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Stakeholder 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

Discussed and finalised in the Ad-hoc Stakeholder meeting on 10 February 2020

Background

The Council has requested [1] the Commission to submit, by 30 April 2021, "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).

To respond to this Council's request, the Commission is collecting contributions from the stakeholders through the questionnaire below. The study covers all new genomic techniques that have been developed after 2001.

Instructions

For the purpose of the study, the following definition for new genomic techniques (NGTs) is used: techniques that are capable of altering 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-organisms and derived food and feed products obtained by NGTs for agri-food, medicinal and industrial applications and for research.

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 specific NGTs/organisms, please indicate this in the reply.

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

Guidelines

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 15 May 2020 (close of business) to submit the questionnaire via EUsurvey.

QUESTIONNAIRE

Please provide the full name and acronym of the EU-level association that you are representing, as well as your Transparency Registry number (if you are registered)

If the name of the association is not in English, please provide an English translation in a parenthesis

European Forum of Farm Animal Breeders (28175274067-75)

Please mention the sectors of activity/fields of interest of your association

Animal Breeding and research in animal breeding and reproduction

If applicable, please indicate which member associations (national or EU-level), or individual companies /other entities have contributed to this questionnaire

EFFAB and FABRE TP membership (animal breeding companies and cooperatives, national umbrella associations and research institutes) has helped to provides answers to the questionnaire.

If applicable, indicate if all the replies refer to a specific technique or a specific organism

Responses from EFFAB and FABRE TP refer to terrestrial and aquatic animals for breeding purposes. Animal breeders provide breeding animals, hatching eggs and germinal products to land and fish farmers. EFFAB-FABRE membership covers a large majority of animal breeding commercial and research activities in Europe. However, we would like to flag before the start of the survey that we don't cover all of current and future or new activities could be called farm animal breeding in the future (e.g. insects). And we are not referring here but could be interesting in the future.

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

* **1. Are your members developing, using, or planning to use NGTs/NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

We would like to separate the use/development/plans to use NGTs and NGTs products. European animal breeders are not currently using NGTs for commercial purpose. So far, no genetically modified animal (transgenesis) has been approved for human consumption until now for farming and commercial purposes. A part of the membership of EFFAB is using the technology as a research tool, with not further intention at this moment to market any product. The reasons are regulation uncertainty and doubts about public acceptance (because they are legally GMOs). We need more knowledge and feedback on safety before a large-scale use of these technologies. There are ongoing projects where traits, market possibilities, legislation, consumer acceptance and IPR are discussed. Members of EFFAB are studying the possibility to tackle animal diseases and improve animal welfare (85% of EFFAB and FABRE TP members investigating with this tool) Details on future applications are given in question 10

* **2. Have your members taken or planned to take measures to protect themselves from unintentional use of NGT-products?**

- ( ) Yes
- (●) No
- ( ) Not applicable

* Please explain why not

Not applicable in short term. However, EFFAB position is that Breeding and AI companies are discussing the feasibility of introducing specific legal provisions in their contracts to avoid importing animals obtained by GE as well as genome edited semen form third countries and other EU partners. Dairy sector has proposed guidelines to identify animals obtained by GE. The main issue is how to control that these provisions / guidelines are well observed as no detection method is available. We don't also know how NGT products are defined in other countries

* 2 bis. Have you encountered any challenges?

- (●) Yes
- ( ) No

* Please provide details

Detection methods are not available. To have a common definition of NGTs

*** 3. Are you aware of initiatives in your sector to develop, use, or of plans to use NGTs/NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

- projects only as a research tool and (or) as a topic for research with the objectif to study potential application and possible concerns and opportunities of benefits and sustainability.
- a handful of initiatives on the use of NGTs for developing novel traits. Improvement of the genetic potential in trait complexes such as disease resistance
- production and marketing of genome edited hornless cows in NA. Genome edited cows to improve resistance to several diseases (tuberculosis, Foot-and-mouth disease), heat tolerance / adaptation to climate change.

Gene editing regulation tracker hosted by Genetic Literacy Project cites 78 products and research projects.
https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/
These are broadly distributed worldwide:
・North America (USA, Canada): 12, including Aquadvantage salmon, cows, pigs, catfish, lizards, coral
・Central and South America (Brazil, Chile, Uruguay, Argentina): 9, including fruit flies, cows, tilapia, horses, salmon
・Africa: 7, chicken, rhino, mostly cows
・Europe and Israel: 12, including pigs, sheep and chickens, mice, flies
・Asia (concentrated in China, India and Japan): 29, including pigs, monkeys, dogs, cows/heifers, goats, mosquitoes, mice, rats, coral, and fish (tuna, anchovy, red sea bream)
・Australia and NZ: 9, including toad, carp, cattle, chickens, mice, coral

*** 4. Do you know of any initiatives in your sector to guard against unintentional use of NGT-products?**

- ( ) Yes

- (●) No
- ( ) Not applicable

* 4 bis. Are you aware of any challenges encountered?

