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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?

Finland

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

The Board for Gene Technology (GTLK), which is the CA of Directives 2001/18/EC (deliberate release = DR) and 2009/41/EC (contained use = CU) has received several requests on the legal status of RTDS and CRISPR-Cas9 techniques both for DR (field trials) and CU. See details in Annex 1.

The Laboratory for the Finnish Food Authority, which is the CA for Regulation EC N:o 1829/2003 (F/F), reports that university researchers are very interested in the legal status of NGTs, how it will affect their research programs and plans, in-vitro and in-vivo greenhouse/field trials and experiments – including plants, animals and microbes.

The supervising authority for CU reports that users ask about the GMO status of organisms which have been modified/edited using CRISPR/Cas9 techniques.

The supervising authorities for DR do not report any such inquiries.

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

- (●) Yes
- ( ) No

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

The Board for Gene Technology (GTLK), which is the CA of Directives 2001/18/EC (deliberate release = DR) and 2009/41/EC (contained use = CU) has made several interim decisions on the legal status of NGTs both for field trials and CU considering notifications to conduct research on plants and animals. Variations of the techniques have been thoroughly considered to decide if these techniques produce GMOs according to the criteria of the Gene Technology Act and Gene Technology Decree. The decisions made by GTLK were not unanimous. Please see Annex 1 for details.

The CA of Food/Feed and the Laboratory of the Finnish Food Authority have gathered information from various sources on the possible methods (both related to documentation and analytics) which could be used in gene editing (GE) detection, and how to implement such measures or methods (if existing) into their laboratory practices. Unfortunately, these measures have not been effective and there is no collective view on how to follow / detect and analyze GE organisms. The CA for F/F & Laboratory representatives state, that unless the new GE organisms essentially differ compositionally from conventionally bred or traditional GM varieties, they do not have any means of detecting them.

In addition to inspection, CA for F/F are constantly informing and discussing with stakeholders about the

nature and legislation of GMOs. According to CAs experience, it has been very difficult to make stakeholders understand even the nature of “traditional” authorized GMs, as the only way to differentiate them from conventional non-GM varieties in food chain is by laboratory tests. This is even more challenging in regards of GE organisms due to lack of proper laboratory methods. After the ECJ ruling, CAs have discussed in-house on how to explain the situation to various stakeholders but have not taken action yet.

On the other hand, the Competent Authority for seed registers reports that so far there have been no applications for NGT plant varieties, nor are there any NGT varieties registered in Finland. There is no need for specific measures, since NGT varieties would be treated the same way as other GMOs.

Also the Finnish Medicines Agency reports that thus far no medicinal product applications involving NGT have been received. Any such application would be treated the same way as for any other GMO.

* What best practices can you share?

The CA for F/F & Laboratory states that to their knowledge no “best practices” exist for analytics.

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

- (●) Yes
- ( ) No

* Please describe

The CA for F/F has not so far detected any NGT-feeds, foods or microbes on the market. However, the lack of detection does not imply absence of such organisms on the market, it merely reflects the absence of suitable detection methods and documentation available for the CA. As documentation for NGTs is required, it is established based on existing GMO documentation guidelines.

Considering the current resources of the CA for the DR and CU, there has been a considerable administrative burden in dealing with the requests on the legal status of certain NGT modified organisms. Also, GTLK addressed the issue of safe history of use in its letter to the Commission on 13.11.2018 (see Annex 2).

It has also been very challenging to justify the present GMO legislation principles to users, especially in situations where genetically identical organisms or organisms with exactly similar traits are regulated differently depending on the method with which they were produced. Users of some NGTs have criticized the legislation also in situations, where they regard the use of NGT inherently safer than traditional genomic modification or breeding techniques. If NGTs are regulated similarly to traditional GMOs also in contained use (Commission Legal Services yet to confirm), this leads to a situation where genetically similar organisms have to be managed differently (e.g. regarding premises, infrastructure, transportation, labelling, inactivation, waste management, waste transportation, recycling etc.). This has of course been the situation earlier with traditional GMOs and traditional mutagenesis techniques, but the situation becomes more prominent while NGTs will be used in many applications. Combined with the GMO administrative requirements, this appears as a burden especially for small research groups and startup companies with limited financial resources and infrastructure.

From the regulatory authority point of view, it is also clear that the implementation of GMO legislation cannot be effective when it comes to analytical controlling of NGTs where the identification methodology is lacking or unsatisfactory. When suspecting a violation of the notification procedures, failure of contained use risk management procedures, or unintentional release of an NGT organism, the GMO authorities have very

limited tools to confirm the origin of the organism in some cases. This of course holds true to many organisms produced by traditional gene technology, if there is no prior information what to detect. Knowledge of this situation may leave the field open to operators which disregard the GMO legislation.

Considering that NGTs may be a used in the indoor farming of plants, animals and fungi, the current difficulties in harmonizing the requirements under GMO directives, f/f regulation, waste regulations and sometimes also medicines regulation apply also to NGT plants, animals and fungi.

* How could these challenges or limitations be overcome?

Nationally the challenges can be overcome by considerable resource mobilisation into CU supervision, digitalisation of the gene technology register and by increasing the resources of the CA. DR control authorities need more resources for analyses as well as harmonized procedures for supervising products, for which the method of production is not known. The resources are probably adequate for supervising DR of authorized NGT organisms under DR Directive as no NGT products are expected to enter the EU market, except possibly under F/F Regulation.

The current EU regulatory framework should be examined to confirm that the requirements under GMO directives, f/f regulation, waste regulations and possibly also medicines regulation are clear for the stakeholders during different phases of research, development and production of organisms modified by NGTs.

Finnish CA F/F states that due to the methodological challenges in monitoring NGT organisms CA can only rely on the labelling and provided documentation of the products, especially on imported feeds and foods. The manufacturers using feed or food that could originate from NGT varieties trust the available documentation in the supply chain. Some food business operators (FBO) have contracts and some food operators require product specifications that also take into account the GMO issues.

* **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

The Finnish control authorities for F/F and DR are waiting the European Commission to advise on this, as they see that NGT-products are impossible to control without any official guidance or analytical methods. More information is also needed on what are the risks of these products and how these NGTs can be controlled effectively in our risk-based control systems.

In the feed/food sector, GM ingredients and products must be labelled at the very beginning of the food/feed chain, which is actively controlled. Equally NGT-ingredients and products need to be labelled.

In both the food and feed sector, the control focuses on ingredients described as “risk products”. These ingredients are controlled within general inspections when they are imported or used for manufacturing by the food business operators (FBO), or when voluntary “GMO-free” marketing claim is used. If NGT-products are considered as risk products, NGT-products will be controlled similarly to traditional GMOs.

In addition, due to the obvious and severe limitations in NGT detection methodology (listed in the following section of the questionnaire), the CA of F/F finds it extremely difficult to explain and justify the ECJ ruling to

national and global stakeholders who should maintain proper in-house control for their products and maintain the chain of proper documentation and labelling.

The Finnish Medicines Agency and Finnish Environment Institute report that if the national CA for CU and DR directives determines the NGT organism as a GMO, its use is controlled similarly to traditional GMOs. Same procedures apply to known NGT plant varieties, medicinal products, and NGT modified organisms in DR or CU.

Also the Ministry of Environment stressed the need for further development of both detection methods and robust guidance where traceability is document-based.

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

- (●) Yes
- ( ) No

* Please describe

The CA for F/F at the Finnish Food Agency reminds that from the consumers' point of view, traditional GM varieties do not in most cases vary from conventionally bred non-GM varieties in their composition and traits. Still, traditional GM varieties can be detected using existing harmonized analytical methods as they contain distinct genetic sequences that are missing from the parental genomes (i.e. non-GM varieties). However, unlike with traditional GMOs, the genetic differences between GE varieties and conventionally bred varieties may exist only at the level of single nucleotides. This is also the case even when the NGT organisms differ from conventional varieties in their composition and traits.

They also state that in theory, GE detection is possible if one knows what to look for (insertion, deletion, inversion etc.), where in the genome the editing has been targeted/done (target gene) and the material to be analyzed is "pure" and of good quality (i.e. single origin sample with enough DNA). However, detection of single nucleotide changes or even larger genomic events (let alone epigenetically modified traits which may not affect DNA structure) is extremely difficult even from homozygous fully sequenced single origin plant material. When analyzing complicated food or feed matrices, such analyses will be nearly impossible to perform with currently feasible laboratory practices, let alone at a reasonable cost. Moreover, even if efficient analysis methods would arise and could be accredited for registered NGT varieties, mutations created with NGTs cannot in practice be distinguished from natural mutations, conventionally bred mutations (chemical or radiation mutagenesis or cross breeding), or even from "copied" NGT events (e.g. unauthorized events). Thus, CA for F/F believe the control is not reliable as no samples can be checked conclusively.

Also the Finnish Medicines Agency states that they have no method for recognizing unregistered NGT material. However, for medicinal products the information of the modified sequence is always required regardless of the method used in development of the product.

The Finnish Customs reported that there is no problem in the documentary check as it is similar to traditional GMs and the protocol is clear. The problem is that there are no analytical methods to verify the validity of documents. Inspection practices should be guided by the European Commission.

* How could these challenges or limitations be overcome?

The Finnish CA for F/F states that reliable methodology for the detection of products modified with novel mutagenesis methods is absolutely required to ensure legal certainty. This is especially crucial for organisms with point and deletion mutations, which may be challenging to tell apart from any natural counterparts. Also,

a constantly updated listing of products on the market outside the EU is essential to focus the supervision on relevant products. Estimates are needed about the amount of additional supervision resources needed annually to ensure sufficient supervision capacity within the EU. A certificate describing which breeding method was used in the development of a particular animal, plant or microbial strain could help supervision, but it would also constitute a substantial administrative burden in the various production chains.

The Finnish Medicines Agency, which supervises contained use of GMOs as well as deliberate release GMOs in health issues, stresses the importance of informing the operators and the identified potential users about their duty to apply the GMO legislation also in NGT use. Development of the field should be followed as part of the supervision, and the potential uses of NGT organisms in contained and deliberate use can be identified by risk evaluation and by following the literature and media. They find that identified potential NGT use can be supervised according to the normal procedures of the supervision of GMO use.

* **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

Finnish CA for F/F, seed unit and laboratory have experience on the traceability strategies. This issue is also in the priority list of the CA for F/F, and Finnish Medicines Agency confirms that similar traceability strategies would be used as for other GMOs. However, the Customs has no experience on traceability strategies suitable for the NGT products.

Finnish Medicines Agency reported that they intend to follow the legislation on the traceability of GMOs including labeling. NGT products would be considered similarly as other GMOs.

* What best practices can you share?

Finnish Food Authority/Laboratory considers that currently the only truly viable and executable options would be to screen for authorized NGT events that could be compared to certified reference materials – which have not been made available by any stakeholder in the EU. In theory targeted sequencing and/or digital PCR /qPCR could be used for detection – but as stated, methods do not exist yet, reference materials have not been made available to even develop such detection methods, and as a result, no harmonization has been done between analysis laboratories. Also, this approach would only apply to known and authorized NGT events. The status of detecting unauthorized or unknown events would still be totally open and unresolved for epigenetics and certain GE techniques, because unlike traditional GMOs they do not contain genetic sequences that can be screened for and unauthorized NGT varieties may not be listed in any databases. While traditional GMOs might not be authorized in the EU, information may be available via patent and/or global GM variety databases, this may not be possible for NGT varieties.

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

- (●) Yes
- ( ) No

* Please describe

Finnish Food Authority CA for seeds states that seed bought by farmers directly or by internet from another EU member state is very challenging to trace, similarly to traditional GMOs.

Finnish Food Authority Laboratory states that the NGT or GE or GMM analysis will be very costly, and the success rate of such analyses is questionable to say the least. No guidance documents or best practices exist.

The Customs reported none, as there is no experience on traceability strategies suitable for NGT products.

* How could these challenges or limitations be overcome?

As the scientific advisers of the Commission have pointed out, new scientific data and recent technical development have resulted in a situation where the GMO directive is no longer suitable for its purpose. Thus, it would seem reasonable to re-examine the EU gene technology directives, and particularly the GMO definitions therein.

