
Challenges/concerns are not associated with technology per se. As with the use of any product generated by novel technology, the use of particular organisms in which genetic properties have been altered can raise challenges/concerns for the environment, human, animal and plant health, as well as social and economic challenges.

The organic sector has concerns about integration errors during the application of NGTs. This can lead to unwanted residues of DNA in the final product, which are a potential risk to health & the environment. In the known case of a genome-edited cattle in the US, unwanted fragments of DNA ended up in the final organism, including an antibiotic resistance gene.
They also stressed that without adequate traceability measures at EU and national level, NGT products could contaminate non-GMO products which could have an economic impact for the farming & food processing sectors. They are also concerned about ethics and animal welfare if applied in the context of genetically modified farm animals.

* 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

The very extensive and expensive EU approval procedure for GMOs (incl those developed with NGTs) makes it very difficult/impossible for SMEs to develop those GMOs.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

The organic sector is on the opinion that the patenting and licensing landscape for NGT applications is limiting the access to the technology for SMEs and small players that have restricted means to negotiate the terms for the application of e.g. Crispr/Cas technology.
Concentration in the seed market among a few players makes it very difficult for SMEs to establish themselves as an independent player in the market and leads to high rates of external takeovers. NGT products that are similar to products of conventional breeding might raise issues regarding the farmer's

rights to save and reproduce seeds and to breed animals, given the patentability of the products of new genomic techniques. The farmer's privilege is internalized in Art 14(1) Council regulation (EC) 2100/94: 'for the purposes of safeguarding agricultural production, farmers are authorized to use for propagating purposes in the field, on their own holding the product of the harvest which they have obtained by planting, on their own holding, propagating material of a variety other than a hybrid or synthetic variety, which is covered by a Community plant variety right'.

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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

A lot of information's in our answers to the questionnaire were already provided by Belgium in December 2018.

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Contact

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