- (●) Yes
- ( ) No

* Please provide details

A specific framework for animals would be of interest, since issues are different than in plants. For instance, unintentional use/release of NGTs in environment is unlikely for livestock, even if possible (e.g. experimental GE released in slaughterhouse). There will be a potential risk for unintentional use of NGT-products, because there are no verification procedures, available detection methods and mandatory requirement to provide evidence of the use of NGTs.

* **5. Are your members taking specific measures to comply with the GMO legislation as regards organisms obtained by NGTs?**

Please also see question 8 specifically on labelling

- ( ) Yes
- (●) No
- ( ) Not applicable

* Please explain why not

The requirements in GMO directive cannot fit with the livestock sector and doesn't allow to fulfil the market procedure to place NGTs products obtained by NGTs in the market. Legislation outdated versus the scientific progress in this field of science. Further, the focus of the current legislation is only taking into account technology (NGT is considered GMO) and not the genetic manipulation of the trait itself.

* 5 bis. What challenges have you encountered?

The GMO directive’s risk evaluation is not designed to assess NGTs in livestock. Unlike the process to develop GMO products, gene editing’s highly targeted approach allows us to make small, precise changes to an animal's specific DNA sequence and no detection is method is available.

* **6. Has your organisation/your members been adequately supported by national and European authorities to conform to the legislation?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe what type of support and what best practices you can share

Not applicable to market products. Relevant for research projects.
Members of EFFAB are part of projects where one of the work packages concerns legislation and the updating of the national use of NGT, in collaboration with national authorities

In research and innovation, requests and guidelines, support from National authorities for securing responsible research and innovation (RRI), particularly in this field.

National authorities as a discussion partner for the future on opportunities for market, what is needed in the future to meet challenges

* **7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

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

Breeding companies and associations have already have a long-standing experience in tracing semen, pedigrees and performance records within breeding programs at the animal breeding level. For cattle, there are further possibilities because of the individual identification. All data are recorded in worldwide/national /companies databases. It would be easy to collect (if available) and store additional information about NGTs to ensure traceability as well as long term evaluation of the impacts.

GMO traceability procedure could be applied for NGTs based on goodwill of economic players, but when it comes to control, it may be impossible to detect frauds e.g. unregistered NGTs obtained using single base mutations, which may have occurred naturally. For traceability purposes and to avoid fraud, an international initiative could be set up to enforce the whole genome sequencing of all marketed bulls and their parents, so it could be possible to detect neomutations pointing to a genome edition event. This would be costly and partly inefficient, since it would still be possible to genome edit females without any control. In Norway, there is the national GMO surveillance programme. For established NGT products in the future the current infrastructure to monitor GMOs could be used.

Furthermore, NGT-animals have to be notified for market approval in the EU (under GMO legislation), applicants must provide an analytical method (difficult) that will be able to identify NGTs animal lines. Traceability describes a completely documented chain of the development of NGT-animals as well as the commercialization of NGT-products. For the traceability of NGT-products different information are necessary:
- Gene or SNP of interest, gene function and signalling pathway
- The genetic modification strategy: (1) engineered endonuclease technology (e.g. CRISPR/CAS9, microinjection), (2) DNA construct, including the nature and function of the various elements, (3) breeding organisation and the laboratory, (4) genetic
-General background information on the recipient animal, founder animals and the donor organism
- Minimizing off-target effects; information of methods to reduce the off-target effects, provide evidence of security for off-target effects
- Purpose of NGTs and NGT-products

* **8. Are your members taking specific measures for NGT-products to ensure the compliance with the labelling requirements of the GMO legislation?**

- ○ Yes
- ○ No
- ◉ Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

not applicable

* What best practices can you share?

not applicable

* Please explain why not

not applicable

* 8 bis. What challenges have you encountered?

not applicable

* **9. Do you have other experience or knowledge that you can share on the application of the GMO legislation, including experimental releases (such as field trials or clinical trials), concerning NGTs/NGT-products ?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please describe for the:

- ☑ Agri-food sector
- ☐ Industrial sector
- ☐ Medicinal sector

Agri-food sector

In Norway, the current national bodies are quite effective when it comes to approve experiments. Two separate applications have to be sent to two different governmental agencies.