* **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?**
- ☑ **Medicinal sector?**

Agri-food sector

The Natural Resources Institute Finland (LUKE) is carrying out genome editing (GE) in barley, with plans to expand into other crop species. As they need to treat the GE lines as GMOs, they report an increased administrative burden which slows the research because the administration falls on the researchers. Because of the burdensome paperwork for the GMO approval practice and small likelihood of being cultivated in Europe, LUKE finds it very difficult to get industrial support for even agronomically and nutritionally superior lines that they aim to produce. Luke is also carrying out GE in animal cell lines, currently only as a research tool with no applications to be released as animals or products. LUKE reports difficulties in animal sector in getting industrial support for developing applications for breeding, such as editing genes in embryos.

We do not have other experience, as there have been no field trials applications thus far concerning NGT products, as the plant breeding sector and seed retailers do not find NGTs relevant due to the present legislation in the EU. Nor is there any other experience from the animal breeding sector so far, but the sector foresees some very interesting advantages, for example to get hornless cattle or increase resistance against viruses.

Industrial sector

No experience as yet and no comments were received. The CA for DR and CU (the Board for Gene Technology; GTLK) has made an interim decision that in the absence of legal certainty, the ECJ ruling is not extended to CU before a binding legal analysis of it is received from the Commission Legal Service. Also, for the same reason GTLK decided on 5.2.2020 not to overrule its earlier decisions that deletion mutants obtained with new mutagenesis techniques are not in the scope of Gene Technology Act, if no foreign genetic material remains in the final organism. Because of this, no information has been actively collected on risk assessments and utilization of these techniques in CU, except for what is received from inquiries and

notifications from CU operators and during CU inspections. However, a governmental study project on NGT use in Finland is going to start in 2020. The public report of its results will be submitted to the Commission.

Medicinal sector

There is no experience, as so far there have been no clinical trial notifications either for DR or CU concerning NGT products.

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

- ○ Yes
- ◉ No

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

- ◉ Yes
- ○ No

* Please specify

Finnish Food Authority/Secretary of Plant Variety Board states that in the application forms there is a question, if the variety is a NGT variety. If it is, all the same information is required as for other GMOs.

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

The maximum file size is 1 MB

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B - Information on research 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

In general, the Academy of Finland, the key public funding agency for scientific research in Finland, has supported 58 NGT-related research projects with approximately 23 M€ within the last 5 years (2015-2019). Almost exclusively (98 %), the funding was for basic research projects. Two of the projects were funded via a Targeted Program (Molecular Regulatory Networks of Life), the objectives of which was to promote the adoption of the latest scientific methods including new genomic and epigenomic modification methods. All the receiving entities are public universities or research institutes.

At state-owned VTT Technical Research Centre of Finland, a Living Factories Strategic research project was running 2014-2016. The mission of the “Living Factories (LiF): Synthetic Biology for a sustainable Bioeconomy” project was to realize the potential of the breakthrough technology of synthetic biology (synbio) and enable its exploitation by Finnish industry, thus promoting sustainable bioeconomy in Finland. Approximate funding for the topic specified in the question was 700 000 €.

A project on adaptation of CRISPR/Cas9 technology on secondary metabolism engineering of plants was running in 2019 (25 000 €). A new research project on large-scale genome engineering of yeast will be running 2020-2023. The project studies the interplay of genome structure and metabolic network in adaptation. The interplay will be elucidated by combining eukaryotic synthetic biology, genome-scale metabolic modelling, adaptive laboratory evolution, evolutionary data analysis, and machine learning (800 000 €).

At the University of Turku, Department of Biochemistry, a project “Molecular Biology of Primary Producers” was running during 2014-2019. NGT-related research was pursued with a model plant Arabidopsis thaliana and several green algae and cyanobacteria strains. The project focused both on fundamental and applied research. Fundamental research focused on solving the regulatory mechanisms of plant, moss, algae and cyanobacteria photosynthesis, particularly the light harvesting and energy transduction mechanisms. Applied research focused on improving the photosynthetic efficiency in order to increase the productivity of crop yields as well as that of the algae and cyanobacteria, the latter ones particularly in the living cell factories. Living cell factories are based on synthetic biology approaches that are fully based on NGTs (5 M€).

A national FinnDisMice research consortium was established in 2020 to focus on modelling a set of Finnish disease heritage in mouse models. The goal of the project is to facilitate understanding of disease pathomechanisms that are causative for these rare diseases (1.2 M€). As a new initiative, a national mouse modelling platform FinGMice is dedicated to establishing a well-structured pipeline for mouse model phenotyping called “Mouse Clinic Finland”. The aim is to facilitate full utilization of new and existing animal models offering an easy access to phenotyping services for the Finnish research community. With this strategy, phenotyping services will be readily accessible to all researchers in Finland (752 280 €). University of Oulu represents Finland in INFRAFRONTIER, and Bio-center Oulu Transgenic Core Facility serves as the Finnish EMMA (European Mouse Mutant Archive) node. INFRAFRONTIER is the European Research Infrastructure for the generation, phenotyping, archiving and distribution of model mammalian genomes lines by EMMA. The Oulu archive holds 75 mouse strains submitted by researchers in national and international universities, and 153 strains from the IMPC project (558 470 €).

At the University of Oulu/Faculty of Biochemistry and Molecular Medicine two projects study the microenvironmental regulation of prostate cancer cell growth and migratory properties. NGTs are used in both of the projects to generate specific study models (genetically engineered cell lines) to address specific hypotheses. The PROFI3 project focuses on characterization of integrin adhesion complex interactomes and the regulation of the complexes in prostate epithelial cells under different microenvironmental conditions (normal epithelium on basement membranes and cancer epithelium on fibrotic/stromal ECM) (450 000 €). The JAES project studies crosstalk between two types of integrin-mediated adhesions, focal adhesions and hemi-desmosomes during prostate cancer progression. Here the aim is to study the dynamics of the two adhesion types in normal and in tumorigenic prostate epithelial cells and their contribution to growth and spreading of the primary tumor (300 000 €).

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

For the public funding agency Academy of Finland, there are no actual challenges, since it is the site of research that commits to overseeing that the funded project follows the legislation and the ethical regulations and recommendations. The research institutes and universities that replied are of the opinion that there are no immediate effects on the research projects and no immediate effect on commercialization or market, however when collaborating with the Finnish industry potential challenges are taken into consideration.

University of Turku /Department of Biochemistry pointed out that all fundamental research has so far been conducted in contained systems with no specific challenges. Efforts to mimic natural environmental conditions in contained systems have been carried out but results show that it cannot be done properly in growth chambers. Thus, the applied research critically needs to be expanded to natural environmental conditions to be able to judge the real benefits of the gene modifications for plant productivity.

University of Oulu/Faculty of Biochemistry and Molecular Medicine commented that since NGT tools exist already in most properly equipped molecular biology labs, the challenge is purely an ethical one as to which projects to support. NGTs are merely seen as a technology that is essential for modern research and which can be relatively easily adapted for any type of research. Therefore, inclusion of NGT in a project is not a critical determinant. What is critical is for what the technology is being used for.

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

The question was answered by universities and other research institutes operating in different fields. There was a unanimous view that the NGT-related research is going to be fast, cover numerous different disciplines and evolve globally.

In particular, an emerging need was seen in using gene editing in agriculture and breeding of plants. It was pointed out that the technology itself should not be the one that determines whether a product can be used for food, feed, fuel etc. NGTs were considered usually much safer than many old breeding technologies (e.g. high energy radiation technology to create new breeding material). Those NGTs that produce material (e.g. crops) that contains no foreign DNA material in the final product were thought to be the safest way to diversify and increase the productivity in all different aspects.

It was stressed that Finland should be able to guarantee pest- and pathogen-free crops and trees in the time of climate change and unexpected spread of pests and pathogens.

In the medical research field in vitro modelling, humanized research animals for production of human organs, and use of NGTs were expected to increase. Also, iPS (induced pluripotent stem) cells and organoids are going to be used more widely, and CRISPR-Cas9-based genome editing techniques are used for these.

The GM animal models were thought to be especially important and invaluable tools when assessing systemic regulatory mechanisms involving several organs and requiring a well-defined and thoroughly characterized genetic background. Furthermore, development of new treatment options requires research at the organism level in order to recognize possible adverse effects. Thus, the use of GM mice, especially as disease models, is expected to further increase in the future, as the CRISPR-Cas9 technology has facilitated more efficient and costly generation of GM animals, providing possibilities also for smaller research groups to use animal models. The large genome wide association studies (GWAS) have provided numerous novel gene associations for human diseases and by using CRISPR-Cas9 technique these single nucleotide variants can be efficiently studied in vivo decreasing the unwanted off-target effects often associated with total gene knockouts. Furthermore, CRISPR-Cas9 technology has provided an efficient way to focus studies on non-coding, regulatory regions of the genome. Studies on sophisticated animal models for complex diseases, such as cancer and diabetes, will therefore be further advanced, especially the multidisciplinary

expertise, which is required for the phenotyping analyses of mutant mice.

NGT technologies are expected to become more robust (more easy to use, more accurate), and a phase where NGT-based in vivo editing in somatic cells is emerging as a realistic treatment option for monogenic diseases in humans was predicted to be close.

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

- (●) Yes
- ( ) No

* Please specify which needs and how they could be addressed

There were replies from several universities and a research institute, which collaborates with companies. In the following, detailed replies and needs are listed:

- Engineering of industrially relevant production hosts including plants/plant cell cultures
- Mass production of iPS (induced pluripotent stem) cells and reprogrammed cells for bioprinting applications
- Organ regeneration, disease organoid models (gene therapy)
- Genome editing methods have sped up generation of GM rodents and the expected timeline not only for services but also for education and consultation in generation, validation and analysis of the models have increased
- Now that fundamental research on NGT technologies has developed enough to set the stage for NGT-based translational and applied research, the latter one will face increasing funding needs.

*** 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

Science
NGTs give speed, accuracy, and certainty which empower fact-finding and forward movement of science. NGTs broaden significantly the spectrum of organisms that can be engineered. This enables broader than before experimentation on different species to understand how biological systems work.

Plant research
NGTs enable specific mutations in the genes of interest in a directed and precise way and also rapid determination of the function of the genes and connection of gene function to particular plant traits, and creation of a path to improving crop plants.

Medical research
•NGTs contribute to understanding causative defects in diseases. Multiplexed modifications are used to create disease models, such as for cancer in which several tumor suppressors are inactivated simultaneously in different combinations to mimic mutation patterns detected in cancerous tissues. Use of GE in animal models allows manipulation of a gene of interest in its own chromosomal context. When applied to the analysis of protein interactions functionality can be studied maintaining physiological stoichiometry, topology and context.
•Use of NGTs enables studies and development of personalized medicine e.g. new therapies for monogenic

diseases and cell therapies against cancers.
•Recapitulation of disease-causing mutations in mouse, their primary phenotyping and research at organ and tissue level are essential for development of novel therapeutic strategies for these diseases. In vivo modelling of rare diseases may facilitate understanding of the pathomechanisms in more common diseases affecting the same cell and tissue types, e.g. amyotrophic lateral sclerosis, Parkinson's disease and other degenerative disorders.
•New ways of drug delivery to interfere with species of interest in intestinal microbiota are studied to cure intestinal diseases.

Society
NGTs enable improvement of crop plants to deliver benefits to consumers, stakeholders, and society at large. Benefits for food and health include e.g.
•low-acrylamide potato (by eliminating cold-sweetening); high fiber wheat; celiac-tolerant wheat (editing of reactive epitopes); hypo-allergenic fruits (e.g. apple, celery, by epitope editing); high-lycopene tomato
•qualities for specific food-processing sectors: waxy (high-amylose) cereals for improved stability and texture, for soluble fiber, for adhesives, and bio-plastics; high-amylopectin potatoes and cereals, for solubility, freeze-thaw stability without the need for chemical modification; high oleic-acid soybean for improved health
•Improved public health by production of disease-resistant plants to reduce pesticide usage. Disease- and stress-tolerant plants can extend the available diversity of locally produced foods, increasing societal well-being and economic activity.
•greater environmental sustainability through less inputs (water, fertilizers) for more reliable and higher yields
•Increasing animal resistance to diseases will aid in reducing antibiotic use in animal production and contribute to global fight against antimicrobial resistance
•solutions to challenges related to climate change and food security

Agri-food sector/Plants
Overall, for improvement of plant production, research into GE methods will make possible
•plant varieties for farmers that require less inputs, including fertilizer, pesticides, and water
•to provide farmers with more reliable and higher yields, and with harvests that have improved qualities for higher marketplace value. See examples in section "Society".

Agri-food sector/Animals
In general, GE could improve animal welfare and performance while reducing the environmental footprint of livestock production. In animal production (livestock and aquaculture) GE methods could be used to improve animal health and welfare
•by increasing disease resistance in the production lines. Climate change may enhance the spread of many pathogens such as African swine fever in farmed animals. There is already a pig line resistant to ASF produced by modifying a gene towards an allele that gives resistance to ASF in warthogs. Other examples of disease resistance successfully generated by GE already exist (PPRS in pigs)
•by introducing an allele already present in another breed using rapid allele introgression. A successful example is the transfer of the hornless phenotype from beef cattle to a dairy cattle breed (horns being a welfare concern)
•by elimination of deleterious alleles (recessive lethals, other defects) from elite lines

Medical sector
GE-based techniques have made new approaches possible in medical studies and drug discovery
•new site specific targeting possibilities for drug development also providing potentially safer genetic modification
•gene therapy by replacing the inactive gene in e.g. monogenic hematological diseases and cell therapies in cancer (e.g. CAR-T-cells)

•library of mini-organoids on chip for drug testing
•personalized medicine for testing treatments/drug combinations

* **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

Concerns regarding unexpected risks for patients due to limited experience of medicines produced using NGTs were raised. Concerns were also expressed regarding unexpected biological threats such as cancer and iPS cells.

The use of new techniques raises concerns of its use to cause augmented features or to abolish less desired qualities, and the consequences of this in society. Editing of genes of an individual, gene and cell therapy also cause concern.

Ethical questions were raised regarding gene editing/humanization of animals. The ability to more easily modify animals may lead to irresponsible use of these methods in modifying experimental animals, farmed animals and pets. There are various perceptions as to whether it is acceptable that humans interfere with the hereditary material and evolution of organisms and eco-systems.

Correcting known harmful mutations and adding a single resistance gene to generate a crop with improved resistance to certain pests is one thing but starting to build up genomic modifications of a larger spectrum is another. While most of such complex modifications will most likely reduce the viability of the target organism than improve it, we do not know enough and thus up-to-date legislation is needed to avoid uncontrolled wild editing in search for favorable individual features.

Highly efficient genome editing methods enable fast and extensive progress in modifying organisms. Solutions such as gene-drives can cause unintended ecological consequences and cause concern among citizens. Gene-drives should thus be carefully monitored/regulated. However, this should be done separately so as not to prohibit progress of non-gene-drive NGTs.

Economical/ethical challenges were seen regarding techniques, which might be available only for small groups of people. Also, patenting of crucial techniques brings inequality, therefore open access to the science is required.

It was also stated by one respondent that it is absolutely important to use NGTs to address the huge global challenges. NGTs are a great opportunity for humanity. We must also take all available precautions and take care of absolute safety etc., but simply neglecting the opportunities NGTs can provide to solve our big challenges, at least partially, is an obvious injustice.

There was one respondent who did not see challenges or concerns and stated that the agri-breeders and producers have to confirm and make risk assessments for any new products.

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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 Finnish Advisory Board on Biotechnology (BTNK) has prepared two publications:

- Geenien muokkaus uusilla tekniikoilla - Kasvit, eläimet, mikrobit (2018) [in English, Genome editing with new techniques – plants, animals, microbes] (http://www.btnk.fi/files/pdf/Julkaisu /261668_Geenien_muokkaus_verkkoversio_uusi.pdf). This publication illustrates by examples various applications of CRISPR/Cas9 technology, particularly in plant breeding and malaria control, genomic microbial targeting and the construction of self-propagating gene elements (gene drivers) in populations. The publication also looks at agriculture, environment, ethics and legislation.
- Synteettinen biologia (2014) [in English, synthetic biology] (http://www.btnk.fi/files/pdf/Julkaisu /Synteettinen_biologia.pdf). This publication illustrates the current status and future prospects of synthetic biology. The fields of application of synthetic biology are biotechnology, medicine and materials technologies and there are wide prospects for its development. Synthetic biology involves ethical and environmental issues and challenges. Many of them concern issues that have been discussed extensively reflecting on the use of gene technologies. The publication concludes that synthetic biology is a natural continuum of molecular biology method development. Social debate is important for the proper development of synthetic biology-related legislation on the right scale with technological advances in a timely fashion. Early non-discriminatory discussion enables the introduction of synthetic biology in an ethically responsible and generally acceptable way. Earlier (gene)ethical research, guidance and discussion provide a good starting point for synthetic biology introduction because most synthetic biology - related issues are not entirely new.

BTNK has also organized two expert or public seminars:

- “Geeni- ja genomimuokkauksen uudet tekniikat – Genome Editing - Threats and Promises”, Ministry of the Environment” October 2015 (http://www.btnk.fi/files/seminaarit/BTNK_geeni-%20ja% 20genomimuokkaus_kutsuseminaari%2013102015.pdf). In this invitation seminar, the discussed themes dealt with new techniques of plant breeding, genetic engineering in medicine, technology trends and regulatory gaps in synthetic biology and regulation of genetic engineering and environmental impact assessment. No general conclusions were drafted.
- ”Synteettinen biologia – Synthetic Biology”, Chembio Fair, March 2015. (http://www.btnk.fi/files /seminaarit/Synteettinen%20biologi%20Chembio%2018.3.pdf) This seminar did not specifically focus on NGTs, but some of them were mentioned as tools in the SynBio context.

Recently a report was also prepared for the Finnish Parliament’s Committee for the Future (TuVK), complementing the TuVK assessment in 2018 about several new future developments, one of which was gene technology. The new TuVK update (see Annex 3) made a general conclusion that “The development of genetic engineering increases both threats and possibilities. In a global world, the weaker and narrower the national ability to detect and respond to threats, the more the threats multiply. The possibilities offered by genetic engineering are great in solving many major challenges, and this promising development should not be obstructed with unnecessary restrictions. Some of the development is still at a stage in which investment from society is necessary in order to achieve a leap forward before businesses are prepared to invest in the development. It is necessary to make changes to regulation, invest in expertise and support development.”

A governmental study on the use of NGTs in Finland is being launched in spring 2020. This study will approach major stakeholder groups, but is not a public dialogue as such.

* **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

First, national ethical bodies in Finland, especially the Finnish Advisory Board on Biotechnology (BTNK), have discussed briefly the ethical aspects of NGTs in their publications. However, the publications merely include a short ethics section, which briefly summarizes ethical aspects related to NGTs in a general manner. The main conclusion has been that although NGTs give rise to ethical issues, most of these actually present new instances of more general ethical questions extensively discussed before in gene ethics, ethics of stem cell research and, more generally, in bioethics. (Please see a list of the publications below.)

Second, expert and public seminars, which address the ethical issues of NGTs as one of the topics have been organized in Finland. Many of the seminars have included presentations about the opportunities and threats related to NGTs and synthetic biology. Some of them have been specifically concerned with biosafety and biosecurity of synthetic biology research and its applications, for example in the context of defence. One often-reached (ethical) conclusion from these seminars has been the call for upstream and wide public discussion on the ethical issues of synthetic biology. (Please see a list of these seminars below.)

Third, some Academy of Finland research projects and a number of publications relate to NGTs, as they are focusing on synthetic biology, and NGTs are typically considered one research branch of synthetic biology. One conclusion reached (in a paper published in Sci Eng Ethics 2017 23:1541-1561) is that, while most branches of synthetic biology (such as NGTs) fall under gene technology regulation in the EU, this regulation in its current form may not adequately address biosecurity risks. The regulation is mainly concerned with biosafety. This together with certain developments related to synthetic biology provide a weighty reason to review and possibly refine the legislation as well as the supervisory practices in respect to biosecurity. (Please see a list of these projects below.)

See also Finnish Advisory Board on Biotechnology's (BTNK) publications and seminars in Question 13.

Other Expert and Public Seminars (addressing ethical issues as one of the topics; examples listed below):

- The Academy of Finland's workshop "Synthetic Biology Foresight", Helsinki, 19th March 2019. (https://www.aka.fi/synbioworkshop)
- The Finnish Defence Research Agency and the Centre for Military Medicine's seminar "Synteettinen biologia turvallisuus- ja puolustuskontekstissa" [in English, Synthetic biology in the context of security and defence], the Finnish military headquarters, Helsinki 15th Dec. 2017.
- Argumenta project seminar "Geenit ja yhteiskunta" [in English, genes and society], University of Oulu, 20th Nov. 2017.
- ChemBio Finland seminar "CRISPR/Cas9 genome editing: Holy Grail or Doomsday for humankind", arranged by Biobio Society, Helsinki, 30th March 2017.
- The Finnish Academy of Science and Letters' seminar "Geenimuuntelu ja genomieditoinnin mahdollisuudet" [in English, genetic modification and the opportunities in genome editing], Turku, 18th May 2016.

Research projects and their publications as well as other outcomes (examples listed below):

- Professor Matti Häyry's Project "Synthetic Biology and Ethics" as part of Academy of Finland Synthetic Biology (FinSynBio) Programme. On https://www.aka.fi/en/research-and-science-policy/academy-programmes/current-programmes/FinSynBio/
- Professor Tarja Knuuttila's project "Biological Knowledge through Modeling and Engineering: Epistemological and Social Aspects of Synthetic Biology (SynBioMode)" as part of Academy of Finland Synthetic Biology (FinSynBio) Programme. On https://www.aka.fi/en/research-and-science-policy/academy-programmes/current-programmes/FinSynBio/

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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

The most promising areas for NGTs are food, material and energy production and health care. The role of CRISPR technology in a number of tasks was brought up such as its use for affordable identification of DNA sequences, enabling identification of infectious diseases, the composition and origin of food, and the DNA of people. CRISPR technology has rapidly become widespread among researchers due to its easy accessibility, efficiency and simplicity.

BIOTECH SECTOR (by industry and research)

- In enzyme production, NGTs enable extensive BioIT data analysis of both production strains and

enzyme variants leading to improved success rate to develop higher performance products.

- Faster and more extensive engineering of biological systems, both for industrial biotechnology (efficient engineering of existing and novel production hosts) and for sustainable production of chemicals and fuels.

MEDICINAL SECTOR (by regulatory authority, a research institute and the Parliament Future Committee)

- New site-specific targeting possibilities for drug development, also providing potentially safer genetic modification
- New business opportunities to medicinal and industrial sectors
- Gene therapy by replacing the inactive gene in monogenic hematological diseases
- Therapeutic applications e.g. engineering cells for CAR-T cancer treatments
- Improvement of production processes in biotechnology
- New kinds of products possibly with new biological properties
- Diagnostics.

AGRIFOOD SECTOR (industry and research operators)

Plant breeding (breeders, seed companies and seed authority):

- Improving global competitiveness of EU crop production: Yield levels and quality factors must keep up with surrounding world developments and allow plant breeding industry to adapt especially into Nordic conditions, more rapidly, accurately, with potential of plant breeding to generate new varieties.
- Improving disease resistance and quality traits is needed to tackle challenges of environmental and climate change, removal of environmental toxins, address population increase, spreading crop diseases.
- Better land use efficiency due to improved crop yields and adaptation.
- Reduced pesticide usage by knocking out susceptibility genes for disease resistance (e.g. Mlo for mildew resistance) by GE, resulting in lower costs, more and stable harvests and reduced crop losses.
- Reduced or more accurate input of pesticides, water, phosphate and nitrate fertilizers (cleaner waters, decreased carbon footprint and eutrophication lead to greater environmental sustainability).
- Plants suited for indoor/vertical farming/aquaculture with LED lighting; growing in saltwater.
- Benefits for the seed industry (domestic and international customers), and farmers (improved seed qualities, more reliable higher yield, harvests with improved qualities for higher marketplace value) and upwards through the production chain (processing industry and consumers).
- New food products and applications can be introduced in the long term; more healthy and nutritious food (better oil/protein quality, less allergens or introducing new crops to diversify cereal cropping cycles and diets.

Processing industry:

- Production of cereals for improved stability and texture, for soluble fiber, adhesives, and bio-plastics.
- High-amylopectin potatoes and cereals for solubility, and freeze-thaw stability without the need for chemical modification.