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

The maximum file size is 1 MB

B - Information on research on NGTs/NGT-products

* **10. Are your members carrying out NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify including subject, type of research, resources allocated, research location

R&D project on Genome Editing, to optimize the technology, both in terms of yields and safety, and to evaluate its potential and drawbacks. Putative applications would be for research (validation of recessive mutations causing genetic defects)
Research conducted by EFFAB and FABRE TP members is related to animal health and welfare
- Genome editing in the bovine embryos ; INIA and Bonn University
- Use of DNA nucleases to generate hornless cattle Bonn University
- Diseases traits in Salmon
- basic research focusing on identification of targets
- Pig castration – Hendrix Genetics and Roslin
- Gene editing research in pigs: Researchers in Germany studied how to silence genes in pigs using a gene editing technique called ZFNs as a first step to gene edited pigs for agriculture.
- PRRS Virus-resistant pigs: Researchers at Edinburgh University Roslin Institute and the UK company Genus developed pigs resistant to the virus that causes Porcine Reproductive and Respiratory Syndrome (PRRS), one of the costliest animal diseases.
- African and classic Swine fever-resistant pigs: Researchers at the Roslin Institute used ZFNs to develop pigs resistant to African swine fever.
- Influenza-resistant chickens: Researchers at the Roslin Institute and Imperial College London took first steps in developing influenza-resistant chickens to help curb the spread of avian flu to humans.
- Chicken research: Researchers at the Roslin Institute used a gene editing technique called TALENs to begin developing hens that do not produce their own chicks, for use as surrogates to lay eggs from rare breeds, as well as hens that produce human proteins in their eggs for medical purposes.

* **11. Are you aware of other NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify

Q3 already partly responds to this question. Most of the activities in the livestock sector on NGTs are still at the research stage. The link provided on question 3 gives a quite large overview. https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/

Research in NGTs is done to improve animal health, resistance to animal diseases and to breed animals without some identified inherited defects or characteristics without compromising the genetic diversity. The absence or presence of a "gene" keeping the diversity of the population.
Some of the research is done with livestock animals but applications use is related to human health or the medical sector.
Recombinetics and its subsidiary Acceligen are making research to produce genome edited hornless cattle in partnership with SEMEX. Also for bovine resistant to Bovine tuberculosis and Foot-and-mouth disease virus. And edition of animals to improve heat tolerance (slick gene ?).
Pigs with organs for humans: Researchers at the Center for Innovative Medical Models (not animal breeding sector) Facility of Ludwig-Maximilians University used CRISPR to begin developing pigs with organs that are more likely to be accepted when transplanted into a human.
Sheep with larger muscles: Center for Research in Transplantation and Immunology (ITUN) used gene editing to develop larger sheep with more developed muscles.
Human research in pigs ; Technische Universitat Munchen uses GE pigs to study some human diseases (cancer, diabetes, Alzheimer...)
Gene editing (ZFNs) in pigs to silence genes in pigs
Bill Gates Fondation : GE to modify the genes of tropical cattle in order to increase milk production and their heat resilience
Genome editing experiments for agricultural applications in food animal species that have resulted in live edited offspring. (Thomas Frederick Bishop, and Alison Louise Van Eenennaam J Exp Biol 2020;223: jeb207159)

* **12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling on mutagenesis?**

Court of Justice ruling: Case C-528/16 http://curia.europa.eu/juris/documents.jsf?num=C-528/16

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe

Research projects has been resized and reorganized, putting less emphasis on the identification of commercial applications and technical advances compliant with a routine use.

Other company has no plans for research and development, product development or commercial launch into EU following ECJ ruling.

Other companies has moved their research activities to 3rd countries and concluded collaborations with knowledge institutes in 3rd countries or governments

*** 13. Could NGT-related research bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

Main benefits could be :
- the improvement of animal health and welfare (85% of EFFAB and FABRE TP members working with these techniques aim to improve them through disease resistance or avoiding manipulations in livestock (castration, horns)
- to improve efficiency and safety of the technology
- to validate genes and mutation of interest, when several putative causative variants have been identified in a QTL region
- to identify genes of interest and their beneficial mutations. To date, most of cattle known mutations in OMIA are genetic defects!
- To protect genetic diversity
- better understanding and possibly improvements of Genetics, diseases and animal welfare of farm animals
- Improving breeding animal product: best genetic composition, increase frequency of beneficial alleles, breed for traits impossible to breed for (no genetic variation for example - diseases), etc.