Animal breeding:

- Breeding robust animals with longer life-span reduces early culling due to diseases or low fertility, improving sustainability and resource use.
- Increased speed and accuracy for developing new, better lines instead of the current lengthy breeding. evaluation and selection based process aided with “anonymous” genetic markers across the genome.
- Introduction of new traits to an elite line by GE (e.g. genes providing disease resistance), greatly enhancing the possibilities for quick response to emerging challenges, such as spreading of new diseases.
- Rapid allele introgression (introducing an allele from another breed), e.g. the transfer of the polled (hornless) phenotype from beef cattle to dairy cattle, thus solving animal welfare and occupational safety issues.
- GE enables quick elimination of deleterious alleles (recessive lethals or other defects) that breeding

sometimes accumulates in the elite lines.

Microbial processing:
- A potential means for sustainable, carbon-neutral and resource efficient technologies in the agrifood sector considering increasing global population and decreasing natural resources.
- Increasing the applicability and modification for better functionality of specific microbial strains used e. g. as promoters for plant growth (soil microbes), in protein production for food and feed purposes, or as vitamin producers.
- Enhanced manufacturing of protein (by fermentation with single-celled microbes), cultured meat and plant-based imitation meats.

* **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

A wide variety of benefits to consumers, stakeholders, and society were brought up by research institutions and a broad variety of stakeholders.

HUMAN, ANIMAL AND PLANT HEALTH
Pest/disease resistant crop plants diminish environmental hazards (less pesticides and fertilizer leakage etc.) disease resistance in animals (by GE and other NGT) can reduce antibiotics use in animal production (fighting AMR development).

Food related:
- low-acrylamide potato (by eliminating cold-sweetening); high fiber wheat; celiac-tolerant wheat (editing of reactive epitopes); hypo-allergenic fruits (by epitope editing); high oleic-acid legumes; high-lycopene tomato
- GE-aided production of disease-resistant plants (e.g. by knockout of susceptibility genes) can reduce pesticide usage and residues in foodstuffs
- improved nutritional quality (better oil/protein quality, less allergens etc.)

Medical related:
- novel therapeutic approaches
- treatments for non-curable diseases (e.g. CAR-T-cells in cancer therapy, curing mono-allelic conditions)
- microbial cell factories with more efficient compound production processes
- gene drives for eradication of pathogen vectors in areas of severe epidemics
- digital, personalized drug testing allows engineering of new types of synthetic cells, with an eye to production processes and separation techniques
- genome editors as tools for e.g. identification of diseases and hereditary characteristics
- epigenetics: diagnostics and identification of the cell type/state (e.g. blood test for reliable identification of the type/location of an early-stage cancer)
- epigenetics: diagnostics and repair of numerous diseases and aging-related tissue damage types with epigenetic reprogramming
- epigenetics: rejuvenation and changing of individual cells into stem cells (replacing embryonic origin)

SOCIETAL

- disease/stress-tolerant plants can extend the available diversity of locally produced foods, contributing to regional economies
- strengthening ability to identify and develop responses to global spread of plant, animal and human pathogens produced for the purpose of terrorism
- faster development of agri-food sector and improved efficiency of entire food chain to keep up with the global development
- reduced costs of bringing products to the market

ENVIRONMENT

- control of invasive species
- bioremediation
- resurrection biology

INDUSTRIAL PRODUCTION AND MATERIALS

- modification of microbes to efficiently produce desired chemicals and materials for the pharmaceutical, food, chemical or construction industries in more sustainable processes than current chemical and biological processes allow
- LOCKR method allows programming cells to function situation-specifically; LOCKR genome modification makes the cell able to identify selected situations, and activate/deactivate pre-determined genes once the conditions are met
- use of synthetic 6- and 8-letter DNAs to describe a wider variety of proteins than with the 4-letter DNA of biological life; also, they cannot end up as part of living organisms or spread in nature
- production of biofuels and raw materials more efficiently in simplified or automatically adjustable and controllable processes
- production of synthetic fuels / fuel-producing biofilms with microbes
- methylation of microbial genes for production of various material structures, i.e. metamaterials, that are impossible or difficult to produce with traditional methods.
- novel industrial solutions to climate change and circular economy: using industrial by-products and household waste for processing into energy, new raw materials and separate substances that could not be developed with previous technologies

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

As this question was not among the original questions sent by the Commission, it was not included in the questions delivered to stakeholders and hence, we did not receive replies for it.

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

- (●) Yes
- ( ) No

* Please explain under which conditions

Replies were given by enzyme industry, a research institute collaborating with companies and a governmental agency.
•It was thought that if the costs of plant breeding are reduced due to faster and more efficient techniques and decreased need for field trials, SMEs might get more opportunities to have their own special quality varieties /brands.
•Capabilities of data analysis are needed, but less investment is required for use of NGTs than couple of years ago. This enables the use of these tools by SMEs too. Also, developing more accessible NGTs might

provide business opportunities to SMEs.
•Genome editing technologies are easy to employ and are applicable to basically any organism. This brings new organisms and novel biological solutions within reach of SMEs without large initial investments in e.g. infrastructure.
•It was also pointed out that using NGT brings down costs, which will be beneficial to SMEs.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Regarding patenting/accessing patented NGTs no differences were seen compared to other technologies. However, developing and patenting NGTs might give opportunities for SMEs to develop their business and sales. Agri-food sector is in the view that plant varieties should never be patented, only protected with Plant Breeders' Right.

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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

Agri-food:
NGTs in plant breeding/production is a natural evolution of technology and commonly accepted. However, Finnish conditions represent a small niche, where high regulatory costs may, as the use of NGTs is placed under GMO regulation, inhibit their application. Because no foreign breeder can justify the cost of such breeding for niche markets, those markets, such as Finland's become orphans. On the other hand, animal production sector may be more sensitive, and somewhat different regulations may be needed for some applications. Also organic production needs to take a position in respect to NGTs.

The agri-food sector generally needs to take into consideration the consumer point of view when including modified crops or animals in food and feed stuff products. Control of NGT organisms cannot be done by analyzing the end product, so we are heavily relying on labels of products and any written material provided, especially on imported feeds and foods. Most of the agri-food sector thinks that relevant risk based regulation must be in place regarding usage and labelling etc. The food and drink industry believes that once NGTs are properly evaluated, defined and controlled, they will get common acceptance by consumers. The opinion of the food and drink industry is that an extensive dossier procedure comparable to the GMO's case by case is not needed. According to them no consumer labelling is needed, and it would be harmful as

causing pointless confusion and an excess burden to the consumers. Labelling and separated production lines through the food chain would also raise food prices. In the view of the food and drink industry, imported food and commodities would not be labelled reliably anyway.

The agri-food sector has also pointed out that it is not the use of NGTs and NGT-products per se that raises challenges for the agri-food sector, but rather the legal framework due to the ECJ 2018 decision. The NGTs provide speed and accuracy for what breeders have traditionally carried out anyway: identification, generation, and use of genetic diversity to improve plant traits. Hence, there are no special challenges because the lines produced do not differ in kind from those that could be achieved conventionally. If the very fact that two plant lines or plant-derived products can be identical, one produced by NGT and one by conventional methods, but need to regulated differently and tracked differently through the production chain, that raises challenges and concerns for the agri-food sector. If the NGTs would be treated as conventional lines, these challenges would disappear.

Medicinal:
Concerns on unexpected risks for patients due to limited experience of medicines produced using NGTs.

Biotechnology sector:
The genome editing technologies are accelerating the biotechnology industry enabling faster and more extensive engineering of biological systems for industrial biotechnology, agri and therapeutic applications. In all of the sectors the current pace of technology development exceeds the pace of updating the legislation.

Enzyme producers:
The challenges/concerns are similar as with use of other technologies. A good description is needed of what has been done and what has been achieved using the technique in question. E.g. use of NGTs does not make a safe enzyme production strain unsafe. The techniques are as safe as the currently/previously used biotechnological techniques.

* **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

General:
As use of GE technology expands and becomes more diverse, also efficient control of use of the technology is becoming impossible:

- malicious or negligent development work cannot be prevented, e.g. GE pollen which can spread in the air and modify naturally occurring plants even over long distances
- availability and easiness makes GE likely to extend to recreational activity and creates new risks

Another concern is off-target effects of editing, but recent technologies have improved specificity, which may reduce such concerns.

It was considered difficult to obtain information on development carried out in industrial processes, particularly when the development has progressed to the commercial stage.

Agri-food:

Agri-food sector points out that consumer concerns may rise in each case of new type of NGT product release, probably similar to those experienced with GMOs, e.g. effects of NGT products on the environment and human health. It is not clear how well the general public would be able to discriminate between the methods, e.g. GMO or GE. Based on past experience with GMO-based products there is a need to inform in an open way citizens and consumers of the new GE technology, its applications, benefits and concerns. Consumers have the right to base their choices on non-biased information.

Agri-food sector also stated that the environmental impact of “traditional” GMOs, especially crop cultivation, is already well known after 20 years of use, and according to the available information, the risks posed to the environment and human health have been no different to those of crops produced by traditional breeding. CRISPR-Cas9 technology is considered more precise and the outcome is more predictable, and risks posed to the environment and human health were seen as no different to those of crops produced by GMO technology.

Environment:
There is still limited experience with NGT modified organisms and their release into the environment. NGTs will allow multiple changes in the genome and metabolic pathways, changes/traits novel for a given species and thus, also for the receiving environment. The ease to use NGTs will allow their use in semi-domesticated and/or wild species and this will pose challenges to the environmental risk assessment. The more we understand how genetic basis, gene regulation, phenotypic plasticity and epigenetics determine traits, the better we understand the complexity of hereditary nature, and how phenotypes respond to different and/or changing environmental conditions.

Gene drives pose a specific and very demanding situation for the environmental risk assessment. As the method makes it possible to influence whole ecosystems, a cautious approach in adopting the technology is warranted. Gene drives are tools that influence next generations in ways that are difficult to assess. It may be difficult to find suitable comparators and apply the comparative risk assessment framework.

It was questioned whether NGTs will provide efficient, accurate and perpetual solutions to agriculture. Instead of NTG, we need a thorough understanding of the elements of biological diversity beyond the species level and assurance that sufficient genetic potential will remain to support the associated ecosystem functions and services. Extensive monocultures increase the pathogen, pest and weed risks. These risks associated with NTGs are particularly high because the cultivars are based on exceptionally narrow germplasm in breeding. It was also expressed that NGT technologies alone cannot solve the problem of how to feed the world's growing population.

Human, animal and plant health:
Concerns were expressed regarding unexpected risks for patients due to limited experience of medicines produced using NGTs. Availability of GE to households renders personalised drug manufacturing possible for biohackers. Regarding applications where personal health data and DNA sequences are used protection of privacy will be an issue.

Social and Economic:
Ethical issues were brought up such as inequality in the acquisition of gene therapy for genetic diseases and decision whether modification of genome is only allowed to cure diseases or is it allowed to add augmented or new desired properties or to abolish undesired properties of an individual.

Some respondents stated that while NGTs were considered safe in the contained systems of processing technologies, development of food production is restricted by outdated legislation. Indoor farming and biotechnological production of protein offer a contained environment for advancing genetic engineering, which should be made sufficiently simple.

Some respondents voiced concerns that regulating NGTs differently in the EU than in other jurisdictions may cause a competitive advantage for non-EU manufacturers, especially when the NGT product cannot be distinguished from non-engineered products.

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

As this question was not among the original questions sent by the Commission, it was not included in the questions delivered to stakeholders and hence, we did not receive replies for it.

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

- (●) Yes
- ( ) No

* Please explain under which conditions

The plant breeding sector finds that in the present situation it is difficult for SMEs to carry out research and development of NGTs due to the high economical cost needed to reach the market as GMOs. The regulatory framework is the main cause for the high costs. They have also concerns that big companies will patent certain key traits and methods, which will hinder SMEs to utilize these techniques for variety development and there are also other uncertainties regarding this.

The enzyme industry sees no particular challenges compared to corresponding techniques of the past.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Plant breeding industry:
Both patents on genome-editing methods and plants filed by big companies will restrict the access of SMES to the use of NGTs and NGT products. Thus, there is a big threat that these methods will not be accessible to smaller plant breeding companies. Therefore, future EU regulation should ensure that at least naturally occurring DNA sequences and biological processes are outside the scope of patenting. Small and medium sized breeders cannot survive if a patent system puts them in a weaker position than the big companies.

Biotechnology sector:
The patent situation for genome editing technologies is challenging with significant uncertainty to whom and which size licensing cost will be included in the use of the technology.