Genome Editing is another tool for genetic improvement in farm terrestrial and aquatic livestock. Quantitative genetics, genomics and other tools are still needed. There are currently very few traits that can be modified by NGTs. That's why the use of the technology is interesting to improve disease resistance, whilst continuing a breeding program in a population. We can add, replace or delete a small part of the genetic information keeping the whole diversity in the population and avoiding the funnel effect.
An example : Pathogen resistance (e.g. Porcine Reproductive and Respiratory Syndrome disease (PRRSv) of domestic swine, an economically devastating disease in North America, Europe and Asia. It is estimated the impact of the PRRS disease to EU livestock producers exceeds 1.5B euro every year, (https://thepigsite.com/disease-guide/porcine-reproductive-respiratory-syndrome-prrs) which includes costs due to loss of productivity and efforts to implement PRRS control approaches such as measures to prevent entrance and spread of infection in facilities, animal transport and management, and vaccination of breeding populations. Torrents, D., Miranda, J., Pedrazuela, R., Ramirez, A., Linhares, D. (2019) Economic benefit of an increase in piglets weaned after achieving PRRS stability in a large integrated pig production system in Europe. Abstract presented and accepted at ESPHM 2019 (https://thepigsite.com/articles/analysing-the-impact-of-prrs-in-europe) Vaccines and other mechanisms to prevent PRRS have been largely ineffective, even after years of industry and academic study. Gene editing has the potential to greatly improve the lives of pigs around the world, reducing the need for antibiotics and improving their health and wellbeing. And reducing food waste at the farm level.

*** 14. Is NGT-related research facing challenges in your sector/field of interest?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

Farm Animals have a long generation interval, depending on the specie. Their maintenance in confined barns (e.g. till completion of safety procedure) could be costly. Genome editing on zygote is a technical challenge in terms of yields and efficiency (high level of mosaicism). That's why most groups work on fibroblasts and use somatic cloning to produce the living animals. This strategy combines 2 touchy technologies, raising societal concerns. Public and food supply chain acceptance are of course the major challenge.

Legislation uncertainty and costs issues prompt Research Institutes to limit their investment in these technologies.

AS explained in question 13, monogenic traits present good targets for genome editing, but many traits are polygenic - caused by many genes. That´s why, it is so important to know the functions of the genes (DNA segments) as well as to determine the effects of NGTs on the functions of other genes which are involved in the signalling pathway. Especially, the signalling pathways of the immune system are very complex and until now not completely investigated.

Extensive scientific research needs to be carried out. Identification of long-term effects and off-target effects as well as residues in the genome etc. should be further investigated and related projects have to be supported by research funding programs. The results and NGT-products outside EU can be verified, proven or disproved by research. In order to carry out more research further application of NGT-animals/products have to be regulated by EU law, because more NGT-animals will be necessary to investigate long-term effects.

*** 15. Have you identified any NGT-related research needs/gaps?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify which needs/gaps, explain the reasoning and how these needs/gaps could be addressed

- research needs on public perception, mechanisms of awareness and knowledge on science by citizens
- Methods to detect and distinguish modifications obtained by technology and natural mutations
- lacking independent (Public funded) research into unintended side effects and fully RRI involving sufficient stakeholders and concerns in a responsible way
- To efficiently use NGT, we need to know which gene to target and which mutation to introduce. Thus, research is also needed to identify genes of interest and their beneficial mutations. To date, most of known mutations in OMIA are genetic defects. Only a few genes/mutations of interest have been identified for monogenic traits, which are the most interesting targets. Most of the traits under selection are polygenic and only QTLs and candidate mutations have been identified.
Knowledge is required on gene function and gene networks, in order to anticipate the possible outcomes of introducing novel mutations. This is crucial to reduce uncertainty and putative adverse side effect
- Risk / benefit assessment: Continuously data collection and evaluation as well as long term studies have to been carried out to analyse the influence of NGTs on animals, human and environment.
- Since the development of disease-resistant animals (e.g. PRRSV, African swine fever virus) is less successful, further investigations are necessary. Important remarks for further investigations: increase the number of animals, use different virus strains, repeatability, long-term tests, breed differences, ethical conditions, etc.

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

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C - Information on potential opportunities and benefits of NGTs/NGT-products

*** 16. Could NGTs/NGT-products bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Some of the opportunities of improvement related before in the questionnaire can be obtained by conventional and genomic selection (disease resistance..). However, selection is a time-consuming process, even when using genomic selection. Simulation have already been published, suggesting that high gain (X2 compared to genomic section) could be obtained. The major benefit form NGT is thus to speed up the process. This could be crucial in a context of fast changing environment and consumer demand, or to adapt current breeds to an agroecological context, where animals must cope with diverse and less controlled environments. NGTs could thus help reducing the cost of selection programs and thus contribute to the competitiveness of the sector.

Some of other traits selection cannot be achieved by conventional breeding, because of very low genetic variation or the trait is present in a related specie (PRRSv)

NGT-products could help increasing the genetic progress on a diversity of traits (including traits related to climate change, environmental footprint reduction as well as animal health and welfare)

NGT-products may also help maintaining rare alleles in the population, which otherwise tend to be lost due to the selection process (effect of rare alleles is not well estimated, and they are thus overlooked). It could be done combining NGTs with other tools like genomics.

NGT may also help dealing efficiently with genetic defects, especially in local breeds / endangered breeds, making it possible to correct unfavorable alleles without any adverse effect on effective population size and population diversity, which usually occur when breeding organization tend to eradicate genetic disease.