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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

Finnish Parliament's Committee for the Future:
The development of GE increases both threats and possibilities. In a global world, the weaker and narrower the national ability to detect and respond to threats, the more the threats multiply. The possibilities offered by GE in solving many major challenges are great, and promising development should not be obstructed with unnecessary restrictions. Some of the development is still at a stage in which investment from society is necessary in order to achieve a leap forwards before businesses are prepared to invest in the development. It is necessary to make changes to regulations, invest in expertise and support development. (For more details see Annex 3.)

Ministry of Environment:
Due to the interim decisions of the Board of Gene Technology (see Annex 1) it has not been possible to collect data and information on the NGT use and applications. Further, we have no information on risk assessment while RAs were not carried out. This may be true in other MSs too. It is important to understand that even if the technique is regarded as safe, there is limited experience on environmental releases. NGTs allow to make changes not seen before and are new to the environment (many changes at a time, new traits, changes in several metabolic pathways). It is a problem that the scientific opinion on GM plants developed through NGTs from EFSA is only available in October 2020 and only deals with plants. Robust guidance should be developed for document-based traceability. Detection methods should be further developed.

Ministry of Agriculture and Forestry:
Novel breeding techniques promise enormous potential to the agri-food sector. Regulating them in a way that is scientifically sound is the key, if we want to remain competitive in research, innovations and investments globally. The main problem with the current legislation is that the control of NGTs cannot be done by analyzing the end product, as they don't essentially differ compositionally from conventionally bred or traditional GM varieties. The focus should be kept on the safety of end products, i.e. novel traits, not the technique itself. The northern location and relatively small market of Finland create special breeding needs.

Ministry of Social Affairs and Health:
Development of NGTs has led to a situation where the relevant legislation has become obsolete. As the current decision making regarding GMOs is only nominally risk-based and first and foremost political, it does not allow weighing in any possible benefits. While many experts recommend a regulation based on novel traits, not techniques, there are few willing to start discussing which novel traits would be acceptable and on what terms.

Finnish Food Authority:
The impact of the ECJ interpretation of the GM law and status of NGTs is so substantial that it has effectively revised the GM legislation without the ordinary legislative procedure. Hence, the CA F/F felt they had no possibility to influence the interpretation of the legislation.

Finnish Medicines Agency:
Current use of NGTs in pharmaceutical applications does not cause concerns of safety for population or environment due to the nature and way of use of organisms. In medicine development, the evaluation of

patient risk is covered by medicines legislation, and it also diminishes risks to healthcare workers and the general population. As Directive 2009/41/EC Annex II Part A defines self-cloning being out of scope of the directive, it is not clear if some types of NGT usage can be considered as self-cloning.

Technical Research Centre of Finland VTT:
The fast pace of NGT development exceeds the updating pace of legislation for industrial biotechnology, agri, and therapeutic applications. The current EU GMO regulation is outdated and thus it is of outmost necessity that the Commission takes action on this.

Food and Drink Industry:
Because EU defines NBTs as GMOs (without scientific grounds), there is a threat that research, innovations and investments will flow to other parts of the world. The EU farming and food sector needs encouragement and future prospects. The goals of the Farm to Fork strategy of the EU Green Deal seem remote if the technological means to achieve them are lacking. It is important to guarantee the competitiveness of the European food chain.

Forest industry:
EU should not drop out of the development and use of different GE techniques. Third countries are already poised for commercial production of e.g. GE poplar, hybrid aspen, and loblolly pine. The pressure on the FSC and PEFC certificates is high to accept the use of the GE wood raw material. The main focus of the risk assessment should be shifted away from the technique to the potential risk caused by the new trait to humans, animals and the environment. The same applies to traditional breeding, which is much more coincidental than the changes made by new GEs.

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

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ANNEX 1

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?

A. Cibus: On 19.11.2013 the Board for Gene Technology (GTLK), which is the Finnish Competent Authority for Directives 2001/18/EC and 2009/4/EC, received an inquiry regarding the legal status of RTDS-techniques from a representative of the company Cibus.

B. In August 2018 a university research group informed GTLK about their intention to replace their earlier insertional mutation system by a novel CRISPR-Cas9 deletion system. The research group was planning to delete genes of interest of *Clostridium difficile* to study their function in contained use. Plasmids would be introduced into both *Escherichia coli* cloning/donor strains and the *C. botulinum* recipient strain during the mutant construction process. At the end of the process the recipient would lose the plasmid. In contrast to their old system, where the target gene was knocked out by introduction of intron DNA carrying an antibiotic marker, in the CRISPR-Cas9 system the final *C. botulinum* knock-out mutant would not carry any foreign DNA in its genome, but would have a clean deletion of the target gene(s).

C. In February 2016 the Board for Gene Technology (GTLK) received two requests from a university research group on whether the offspring of CRISPR/Cas9 modified thale cress (*Arabidopsis thaliana*) are within the scope the Gene Technology Act. The group was designing a field trial with the offspring, as a part of an international cooperation. In this case, mutations had been produced in the *Arabidopsis* genome using the CRISP/Cas9 system without any template oligonucleotides (gene targeting cassette) to control the repair process, which had resulted in knock-out deletion mutants. As a result of chromosome segregation, no T-DNA would be present in the offspring either, so there would be no foreign DNA in their genome. The research group considered the progeny to fall outside the scope of the Gene Technology Act, as all foreign DNA was missing. It also based its view on a decision of the Swedish Competent Authority, Jordbruksverket, which reached the same conclusion on the basis of the relevant definitions of the EU Genetic Technology Directives 2001/18/EC and 2009/41/EC.

D. In June 2016 the Board for Gene Technology (GTLK) received a request from a university research group on the legal status of zebrafish (*Danio rerio*) modified with CRISPR/Cas9 technique in several different ways. Some of the lines would be clearly GMOs, but the legal status was uncertain when zebrafish would be modified in such a way that no external

DNA is integrated into their genome (Gagnon, J.A. et al. PLOS One 9, e98186 (2014)). A complex of the bacterial enzyme Cas9 and the controlling single guide RNA (sg-RNA) would be injected into the zebrafish zygotes. The components would be separately produced synthetically, and the complex for injection would be formed by incubating the components together with a dye. The Cas9 enzyme would be exported to the cells in a polypeptide form. As RNA is not the heritable material of zebrafish, no encoding genetic material would be integrated into the recipient's genome. The complex of the enzyme Cas9 and the controlling sg-RNA would cause targeted double-strand breaks in the target cell DNA, which the cell would correct with its own mechanisms (non-homologous end joining). This repair process may cause, among other things, short DNA deletions, unless specific template-oligonucleotides (gene targeting cassette) are used to control the repair process. The research group did not intend to use a gene targeting cassette.

E. In March 2016, the Board for Gene Technology received a contained use notification from a research group studying natural gene transfer behind the geographic distributions of the related fruit fly species *Drosophila montana* and *D. flavomontana*, as well as the mating behaviour of *D.montana*, either by removing or transferring to them genetic material. Some study lines would clearly yield GMOs, since different genes related to fly colour, cold, hot and drought resistance or a fluorescent marker protein would be used as inserts. At that time there was no clarity of the legal status of a certain variant of the CRISPR-Cas9 technique, which would be used for producing minor breaks in the genome. The bacterial Cas9 enzyme would be injected into the fly embryos together with the guide RNA and the tracr-RNA. All these components would be artificially synthesised. Cas9 enzyme would be introduced into the cell in polypeptide form, so no encoding genetic material would be integrated into the recipient genome.

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

A) After consulting three external university/research experts, the Board informed on 14 January 2014 Cibus of its opinion that the use of RTDS™-techniques as described by Cibus does not fall under the scope of Directive 2001/18/EC. Therefore, the Board concluded that field trials using plants bred by Cibus with RTDS™-techniques are not subject to the notification procedures stipulated in Section 17 of the Gene Technology Act (377/1995). However, in its conclusion the Board also stated that its interpretation is subordinate to possible changes in the definitions in Directive 2001/18/EC concerning gene technology, or any specific guidance of the EU Commission regarding inclusion of ODM under the scope of EU gene technology legislation. The Board was not unanimous in its decision. After the European Court of Justice ruling on July 25th 2018 that novel mutagenesis techniques fall under the scope of Directive 2001/18/EC, the Board reconsidered its interim decision. On 17.10.2018 GTLK notified Cibus that having regard to the court ruling, any future field trials with their RTDS™ lines are subject to the notification

procedures stipulated in Chapter 5 of the Gene Technology Act. According to the information received from Cibus, the company had not performed any field trials in Finland with oilseed rape lines modified with novel mutagenesis techniques.

B) On 17.10.2018 the Board for Gene Technology made an interim decision that the ruling of the European Union Court of Justice does not extend to the contained use nor are the deletion mutants obtained with new mutagenesis techniques in the scope of Gene Technology Act, if no foreign genetic material remains in the final organism. The Board was not unanimous in its decision. The operator was informed that the situation may change, if the legal interpretation in the EU turns out to be different. Until then, the operator is not obliged to submit a notice of taking GMOs into use in accordance with Decree 272/2006 of the Ministry of Social Affairs and Health. However, the operator's inquiry and its background information provided were entered in the gene technology register. Also, the Board for Gene Technology decided to send an inquiry to the Commission on whether its Legal Service is of the opinion that the EU Court ruling extends to the contained use of GMMs in situations where the genome of an organism is altered in such a way that it results in a deletion, and no foreign genetic material remains in the final organism. The inquiry was sent on 15.11.2018. The Board has not received a formal reply from the Commission.

C) GTLK sought the opinion of three external university/research experts on the interpretation of the gene technology regulations and it also considered the Jordbruksverket's position. In its interim decision on 7.4.2016, GTLK stated that the progeny lines of *Arabidopsis* modified by CRISPR/Cas9, as described in the request and when whole genomic sequencing has confirmed that they do not contain foreign DNA, are not GMOs within the meaning of the Genetic Technology Act (377/1995) and Regulation (928/2004). Consequently, a field trial with them would not be subject to an authorisation procedure under the Genetic Technology Act. The interim decision only applied to the progeny lines in question, and the results of their whole genome sequencing would have to be submitted to the GTLK prior to commencing the field trial. The research group was also informed that the decision is only valid until the EU adopts binding amendments to the definitions of genetic modification in the Directives 2001/18/EC and 2009/41/EC, or until EU makes other binding decisions on whether the CRISPR/Cas9 technologies, organisms modified by them or their descendants are within the scope of GMO regulations. The research group was invited to take special care in carrying out the field trial, taking into account that the legal status of these *Arabidopsis* lines could change rapidly, should an interpretation be made at EU level that the offspring lines are considered to be GMOs. If so, beginning or continuing a field trial would require an application referred to in Section 17 of the Genetic Technology Act, and the risk assessment, risk management and follow-up procedures for field trials on genetically modified plants would be required. After the ECJ Decision GTLK approached the research group on the subject. As no field trial had been carried out, there was no need for further action. GTLK sent the research group a formal letter on 17.10.2018 advising them about the ECJ decision and the relevant notification procedures should the research group plan a field trial in the future.

D) On 10.10.2016 GTLK made an interim decision that modified zebrafish subject to targeted mutagenesis using the above-mentioned CRISPR/Cas9 method and not containing any foreign DNA are not GMOs within the meaning of the Gene Technology Act (377/1995) and Regulation (928/2004). The Board was not

unanimous in its decision. The decision concerns zebrafish lines mutated with the technique described only if guide RNAs exported to the embryo are synthesized as RNA-oligonucleotides, and the Cas9 enzyme is injected into cells in polypeptide form, and no genetic material is integrated into the genome, such as stop-codon cassettes, is introduced into the cells. The research group was also advised to exercise special care in the use of the above-mentioned zebrafish, bearing in mind that the legal status of these fish may subsequently change so that they are considered as GMOs. In that case, their further use would require risk assessment, risk management and recording procedures in accordance with the Genetic Technology Act.

E) After consulting two external university/research experts, the Board for Gene Technology made on 6.7.2016 an interim decision that *Drosophila* modified with the method described and which do not contain foreign DNA are not genetically modified organisms within the meaning of the Genetic Technology Act (377/1995) and Regulation (928/2004), on the condition that the guide-RNAs exported to the cell are synthesised as RNA-oligonucleotides and the enzyme Cas9 is injected into the cells in polypeptide form. The Board was not unanimous in its decision. The operator was also advised to exercise special care in the use of these *Drosophila* bearing in mind that their legal status may subsequently change to GMOs. In that case, further use would require risk assessment, risk management and recordkeeping procedures under the Genetic Technology Act.