NGT may help breaking negative genetic correlation between traits which result from a strong genetic linkage of favorable/unfavorable alleles

Castration in pigs during farming could be avoided (improving farmers management at the farm level)

To cause sterility of farmed fish to prevent genetic interaction with wildlife relatives is interesting for the preservation of nature and biodiversity

Improvement of disease resistance can reduce the use of medicines and antibiotics; benefits for farmers, agriculture, food security, human and animal health and environment

https://www.youtube.com/watch?v=Mj7OZf1RseQ

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

An example is disease resistance : In circumstances where resistance or resilience is observed in a related species, crossbreeding is simply not possible. Genome editing could bridge these gaps. One example of this is resilience of wild suids to African swine fever virus while domestic pigs can suffer from severe disease. It is not possible to crossbreed these species, so introduction of the genetics underlying resilience is not possible by this route.
Addressing PRRSv of domestic swine also. ; treatment, cure and eventual eradication of PRRS disease in swine can only be achieved through gene-editing. It is not possible through traditional breeding.
To be able to make genetic improvement that could not be done by conventional breeding because of the absence of genetic variation
Already mentioned, a better preservation of genetics resources
NGTs could also be used to produce animals that could validate causative mutations to be included in conventional breeding genomic selection prediction with a higher reliability to increase genetic progress and /or to prevent genetic defects
https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1583-1
https://academic.oup.com/af/article/9/3/6/5522878

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Some of the examples have already indirectly been explained in previous questions.
- Reduction of Antimicrobial Resistance : the use of antibiotics can be reduced if we are able to improve the animal health at the farm level. Animal infectious diseases needs treatments, even in the case of virus infections that can be responsible of a lower health status in animals. They will be more affected by other bacterial infections that needs treatments with AB. A reduced use of antibiotics is beneficial for farmers, agriculture, food security, human and animal heath, food waste and environment
- Animal diseases increases mortality (direct or indirect ; to control some animal diseases, current legislation requirements are the killing of all the animals in a farm/area, including healthy ones) These control measures incurs on food waste and genetic resources waste in open genetic systems
- improving animal welfare, avoiding castration at the farm level
- NGTs could reduce impact of livestock in climate change
- NGTs could reduce the cost of breeding thanks to the speed up of the process
- NGTs could decrease interference with wildlife (fish farming)
- Environmental positive effect preserving genetic resources of breeding populations and the benefit of keeping achieved genetic improvement
- Responsible research and innovation on NGTs and their responsible could build bridges between scientists, farmers and citizens and better connect livestock with consumers

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

Under an updated regulation taking into account the specificities of animal breeding and the techniques.
Also under public acceptance of the technique and no confusion with other techniques involving foreign genetic material and are commonly called GMOs by citizens
Without risk for animals, humans and the environment

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

Yes Already mentioned before related to the difficulty to include these traits by conventinal breeding ; disease resistance, sterility of farmed fish, pigs that remain in a pre-pubertal state avoiding castration...

* **18. Do you see particular opportunities for SMEs/small scale operators to access markets with their NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Not with current legislation in Europe. The procedure under GMO directive is not appropriated, with very high administrative and implementation burden for animal breeding. It means very long procedure and high costs, impossible to assume by SMEs

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

- ( ) Yes
- (●) No

* Please explain why not

EFFAB answer is neutral and depends on the sector. Answer to this question could be yes by definition. EFFAB membership sees opportunities on patenting technology to recover investment on research and open competition within companies in animal close breeding systems. However, patenting technology or a product (line) obtained is quite different. From an animal breeding perspective, it differs depending on the breeding system; open or close. Patenting or protecting technology and/or animals on the ruminant open breeding system, could be quite troublesome, putting in a difficult position breeders and farmers. Acceptance by breeders/farmers will be extremely rare. However, protecting lines on the pig and poultry breeding sector could be an opportunity. Patenting could be an opportunity but it's not required or needed to protect technology and lines. On this question, a variety of answers, were collected. Breeding companies in animal close breeding system are already protecting their genetic material from other companies as they own male and females lines. In that case, we can see opportunities.

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

The maximum file size is 1 MB

D - Information on potential challenges and concerns on NGTs/NGT-products

* **20. Could NGTs/NGT-products raise challenges/concerns for your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Some of the answers were given before answering to previous questions, explaining the context.
- Public acceptance
- Risk of unfair competition with other countries if EU law doesn't apply in the same way for imported products without available detection methods.
- Lacking research and knowledge of unintended negative effects
- NGTs product development and market approval uncertainty and cost ; a higher risk of concentration of bigger companies
- there is a risk for the genomic selection system in international breeds if genome edited animals are imported without traceability: their progeny will introduce bias in the reference population, resulting in a loss of genetic progress

* Are these challenges/concerns specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

Public acceptance. Because of the ruling there is a confusion between techniques.
There are no detection methods available for NGTs.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

The environment, humans and animals are complex systems or organisms and it is often challenging to foresee consequences of NGT. Hence, there is a need for broad, independent and often costly studies and involvement to secure RRI, including anticipation, reflexivity, inclusion, responsiveness, openness, educating stakeholders and contributing to the development of a adapted regulation. Producing de novo mutations, which have never been observed previously, could led to unexpected results due to adverse side effects. It's crucial to evaluate properly animal bearing de novo mutation before any large-scale use as reproducer.

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

under an adapted legal framework for animal breeding

* Are these challenges/concerns specific to NGTs/products obtained by NGTs?

- (●) Yes
- ( ) No

* Please explain

Side effects

* **22. Do you see particular challenges for SMEs/small scale operators to access markets with their NGTs /NGT-products?**

- (●) Yes
- ( ) No

* Please explain and provide concrete examples and data

With the current EU legislation, SMEs in Europe do not have the finances to put novel products on the market. NGTs as CRISPR are easy to perform, however it needs public research funded that could cover the costs of testing and studying a range of concerns and issues through comprehensive RRI Projects. This is even more important for the animal breeding sector. Testing in animals is expensive.

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

already answered on Q19 giving a balance on both side concerns/opportunities and difference between sectors

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

E - Safety of NGTs/NGT-products

* **24. What is your view on the safety of NGTs/NGT-products? Please substantiate your reply**

The question suggest non-NGTs are all safe, this is not true. Nature is not safe by itself. There is no technology without risk. EFFAB members priority is safety, animal and human health. Make sure that these techniques are giving the expected trait to animals, and nothing else.
The technology should be improved to reduce off-targetting and to manage them. This is probably a not crucial concern, since neo mutations appear naturally at each generation (some of them producing genetic defects, some others providing opportunities for selection). And because off-targeting can be controlled by whole genome sequencing in order to avoid spreading deleterious mutations.

Off targetting effects are important but also epigenetic as well as epistatic effects, with unknown consequences, at this stage. The difficulty of each of these challenges will vary with a large number of factors, including the characteristics of the technique used, the method and timing of delivery, and the characteristics of the target cells. Until now, the safety of NGTs and NGT products cannot be answered, more projects are necessary to identify the safety of NGTs as well as to describe risks related to the product or its technology.

Using known mutation from one breed to another (introgression) reproduce what can be made by crossing. This application seems to be safe and such products should not require an extensive evaluation.

Creating de novo mutation can lead to unexpected side effects and this application should require an evaluation, proportionate to the risk for animal and human health.

Animal integrity is a specific and important issue.

Escapees of farmed fish can be become safe if fishes are sterile. (safety of the product for the environment)

*** 25. Do you have specific safety considerations on NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please explain

Traceability and reasonable costs of market approval

Detection methods and harmonised procedures for the detection and idenification

Off-target effects evaluation

Edited animals should be tagged to be able to assign responsibility and liability for damages. It would also enable researchers to better track the flow of gene edits through a population animals.

In addition, we would like to mention that the use of NGTs products as food is nutritionally equivalent. We don't see any special safety consideration regarding food.

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

F - Ethical aspects of NGTs/NGT-products

*** 26. What is your view on ethical aspects related to NGTs/NGT-products? Please substantiate your reply**

We don't see specific ethical considerations, since concerns are the same than conventional animal breeding and selection. The ethical issues are related with the purpose of different breeding goals, not with the technology (NGTs or genomics or quantitative genetics). On this purpose, EFFAB has developed a code of best practices of responsible breeding. We have a further question related to the ethical issue if we don't use technology available to increase sustainability of livestock, assuming that the technique is not representing a higher risk than alternatives. The current unaffordable legislation and very difficult to implement could represent an ethical issue on this respect.
We would like to draw your attention on some projects and reports running or published on ethical/societal considerations on NGTs and animal breeding.
http://www.sage-animals.com/
http://www.cbgp.upm.es/files/Report_consumer_attitudes_to_gene_editing_agri_and_aqua_FINAL.pdf
https://citarea.cita-aragon.es/citarea/bitstream/10532/4768/1/2019_311.pdf (the file to upload was more than 1 MB but we can make it follow by email)
https://english.rda.nl/news/news/2019/06/26/crispr-cas-in-animals
https://cogem.net/app/uploads/2019/07/CGM180501-01-CRISPR-Animals-Implications-Genome-Editing-2018_HR1.pdf
Many other publications from national ethics committees have been published
https://www.mpg.de/13509625/statement-genome-editing-englisch.pdf

*** 27. Do you have specific ethical considerations on NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please explain

Unintended impacts on animal Health and welfare as well as ecosystems from farm escapees (only for aquaculture)
Gene editing technologies offer enormous potential for scientific advancement in fields such as medicine and agriculture, but their use also raises serious public policy concerns.