ANNEX 3

Development of genetic engineering in different areas of application 2018–2020

Finnish Parliament's Committee for the Future

1. Summary

This report has been prepared for the Finnish Parliament's Committee for the Future. It identifies the key areas of genetic engineering and the areas of application related to it. It also briefly describes recent breakthroughs noted by Tulevaisuusvaliokunnan radikaalit teknologiat -joukkoistus (Radical technologies crowdsourcing group of the Committee for the Future) since the publication of the report 'Societal transformation 2018–2037: 100 anticipated radical technologies, 20 regimes, case Finland'. The report starts with the summary and conclusions, which are explained in more concrete terms in the following chapters, along with their background. First, technological advancement is described separately for each technology, after which the significance of the technologies for key areas of application is examined. The aim of this text is not to replace but to supplement the reports 'Societal transformation 2018–2037: 100 anticipated radical technologies, 20 regimes, case Finland' (1/2018) and 'Geeniteknologia' (Genetic engineering, 2/2018) by the Committee for the Future. However, the text has been written so as to be readable independently of the aforementioned, particularly if the reader is familiar with the subject matter. Developments prior to 2018 will not be examined here; where they are concerned, this report refers to the observations made in the 1/2018 report.

1.1. Technological advancement

In addition to genome editors, this review covers technologies related to DNA sequencing, identification of sought genomes and cell culture as well as the modelling of the function of DNA and cells. Epigenetics, i.e. the study of the structure that regulates actual DNA, is examined in its own section.

Technological advancement has continued to progress rapidly in every respect over the last two years. The rise of epigenetics into an important topic in many ways is particularly worth noting. It is also important to note the expanding role of CRISPR technology in a great number of tasks, ranging from original genetic engineering to diagnostics and gene therapy. As the use of CRISPR technology expands and becomes more diverse, efficient control of the use of the technology is becoming impossible.

1.2. Development of the areas of utilisation

The most promising areas for utilising genetic engineering are food production, health care, material production and energy production. Among these areas, the technology has been developed the most rapidly for health care applications. Genetic engineering is already

being applied in many ways, in addition to which significant new diagnostic and treatment methods are constantly being discovered. The causes are being identified for many serious hereditary diseases, including national diseases such as degenerative diseases related to old age and cancers. Blind persons have regained their sight and deaf people can hear again. In addition to explaining these diseases, genetic engineering also promises to treat them, and many treatment methods for serious diseases that are based on genetic engineering are already undergoing or progressing towards clinical trials.

In other areas, application has progressed more slowly. At present, the development of food production is restricted by outdated legislation. The need for development is increasing due to climate change, plant diseases and environmental toxins as well as population growth. Indoor farming and the biotechnological production of protein offer a closed environment for advancing genetic engineering, which should be made sufficiently simple, at least with regard to the regulations. Material production and the production of raw materials for energy benefit from genetic engineering, but progress primarily remains at the level of basic research for the time being. The promises are great, but development is still at a relatively early stage for commercial operators to embrace it.

1.3. Political recommendations

The most important political recommendations are related to the strengthening of genetic engineering expertise in all areas and applications of genetic engineering. It must be understood that the broad expertise and practical response preparedness required cannot be maintained nationally or even at the EU level if activities are restricted on account of minor risks and by stricter means than in competing countries. Another thing that must be understood is that a lack of broad expertise and narrow practical preparedness cause their own significant risks in a global environment. The most difficult regulatory restrictions in this respect are related to the application of genetic engineering in plant breeding and other food production. There are also problems with the availability of genetic data related to research and personalised health care as well as the undeveloped state of industrial applications, which should be supported with research investments and education policy measures at the national and EU levels.

2. **Background and progress of technological advancement**

2.1. DNA sequencers

Background: There are several reasons and also several technologies for sequencing DNA. DNA uniquely identifies individuals in criminal investigations, for example, and even helps predict facial features, but it is also used to identify diseases and other characteristics. Counterfeit foods, diagnosis of infectious diseases and numerous other applications focused on well-being benefit from DNA sequencing, which is becoming increasingly affordable.

In addition to DNA, it is possible to sequence the RNA codes of viruses as well as RNA codes related to intracellular function. It is also possible to sequence the epigenetic settings in cell

DNA, i.e. methylation, which tells us which genes are active and which ones are deactivated. This information tells us which cell is in question and provides other information about the state of the cell.

Several techniques are used to sequence DNA. Some of them require the DNA to be amplified before sequencing. The most common technique for this purpose is PCR. Some techniques are sensitive in such a way that amplification is not required. Some techniques are able to use biochips or selective amplification to identify whether a sample contains certain genetic sequences, while others decode the DNA or RNA sequences as they are in the sample.

DNA sequencers are examined in chapters 2.1.2 and 2.1.4 of the 1/2018 report.

Recent events: Oxford Nanopore (https://nanoporetech.com/applications/dna-nanopore-sequencing) has served as a pioneer in technology in which, instead of short and chopped sequences that are assembled digitally afterwards, DNA is sequenced as long strands by drawing them through a nanopore. The technology is becoming efficient and more precise, requiring the sequencing to be carried out fewer times. Illumina, which dominates the industry market with more traditional technology, has promised to drive the cost of sequencing the whole human genome down to $100, but the practical production cost related to high-quality sequencing of the human genome has stagnated at $1,000 for a while, a level that Oxford Nanopore is also already capable of providing.

Many companies have started offering DNA sequencing services to their clients at a price substantially lower than the production cost and at a poor quality. Promises have also already been made to provide DNA sequencing free of charge if the customer allows their genetic data to be used for further purposes. The technology that seems to have advanced the most rapidly is the identification of individual DNA sequences for the purpose of identifying both infectious diseases and cancer and even their epigenetic location. The sequencing of epigenetic data has also advanced rapidly. The use of CRISPR technology for affordable identification of DNA sequences is among the most recent breakthroughs.

Foresight: According to theoretical models, nanopore technology will allow DNA sequencing to be carried out at a price several times cheaper than is possible at present. It seems credible that, over the 2020s and 2030s, households will have access to smartphone accessories that will at first allow the occurrence of selected DNA sequences to be tested and later for the whole genome to be sequenced. This will also make it possible to identify infectious diseases, the composition and origin of food and the DNA of people close to us. The protection of privacy will unavoidably crumble in this respect.

New sources since the 1/2018 report:

Ultrasound can reveal gene expression in the body;
https://www.sciencedaily.com/releases/2019/09/190928082737.htm

The cost of sequencing the human genome has decreased to less than $1,000;
https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

An affordable, portable DNA sequencer delivers 99.9% precision;
https://www.nature.com/articles/s41467-019-09637-5

CRISPR as a diagnostic tool, a prototype for at-home tests;
https://www.theverge.com/2018/4/26/17281724/mammoth-biosciences-crispr-diagnostic-tool-disease-detection

Detection of a target sequence within an uncultured sample with CRISPR-Chip;
https://www.nature.com/articles/s41551-019-0371-x

A test identifies early-stage cancers and their locations, only 1% rate of false positives;
https://www.fiercebiotech.com/medtech/asco-grail-s-blood-test-identifies-a-dozen-cancers-before-they-can-spread-early-results

Free-of-charge DNA sequencing and compensation for the use of the genome;
https://www.npr.org/sections/health-shots/2018/11/15/667946213/startup-offers-to-sequence-your-genome-free-of-charge-then-let-you-profit-from-it

2.2. DNA writing

Background: The writing of DNA sequences does not only serve genetic engineering. DNA sequences can be written both for the purpose of altering the genome controlling a cell's function and by recording data in a DNA sequence. As a method of recording data, DNA writing is, for the time being, only a promising area of research, having not yet reached a practical level. However, the data storage density of DNA exceeds that of all existing data storage devices, but writing and sequencing DNA is, for now, difficult compared to other data storage technologies.

Writing DNA sequences is not necessary for editing a genome if the replacement of individual base pairs is not counted as *DNA-writing*. Furthermore, some genetic engineering is based on genes that occur in other organisms, and DNA writing is not required in transferring them. When DNA writing is used, the change in the genome occurs when the written DNA sequence is transferred with a genome editor to the desired part of the target organism's genome. The function of genome editors is described in more detail in the following section, 2.3.

DNA writing is examined in chapter 2.1.2 of the 1/2018 report.

Recent events: The production of DNA sequences is becoming increasingly routine. The writing process can be carried out almost flawlessly, and this flawlessness can be verified by sequencing the sequences that are written. DNA writing is simultaneously becoming accessible to everyone in terms of the equipment used and so cheap that it cannot be controlled. There are also services being created at the global level that allow customers to order the DNA sequences they want. A good example of this is a group of students who ordered pieces of Anthrax through several different services and combined these pieces into functional Anthrax for a student project.

Foresight: Writing and amplifying DNA sequences will become increasingly easy. If the market evolves in such a way that DNA writing becomes a common service, it can be controlled at least to some degree, and it will be possible to restrict the writing of parts of the DNA of known infectious diseases, for example. If the activities are based on cheap devices purchased by users for themselves, their use will, in practice, be impossible to control.

New sources since the 1/2018 report:
Writing of whole genomes funded and under development;
https://neo.life/2019/11/the-dawn-of-cheap-and-easy-dna-writing/

DNA writing is becoming easy and cheap, while control is becoming impossible;
https://www.npr.org/sections/health-shots/2019/09/24/762834987/as-made-to-order-dna-gets-cheaper-keeping-it-out-of-the-wrong-hands-gets-harder?t=1583496283229

2.3. Genome editors

Background: The task of genome editors is to take the desired DNA sequence inside the target cell and insert it into a specific part of the target cell's genome. In other words, a genome editor must be able to penetrate a cell, locate the part to be edited and insert the selected sequence into the part in question. The transferred sequence can be separately written or copied from another organism. It is also possible for the genome editor to locate the desired part of a genome and edit the base sequence directly in the desired manner.

Use of CRISPR technology has rapidly become widespread among researchers due to its easy accessibility, efficiency and simplicity. There are several variations of the technology, some of which are able to spread widely in tissue cells. These variations differ from each other in terms of precision and the length of the sequence edited as well as in whether or not they cut the genome, make a change to an individual base or insert a DNA sequence without cutting the genome. As the editors also locate the selected part of the genome, their use extends beyond genetic engineering to the identification of diseases and hereditary characteristics, among other things.

In addition to the editing of hereditary genetics, genome editors are used in multi-celled organisms to edit the genome of specialised tissue stem cells and other tissue. This is referred to as gene therapy, and its most common goal is related to health care.

Genome editors are examined in chapter 2.7.60 of the 1/2018 report.

Recent events: The most important phenomenon is the rapid spread of CRISPR technology. A great number of CRISPR variations have been created. Some versions of the editor can be distributed into human tissue widely, even curing hereditary diseases in human adults. One event that can be considered to have shocked the science community and the general public is the birth of the first gene-edited children in China. Before this, a baby was born in the UK with mitochondrial DNA inherited from a different individual than the rest of his X and Y chromosomes, i.e. the child biologically has DNA from three different parents. The need for

this arose from a genetic defect in the mother's mitochondria. The science community was also bewildered by an experiment in which scientists sought to increase the intelligence of monkeys by transferring human DNA to them. The use of CRISPR technology to treat diseases is rapidly becoming more diverse.

Foresight: It is apparent that genome editors are already easily available and usable with the skills and equipment that are typical for students of cell biology and that can be obtained by amateurs. Gene editing is likely to spread beyond business and research activity to recreational activity. Editors will become increasingly efficient in such a way that they can multiply and spread to tissues and all cells through the bloodstream, even changing the DNA of a human adult. Ease speeds up the realisation of the great promises of genetic engineering, but it also creates new risks, the prevention of which requires broad preparedness from genetic engineering, as many of the expected problems cannot be prevented with traditional methods.