Please upload any supporting documentation for this section here

The maximum file size is 1 MB

G - Consumers' right for information/freedom of choice

*** 28. What is your view on the labelling of NGT-products? Please substantiate your reply**

EFFAB members are not at the end of the food chain. Animal breeding has/can inform farmers as genome edited animals or germinal products from them have benefits for farming and society. EU market should have same labelling rules. However, products coming from 3rd countries should be labelled same as in the EU. This could be essential for public acceptance. However, control is a challenge since no detection method is available.

Labelling could have benefits such as being transparent, respecting the rules, social acceptance. etc.

After farming, the question is to know if there is a need to inform the consumer about the selection or breeding method/tool if it doesn't affect the characteristics of the final product.

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

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H - Final question

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

- (●) Yes
- ( ) No

Please provide your comments here

EFFAB is representing a large number of commercial breeding activities and refer to terrestrial and aquatic animals for breeding purposes. Animal breeders provide breeding animals, hatching eggs and germinal products to land and fish farmers. EFFAB-FABRE membership covers a large majority of animal breeding commercial and research activities in Europe but we would like to flag again that we don't cover all the livestock breeding sector and new activities could be called farm animal breeding in the future (e.g. insects) and we haven' referred above to them.

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

32880089-6cdd-4750-9ff9-2bac5a67cc94/introgression_vs_GE_.pdf
4ab0ade0-8115-4ac9-a566-5c7961bedba3/NBT_Survey_Results_June_2019.pdf

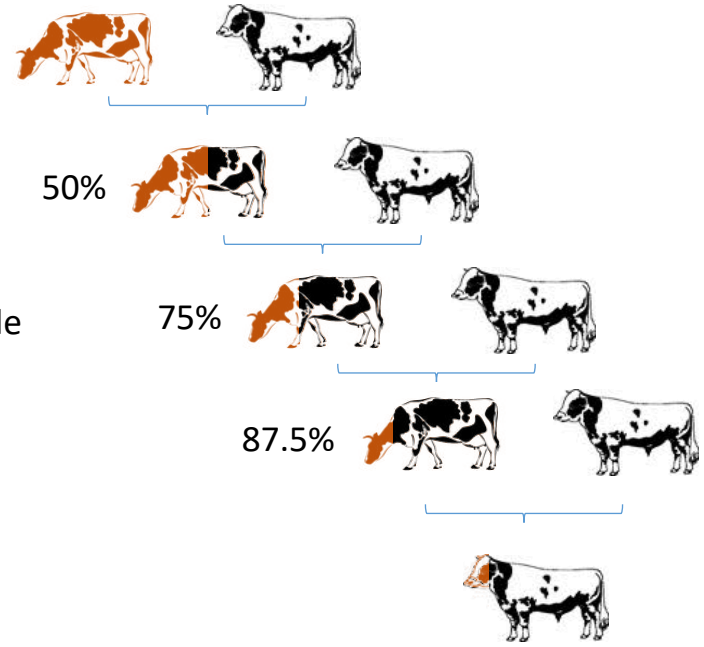
Contact

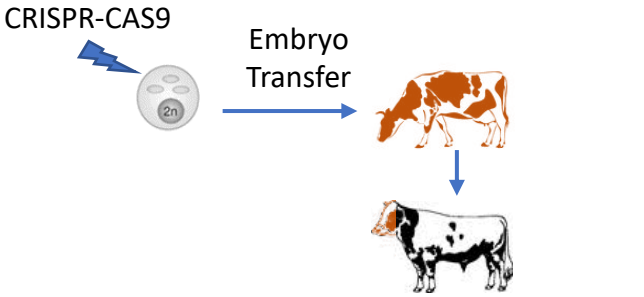
SANTE-NGT-STUDY@ec.europa.eu

One technology, many applications

- Introducing alleles from one breed to another
  - Speed up genetic progress (x2) and save time (7-10 years)

Introgression process:
Crossbreeding followed by multiple generations of backcrossing





Same animals
but subjected to different rules

RESULTS OF THE NEW BREEDING TECHNIQUES SURVEY

1. Introduction

The Farm Animal Breeding and Reproduction Technology Platform (FABRE TP) is the main contact point for farm animal breeding and reproduction promoting research, technological development and innovation for sustainable animal breeding and reproduction in Europe. FABRE TP connects EFFAB members from the private sector and knowledge institutes and Universities.