New sources since the 1/2018 report:

CRISPR/Cas9 is precise and predictable when used correctly;
https://phys.org/news/2018-12-scientists-crispr-code-precise-human.html

Gene-edited children, Lulu and Nana;
https://www.technologyreview.com/s/614762/crispr-baby-twins-lulu-and-nana-what-happened/

Increasing the intelligence of monkeys with a human gene;
https://www.discovermagazine.com/mind/scientists-put-a-human-intelligence-gene-into-a-monkey-other-scientists-are

The lifespan of a nematode has been amplified fivefold with genetic engineering;
https://www.sciencedaily.com/releases/2020/01/200108160338.htm

Prime: a precise CRISPR editor that does not sever the DNA strand (the problem is that the vector is not efficient and does not penetrate all cell walls);
https://www.technologyreview.com/s/614599/the-newest-gene-editor-radically-improves-on-crispr/

New CRISPR technique inserts long DNA sequences without cutting the genome;
https://www.nature.com/articles/d41586-019-01824-0

A CRISPR method for fighting viruses inside cells;
https://www.scientificamerican.com/article/scientists-program-crispr-to-fight-viruses-in-human-cells/

Fighting antibiotic resistance with CRISPR technology;
https://phys.org/news/2019-12-crispr-based-amplified-antibiotic-resistant-genes.amp

Switch for organ regeneration found in junk DNA;
https://www.telegraph.co.uk/science/2019/03/14/harvard-university-uncovers-dna-switch-controls-genes-whole/

Reprogramming a broad gene matrix with a new CRISPR technique; https://ethz.ch/en/news-and-events/eth-news/news/2019/08/revolutionising-the-crispr-method.html

2.4. Cell culture

Background: The purpose of cell culture is to reproduce a cell. The cell in question may be genetically modified. The tissue created with cell culture can be used for many purposes, such as for raw material in biotechnology or as part of a production process. In the food industry, it can be used for food. In medicine, genetically modified cells can be injected into the body for medical purposes, 3D printed into tissue or organs or used for research purposes.

Cell culture is examined in chapter 2.7.63 of the 1/2018 report.

Recent events: When researchers learned to convert specialised cells back into unspecialised stem cells, cell culture became faster, and the number of different types of experiments increased, also producing a great number of successful research outcomes. The specialisation of stem cells and the culturing of cells belonging to the desired tissue type is starting to be a routine activity. Scientists have also learned to print living cells into a tissue structure with the help of support structures that are absorbed into the tissue. This is used to produce organs that are viable for transplantation. Genetically modified and cultured tissue has been injected into tissue and the bloodstream for treatment purposes almost on a routine basis. Cell culture is also being developed for industrial purposes, but it is more difficult to obtain information on development carried out in industrial processes, particularly when the development has progressed to the commercial stage.

Foresight: Cell culture will become routine activity in which the selected cell is converted into a stem cell, its cell type is chosen and the cell is reproduced. This activity will become computer-assisted and it may be combined with genetic engineering. Cultivated tissue can be used as raw material or as a producer of raw material in industry, energy production, food production or medicine. The method will also become available to households, which will make personalised drug manufacturing possible for biohackers, for example. Controlling this type of private activity may become challenging in the same manner as controlling the producers of computer viruses.

New sources since the 1/2018 report:

3D printing of living skin and blood vessels for skin grafts; https://news.rpi.edu/content/2019/11/01/living-skin-can-now-be-3d-printed-blood-vessels-included

A functional, 3D printed heart cultivated from stem cells; https://onlinelibrary.wiley.com/doi/full/10.1002/advs.201900344

A functional, 3D printed mini liver cultivated from the patient's reprogrammed cells; http://agencia.fapesp.br/researchers-create-functional-mini-liver-by-3d-bioprinting/32217/

Vision restored with a transplant engineered from stem cells; https://www.moorfields.nhs.uk/news/successful-trials-new-treatment-moorfields-fight-against-sight-loss-caused-amd

A- and B-type blood converted into O-type blood; https://naturemicrobiologycommunity.nature.com/users/261113-peter-rahfeld/posts/49635-an-enzymatic-pathway-in-the-human-gut-microbiome-that-converts-a-to-universal-o-type-blood

2.5. Epigenetics

Background: Epigenetics is a rapidly rising area of research. The most important part of the genome, which distinguishes organisms, is formed by the genes that code proteins. Genes decide the sequence of amino acids in proteins, which in turn affects the shape of the proteins and the ways in which they function in the body. Different proteins are produced in different situations, and the most important thing for the body is the data on the cell type. For example, whether the cell is a root hair cell, nerve cell or blood cell. This data is encoded into the genome of each cell with methylation. All of this together is called epigenetics. In other words, we are talking about data on the status of each cell, but it has been proven that this too might be partly hereditary, even if it is a 'learned characteristic'.

Methylation sequencing identifies which cell type the DNA is from. When cancer destroys cells, DNA sequences that allow the type and location of the cancer to be identified are released into the bloodstream. By editing methylation, it is possible to change the cell type and edit a skin cell into a gamete or produce stem cells for cell culture, for example. It also seems that the cell ageing mechanism, 'the biological clock', is encoded into methylation and that cells can be rejuvenated. If we want to make cells produce the desired proteins or prevent their production, this can also be realised by means of epigenetics.

Epigenetics is examined in chapter 2.7.62 of the 1/2018 report.

Recent events: Epigenetics has evolved particularly rapidly in the area of diagnostics. It appears that the identification of the cell type and the state of a cell, e.g. reliable identification of the type and location of an early-stage cancer with a blood test, is at the breakthrough stage. The significance of epigenetics for ageing and the rejuvenation and changing of individual cells into stem cells are relatively recent developments, and collecting stem cells from embryos is hardly ever discussed anymore.

Foresight: All the promises of epigenetics are still in the process of being revealed, but it now seems possible and even likely that numerous diseases and types of tissue damage related to ageing can be both diagnosed and repaired with epigenetic reprogramming. With methylation, it is also possible for microbes to be made to produce a variety of material

structures, i.e. metamaterials, that are impossible or difficult to produce with traditional methods.

New sources since the 1/2018 report:

Modification of the cells in the immune system to cure allergies;
https://www.sciencedirect.com/science/article/pii/S0142961219305319

In addition to methylation, another mechanism that regulates the function of the genome has been discovered;
https://phys.org/news/2020-01-discovery-gene.html

Methylation holds the key to ageing, stem cells have been rejuvenated;
https://medicalxpress.com/news/2020-02-molecular-reverses-chronic-inflammation-aging.html

Cells can be rejuvenated with epigenetics;
https://www.nature.com/articles/d41586-019-02638-w

A review of rejuvenation treatments with the help of epigenetics;
https://joshmitteldorf.scienceblog.com/2019/07/30/rejuvenation-at-the-cell-level/

2.6. Cell modelling and synthetic biology

Background: The function of cells has been modelled for a very long time. The greatest breakthrough in modelling took place when DNA was discovered, but details have been added at an accelerating pace since then. The prospect is that the function of a cell could be simulated, covering everything from hereditary factors to internal and external cell signals, protein metabolism and other functions. This data makes it possible to simulate the effect of hereditary factors, methylation, medications and the environment on the function of cells and organs. For the time being, the models are still rough.

Cell modelling also offers an opportunity for synthetic biology. The effect of genetic engineering on the function of a cell can be planned and tested with the help of a simulation model, which makes both the testing and collection of results several times easier than repeating the same tests in real life. This makes it possible to conduct numerous tests and even assign the testing to an AI, after which the successful variations can be verified with real-life testing.

Synthetic biology means creating partly or completely new DNA in an organism. Viruses, yeasts and bacteria are the simplest to experiment with, and their significance in biotechnological production is increasing. One exotic variation of synthetic biology is six- and eight-letter DNA, which have been proven to be stable and capable of self-replication. They make it possible to describe a variety of proteins several times greater than is possible with the four-letter DNA found in biological life. Additionally, the risk of this type of DNA ending up as part of living organisms or being able to spread in nature is completely inexistent.

Cell modelling and synthetic biology are examined in chapter 2.7.61 of the 1/2018 report.

Recent events: Precise modelling of the function of cells is evolving gradually as understanding of intracellular mechanisms and the simulation capacity of information technology increase. There are still unknown principles associated with intracellular mechanisms. Synthetic biology is even evolving in surprising directions after six- and eight-letter DNA proved to be stable. The whole DNA of E. coli and a significant part of the DNA of yeast have been successfully replaced with synthetic DNA.

Foresight: When the internal and external functions of cells are successfully modelled and simulated, starting from the genome, it will become possible to digitally test the response of cells to genetic modifications and external stimuli, such as food and medications. Then it will be possible to conduct tests to the extent allowed by computer capacity, with both humans and AI controlling the tests. A cell simulation model allows digital drug tests to be conducted on tissue type specific cells according to an individual's own DNA but also for the genome's modification to be engineered and tested and for completely new types of synthetic cells to be engineered with an eye to production processes and separation techniques.

New sources since the 1/2018 report:

Building a synthetic cell from the bottom up in 10 years;
https://www.nature.com/articles/d41586-018-07289-x

Human Cell Atlas catalogues every type of cell in the human body;
https://www.npr.org/sections/health-shots/2018/08/13/636938467/ambitious-human-cell-atlas-aims-to-catalog-every-type-of-cell-in-the-body

The genome of E. coli has been fully swapped with an artificial one;
https://www.technologyreview.com/s/613534/researchers-swap-genome-of-gut-germ-e-coli-for-an-artificial-one/

Eight-letter DNA proven to be stable;
https://gizmodo.com/freaky-eight-letter-dna-could-be-the-stuff-aliens-are-m-1832823430

3. Background and development of areas of application

3.1. Food production and nutrition

Background: With the evolution of CRISPR technology, genetic engineering has become precise and efficient compared to traditional breeding. As the climate warms up, environmental toxins spread and the global population increases, many needs for plant breeding have arisen. Examples of the characteristics sought include plants that have a higher yield and require less pesticides, plants that are suited for vertical farming/aquaculture with LED lighting and plants that grow in salt water. Genetic engineering could also enhance the manufacturing of protein grown by fermentation with

the help of single-celled microbes as well as the manufacturing of cultured, biotechnologically produced meat and plant-based imitation meats.

Genetic engineering in food production is briefly touched upon in several sections of chapters 1.4 and 2.7 of the 1/2018 report.

Recent events: Indoor farming has rapidly become more common, and there is now active debate about lighter regulation of genetic engineering of plants intended for indoor farming. It has also been proposed that the restrictions on genetic engineering be relaxed with regard to biotechnologically produced protein due to the low risks involved. Because of expected challenges in food production, investments are rapidly increasing, even in radical breeding. Useful discoveries include nitrogen-fixing maize, grain that grows in salt water and grain with more efficient photosynthesis, among other things.

Foresight: Genetically modified plants suited for aquaculture in vertical stacked layers under LED lighting significantly increase the efficiency of indoor farming and the variety of plants. Genetic engineering brings diversity to the biotechnological production of meat and protein. As a result, an increasing number of producers abandon food production that takes up a great amount of space.

New sources since the 1/2018 report:

A rice strain engineered in China grows in salt water;
https://nextshark.com/china-invents-rice-can-grow-salt-water-can-feed-200-million-people/

Solein, which is produced by electricity, can successfully compete against soya;
https://www.bbc.com/news/science-environment-51019798

Nitrogen-fixing maize has been developed;
https://journals.plos.org/plosbiology/article?id=10.1371%2Fjournal.pbio.2006352

The yield of crop plants has been improved by enhancing photosynthesis;
https://www.nature.com/articles/s42003-019-0561-9

Introduction of cultured meat to the market in 2021?
https://wsvn.com/news/us-world/how-close-are-we-to-a-hamburger-grown-in-a-lab/

Dubai will introduce the world's largest LED farm;
https://amp.thisisinsider.com/dubai-emirates-airlines-world-largest-vertical-farm-2018-7

3.2. Industrial production and materials

Background: Many natural materials are bewilderingly sophisticated compared to industrially produced materials. Examples include leather and nacre. Producers seek to harness bacteria and yeasts into factories that are controlled with the help of genetic engineering and methylation to produce the materials desired in any one place and at any one time so that they attach to the surfaces. This allows layered and even complex

structures to be produced. At their simplest, microbes are made to produce the desired chemicals for the needs of the pharmaceutical, food, chemical or construction industries.

New materials are increasingly developed digitally instead of in chemists' laboratories. Atoms, the molecules they form and the metamaterials created from them in various forms can be modelled digitally. Simulations and AI make it possible to test various compounds and their behaviour. The materials discovered through this method can be superior in terms of their properties but impossible to manufacture by traditional methods. Genetically modified microbes may be a solution to the efficient production of these types of materials. Biotechnological processes normally occur in room temperature, and they are typically energy-efficient and scalable to industrial levels.

Genetic engineering related to material technology is briefly touched upon in several sections of chapters 1.6 and 2.7 of the 1/2018 report.

Recent events: A new method called LOCKR has been developed. It allows cells to be programmed to function in the desired manner, depending on the situation. LOCKR is a genetic modification made to a cell's genome with e.g. CRISPR technology, after which the cell is able to identify selected situations and, once the conditions are met, activate and deactivate pre-determined genes. There has also been significant development in research into biofuels. By using microbes, sunlight, carbon dioxide and water, researchers are learning to produce raw materials increasingly efficiently.

Foresight: The biotechnological production of many raw materials and other materials will become easy once the adjustment and control of processes becomes automated and once we learn to stimulate the internal processes of microbes and control them based on the genome and epigenetics. In the future, the biotechnological production of materials will prove to be more sustainable than both chemical and traditional biological processes. The production of synthetic fuels with the help of microbes will most likely become an important development trend.

New sources since the 1/2018 report:

General news about material technology under the section 'biotechnology';
https://tulevaisuuspankki.fi/en/articles

Genetically modified chickens lay eggs containing anti-cancer drugs;
https://www.bbc.com/news/science-environment-46993649

LOCKR programming activates the cell in the desired manner in the selected situation;
https://www.bbc.com/news/science-environment-46993649

Microorganisms with a nanosurface produce plastic and fuels from light and carbon dioxide;
https://m.phys.org/news/2019-06-light-powered-nano-organisms-consume-co2-eco-friendly.html

3.3. Well-being and health

Background: The sequencing of the human genome is becoming increasingly affordable and beneficial. The genetic causes of hereditary diseases and exposure to them are being discovered relatively quickly, and scientists have learned to cure many serious diseases with the help of genetic engineering. At the same time, numerous hereditary characteristics have been identified in a manner that allows considerably more effective and precise advice based on unique DNA to be provided instead of demographic guidelines issued for lifestyles and nutrition.

Gene therapy has proven to be a promising and, in narrow areas, already functional method in the treatment of various cancers and hereditary diseases. Epigenetics, together with cell culture, has also yielded results in the treatment of many types of tissue damage and even the symptoms of old age.

Genetic engineering related to health care is briefly touched upon in several sections of chapters 1.12, 2.1.2–2.1.4 and 2.7 of the 1/2018 report.

Recent events: The use of the CRISPR method in diagnostics has advanced rapidly. The role of epigenetics in diagnostics, cell culture, pharmacotherapy and the rejuvenation of tissue has become an important subject of research, and promising trends similar to breakthroughs can be seen in all these areas.

For an increasing number of diseases, treatments developed with the help of stem-cell therapy and cell culture have progressed to clinical trials with promising results. Artificial organs developed with the help of cell culture and 3D printing of cells are already functional for many organs and approaching clinical trials. Organ parts that are the easiest to produce have been grown, and there have been reports of successful human trials.

Foresight: Wellness and health technology are evolving increasingly rapidly. Rising trends include remote and self-diagnostics, personalised medication adjusted to the individual's DNA, lifestyle and metabolism as well as dietary and other lifestyle guidance. A significant part of this development is tied to genetic engineering. An increasing number of diseases that are considered to be serious will be learned to be diagnosed at an early stage and even cured completely. It is possible that methods to prolong the healthy life expectancy of humans by 20–30% will already be discovered in the 2020s or 2030s.

New sources since the 1/2018 report:

CRISPR diagnosis tool used at home identifies diseases;
https://www.theverge.com/2018/4/26/17281724/mammoth-biosciences-crispr-diagnostic-tool-disease-detection

A prototype identifies 13 cancers from a blood sample at a production cost of €200;
https://www.toshiba.co.jp/rdc/rd/detail_e/e1911_06.html

The immune system provides a new channel for attacking cancer cells;
https://www.hs.fi/tiede/art-2000006380050.html

Using a portable device to print cultivated skin to cover a burn wound;
https://www.sciencedaily.com/releases/2020/02/200204163652.htm

A smartphone accessory analyses several diseases from spit samples;
https://www.eurekalert.org/pub_releases/2020-02/uoc-ply020620.php

Curing blindness with CRISPR therapy;
https://futurism.com/neoscope/scientists-attempt-cure-blindness-crispr

Treating sickle cell disease with a CRISPR-modified cell culture;
https://www.npr.org/sections/health-shots/2019/07/29/744826505/sickle-cell-patient-reveals-why-she-is-volunteering-for-landmark-gene-editing-st

Inhalable mRNA medication under development;
http://news.mit.edu/2019/inhalable-messenger-rna-lung-disease-0104

An mRNA melanoma vaccine that modifies T cells succeeds in human trials;
https://www.labiotech.eu/medical/universal-cancer-vaccine-biontech/

3.4. Living environment and sustainable development

Background: Genetic engineering has been considered to be a risk for the living environment. The growing pressure related to the living environment has increased research in which genetic engineering is used to reduce the burden on the environment. Indoor farming, biotechnologically produced meat, plants that are resistant to pests and plant diseases, production that requires less space and has a higher yield, biofilms that produce fuels, and many other goal-oriented technologies seek success with the help of genetic engineering.

The continuously improving ability to read and process genetic data helps us study and understand the environment and its burdens. The strengthening ability to identify and develop responses to globally spreading plant diseases, viruses that spread to humans and animals as well as viruses and bacteria produced for the purpose of terrorism plays an important role. Genetic engineering has become so easy that its criminal use cannot be controlled. The only efficient method is to harness the technology for beneficial use to such a large degree that the ability to respond to problem situations is strengthened.

Genetic engineering related to the living environment and sustainable development is briefly touched upon in several sections of chapters 2.6.50, 2.7 and 2.8.74 of the 1/2018 report.

Recent events: DNA sequencing has been extensively utilised in the study of the routes of the spread of the coronavirus for the purpose of cutting off the chains of infection and developing a vaccine. Research investments have been directed towards the needs of the environment and sustainable development, which has begun to show in research results. The wide spread of CRISPR technology yields both benefits and risks. Genetic engineering can be carried out with very modest resources. Development cannot be controlled, and malicious or negligent development work cannot be prevented. Additionally, researchers

are now able to spread the CRISPR editor with the help of pollen. In practice, this means that pollen that contains a genome editor can be spread into the air, where it travels to plants, pollinates them and simultaneously modifies the DNA of the seeds. This makes it possible to modify naturally occurring plants even over long distances. As this cannot be controlled or prevented in practice, we must develop capabilities to detect and respond to this.

Foresight: Industrial byproducts and household waste will be increasingly promising raw materials for the circular economy once we learn to process them with genetically modified organisms into energy and new raw materials and separate substances from them that could not be separated with previous technology. In the future, bio-based separation and processing methods that are based on genetic engineering also promise to reduce energy consumption by industry and agriculture and the use of chemicals. Observation of the harmful chemicals and microbes in the environment will become an everyday civic activity. On the other hand, environmental risks will also increase due to climate change, chemicalisation and bioterrorism.

New sources since the 1/2018 report:

Genetically modified E. coli uses carbon dioxide as a source of carbon (similarly to plants); https://www.nature.com/articles/d41586-019-03679-x

DNA sequencing used in identifying the routes of the spread of the coronavirus; https://www.technologyreview.com/s/615317/gene-sleuths-are-tracking-the-coronavirus-outbreak-as-it-happens/

Transgenic fungi kill malaria mosquitoes efficiently; https://phys.org/news/2019-05-transgenic-fungus-rapidly-malaria-mosquitoes.html

Pollen carries CRISPR to its target; https://www.sciencemag.org/news/2019/03/corn-and-other-important-crops-can-now-be-gene-edited-pollen-carrying-crispr

An AI that quickly synthesises and identifies protein structures; https://www.chemistryworld.com/news/neural-network-folds-proteins-a-million-times-faster-than-its-competitors/3010451.article

4. General conclusions

The development of genetic engineering increases both threats and possibilities. In a global world, the weaker and narrower the national ability to detect and respond to threats, the more the threats multiply. The possibilities offered by genetic engineering are great in solving many major challenges, and promising development should not be obstructed with unnecessary restrictions. Some of the development is still at a stage in which investment from society is necessary in order to achieve a leap forwards before businesses are prepared

to invest in the development. It is necessary to make changes to regulation, invest in expertise and support development.

13.11.2018

Board for Gene Technology

European Commission
DG SANTE

ECJ RULING ON MUTAGENESIS TECHNIQUES

The Finnish Competent Authority for Directive 2009/41/EC, the Board for Gene Technology, decided on its meeting on October 17th 2018 to send a request to the Commission on the interpretation of the European Court of Justice (ECJ) ruling on July 27 2018 on case C-528/16. The case brought to ECJ concerned the legal status of mutagenesis techniques as stipulated in the Directive 2001/18/EC on the deliberate release of genetically modified organisms (GMOs) to the environment. The ECJ ruling does not refer to Directive 2009/41/EC on the contained use of genetically modified micro-organisms (GMMs). Therefore, it is currently unclear if the ECJ ruling extends to contained use.

Part A of Annex II of Directive 2009/41/EC exclusively states that mutagenesis techniques are excluded from the Directive "on condition that they do not involve the use of recombinant-nucleic acid molecules or GMMs other than those produced by one or more of the techniques/methods listed below". Moreover, Directive 2009/41/EC does not contain anything similar to Recital 17 of Directive 2001/18(EC which played a central role in the justifications of the ECJ Ruling.

During the past years - also after the ECJ ruling - the Board for Gene Technology has received several requests regarding the legal status of a certain type of mutagenesis, namely a situation where site-specific mutagenesis results in a deletion in the genome without leaving any foreign genetic material in the organism. As deletion mutagenesis is a commonly used technique in the basic research field within the Union, the Board now wishes to have a harmonized interpretation by the Commission Legal Service on the applicability of the ECJ ruling of such techniques in contained use.

The Board, which is also the Competent Authority for Directive 2001/18/EC, also wishes to have further clarifications as to the deliberate release of GMOs produced with mutagenesis techniques. The issues needing clarification are as follows:

- The ECJ ruling specifically mentioned chemical and radiation mutagenesis as techniques which are out of scope of Directive 2001/18/EC because they have a long safety record. Transposon mutagenesis is a technique that has been used for thousands of years for maize and several decades for fruit flies and bacteria. Should ECJ decision be interpreted so that transposon mutagenesis is also out of scope, or is it just out of scope for these particular organisms?
- The ECJ ruling stressed the importance of a long safety record for the exempted mutagenesis techniques, which indicates that the safety of a mutagenesis technique should be

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evaluated after a certain time point. How is the Court Decision to be interpreted as to the time point and criteria for evaluating the safety of a mutagenesis method?

- How should the ECJ ruling refocus the MS inspections on imported products, what are the most relevant analysis methods for new mutagenesis techniques in accredited laboratories and is there any estimate on the costs for supervision?
- How is the ECJ ruling interpreted as to the LMO definition in Convention of Biological Diversity (CBD); i.e. are the obligations of the Cartagena Protocol categorically applied to organisms modified with novel mutagenesis techniques?
- How should the ECJ ruling be applied with regard to the regulations on the transportation of dangerous goods; i.e. does the Court Decision mean that all the organisms mutagenized with site-specific techniques should be treated as dangerous goods?

The Board also wants to address the recent COM proposal for a regulation on the making available on the market of CE marked fertilizing products (2018/C 346/46). The proposal aims in facilitating circular economy when it comes to fertilizing products. The Board has handled several requests by biotech companies wanting to recycle their Class 1 GMM fermenting waste through composting to produce fertilizers to produce added value. Additionally, composting is considered environmentally more sustainable than incinerating the wet biomass. Whereas the fermentation process itself is clearly contained use, marketing the composted product potentially still containing living GMOs would be subject to the Part C notification procedures of Directive 2001/18/EC. Such an expensive notification process is not likely a suitable option for the industry. As organisms produced with new mutagenesis techniques are an appealing tool for the biotech industry, the Board wants to point out that the legal and practical problems about handling fermenting waste are likely to scale up after the ECJ Ruling. The situation is not due to specific national legislation, and hence needs to be addressed at the EU level.

On behalf of the Board for Gene Technology

Secretary General Kirsi Törmäkangas