On 25th of July, the European Court of Justice (ECJ) published ruling C-528/16 where it is stated that all organisms obtained by mutagenesis are GMOs, in sense of the definition of GMO directive (2001/18/EC). It means that the approval process under the scope of GMO directive for mutagenesis targeted animals will be costly and lengthy in EU and can put European Animal Breeding and Research sectors at a competitive disadvantage compared to other regions. November 13, 2018 the European Commission's Scientific Advice Mechanism (SAM) Group of Chief Scientific Advisors has published a statement providing a scientific perspective on the regulatory status of products derived from gene editing, and the consequences for the innovation in agriculture sector of the ruling. The ruling is also difficult to implement and virtually impossible to enforce, given that many gene-edited products may be indistinguishable from products changed by natural processes or with conventional breeding techniques, as reconfirmed by the report of the Joint research Centre "Detection of food and feed plant products obtained by new mutagenesis techniques", published on 26 March 2019.

FABRE TP prepared a NBT survey in order to collect information on the effect of the ruling on animal breeding sector, competitiveness and research opportunities and examples of Genome Editing (GE) applications. The survey collected responses between 16 November 2018 and 3 April 2019. In total 28 responses were collected, however not all the respondents responded to all the questions.

2. Survey Results

a. Genome Editing opportunities :

According to the survey results, the main reason for FABRE TP members to apply the genome editing is that GE is a **powerful research tool to improve animal health, animal welfare, environmental sustainability** and, to a lesser extent, productivity. It also improves **understanding of biological mechanisms of animals** and i**mportant traits that are hard, costly or timely through traditional breeding methods**. GE can help to reduce environmental footprint, the use of chemicals and antibiotics. It provides faster adjustment of genotypes to market needs.

GE speeds up spread of identified major alleles from one source population to a closed breeding population keeping genetic diversity. It has a return on investment and potential for other management (genetic activity) to address and solve target problems.

b. FABRE TP members and Genome Editing :

Survey results show that **46,4% of FABRE TP members is currently conducting research on GE** and both germinal (88%) and somatic cells (53%) are intended to be modified.

50% thinks about introducing legal protection for marketing GE (e.g. patent). On the other hand, almost 72% of the respondents do not plan to use GE and 67% has no plans to market GE products within the EU.

c. Genome Editing "thinks to solve" :

The main reason why members might be reluctant to apply GE is the **public concern**. Also, the mechanisms and consequences of applying GE are still unknown to a large extend. **Additionally, further research and knowledge on possible negative side effects is requested** before market intentions can be done.

d. Consequences of the ruling :

FABRE TP members considered that the **ruling will have a very large consequences on the competitiveness of EU companies**. The survey results show that due to the ruling, EU companies could stop research to produce GE animals in the EU, stop their R&D activities in EU on GE and move outside the EU to continue their work on GE. Additionally, it was mentioned that confusion about mismatch between EU regulations with other countries in the world could occur.

As the GE animals are now regulated as GMOs, most of the members believe that will cause a bad image due to low social acceptance of GMO and there must be a requirement of control mechanisms of product and competitions against products from third countries. In one response, it is stated that regardless the regulation, the industry needs to do the research and innovations on GE within the framework of Responsible Research and Innovation (RRI) in EU research programs. It implies that it must be anticipating, reflexive, responsive and inclusive of all relevant stakeholders, including the skeptical consumer segments and NGOS. Pushing the regulations towards a much more liberal practice may work the opposite way of what the industry wants, i.e. consumers that become even more skeptical to GE animals/GMOs.

For the new legislation concerning GE animals, 60% of the members mentioned that the legislation should be product based, instead of technology based.

e. Preliminary conditions :

Regarding the conditions to be met before applying GE, the respondents to the survey stated that **clear regulations are needed with different criteria than GMO**, allowing GE in Europe and the world. Public sector, consumer and market acceptance are also needed. Mechanisms and consequences to apply GE in reproduction and animal breeding need to be clear. Scientific risk controls and identified target alleles are important. There should be more studies on environmental impact of the new breed. GE should be safe for the animal and contribute to animal welfare.

f. Research areas of the FABRE TP members :

Members also mentioned about their objects of their research about GE in their company/institution. These are:

- Sexual development in salmon
- Hornless cattle with elite genetic merit
- Naturally castrated male piglets born
- Increasing animal disease resistance and resilience
- Animals with gene knockouts
- Increasing understanding of biological mechanism and gene regulations
- Climate adaptation & mitigation
- Basic mechanisms like albino-gene, known QTL's, to study the method, learn about transfer protocols and biological success rate in cooperation to universities

3. Conclusions

As the outcome of the survey, it is stated by most of the respondents that **clearer, safer and modern regulations on GE are needed** - with different criteria than GMO - as it offers possibilities. However, as the acceptance from public sector, consumer and market is important, the private sector needs to do the research and innovations on Genome Editing within the framework of Responsible Research and Innovation.