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COMMISSION STAFF WORKING DOCUMENT

Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16

Contents

1. Executive summary

The Council of the European Union[1] asked 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* ***new genomic techniques*** *under Union law*. It also asked the Commission to submit a proposal accompanied by an impact assessment, if appropriate in view of the outcomes of the study, or otherwise to inform it of other measures required as a follow-up to the study.

For this study, 'new genomic techniques' (NGTs) are defined as techniques that are capable of altering the genetic material of an organism and that have emerged or have been developed since 2001, when the current legislation on genetically modified organisms (GMOs) was adopted. Information and views on the status and use of new genomic techniques in plants, animals and micro-organisms for agri-food, industrial and pharmaceutical applications were gathered from Member States and EU-level stakeholders via a targeted consultation. The study was further supported by expert contributions[2] on specific aspects regarding safety, testing methods and technological and market developments.

The study makes it clear that organisms obtained through new genomic techniques are subject to the GMO legislation. However, developments in biotechnology, combined with a lack of definitions (or clarity as to the meaning) of key terms, are still giving rise to ambiguity in the interpretation of some concepts, potentially leading to regulatory uncertainty.

NGTs and their products have developed rapidly in the last two decades in many parts of the world, with some applications already on the market and more applications in different sectors expected in the coming years. This study confirms that there is considerable interest in research on new genomic techniques in the EU, but most of development is taking place outside the EU. Following the ruling of the Court of Justice of the European Union (CJEU), there have been reports of negative impacts on public and private research on new genomic techniques in the EU due to the current regulatory framework.

Several of the plant products obtained from NGTs have the potential to contribute to the objectives of the EU's Green Deal and in particular to the 'farm to fork' and biodiversity strategies and the United Nations' sustainable development goals (SDGs) for a more resilient and sustainable agri-food system. Examples include plants more resistant to diseases and environmental conditions or climate change effects in general, improved agronomic or nutritional traits, reduced use of agricultural inputs (including plant protection products) and faster plant breeding.

However, some stakeholders consider that these benefits are hypothetical and achievable by means other than biotechnology. In particular, the organic and GM-free premium market sector reported that they might face threats from coexistence with new genomic techniques and, therefore, any

[1] Council Decision (EU) 2019/1904.

[2] From the European Food Safety Authority (EFSA), the Commission's Joint Research Centre (JRC) and the European Network of GMO Laboratories (ENGL).

consideration of NGT products outside the scope of the current GMO regulatory framework would deal a severe blow to their value chain and risk damage consumer trust in their sector.

NGTs constitute a diverse group of techniques, each of which can be used in various ways to achieve different results and products. Therefore, safety considerations depend on the technique, how it is used and the characteristics of the resulting product and cannot be made on all techniques as a whole. Some NGTs[3] in plant applications are widely addressed in expert opinions from the European Food Safety Authority (EFSA) and Member State authorities, and in Member States' and stakeholders' views on safety and risk assessment; less information is available on other NGTs and micro-organism or animal applications.

For certain NGTs[4], EFSA has not identified new hazards compared to both conventional breeding and established genomic techniques (EGTs). EFSA has also noted that random changes to the genome occur independently of the breeding methodology. Insertions, deletions or rearrangements of genetic material arise in conventional breeding, genome editing, cisgenesis, intragenesis and transgenesis. In addition, EFSA has concluded that off-target mutations potentially induced by site-directed nuclease (SDN) techniques are of the same type as, and fewer than, those mutations in conventional breeding. Therefore, in certain cases, targeted mutagenesis and cisgenesis carry the same level of risk as conventional breeding techniques.

Expert opinions at EU and national level have noted the need for flexibility and proportionality in risk assessment, although not all stakeholders share this view. Another aspect that has been raised is the need to develop risk assessment procedures that are specific to NGTs.

Respondents to the consultation expressed diverse, sometimes opposite views as regards the level of safety of NGTs and their products, and on the need and requirements for risk assessment. However, case-by-case assessment is widely recognised as the appropriate approach.

The study confirms that the current regulatory system involves implementation and enforcement challenges in the EU, relating in particular to the detection of NGT products that contain no foreign genetic material.

Although existing detection methods may be able to detect even small alterations in the genome, this does not necessarily confirm the presence of a regulated product; the same alteration could have been obtained by conventional breeding, which is not subject to the GMO legislation. This is a problem for enforcement authorities and operators. In addition, applicants seeking authorisation would find it difficult, and even impossible in certain cases, to comply with the legal requirement to submit a reliable detection method. Complementary traceability systems do not appear to offer a solution to this challenge and present a number of limitations.

In light of the different regulatory oversight for NGTs in other countries, the above difficulties could lead to trade limitations and disruptions, and put EU operators at a competitive disadvantage, with further negative consequences. This could also lead to the creation of technical barriers to trade, potentially leading to disputes between the EU and its trade partners.

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[3] Site-directed nuclease (SDN) techniques, oligonucleotide-directed mutagenesis (ODM).

[4] Site-directed nuclease type 1 and type 2 (SDN-1, SDN-2), ODM, cisgenesis.

Regulatory barriers would particularly affect small and medium-sized enterprises (SMEs) and small-scale operators seeking to gain market access with new genomic techniques, even though many Member States and stakeholders see opportunities for them in this sector.

The study acknowledges the benefits of patents and licensing in promoting innovation and the development of new genomic techniques and their products. However, these same aspects (together with high business concentration) can also act as a barrier to market entry for SMEs and can limit access to new technologies and to genetic material, e.g. for breeders and farmers.

The use of NGTs raises ethical concerns, but so does missing opportunities as a result of not using them. Based on the findings of the study, most of the ethical concerns raised relate to how these techniques are used, rather than the techniques themselves.

In Member States, there is interest in addressing NGT-related topics in dialogues and events carried out by various institutions, which can help to raise public awareness and understanding. Public perception of new biotechnologies is key to their market uptake.

Consumers' understanding and awareness enable them to make informed choices, so the provision of consumer information (e.g. via labelling) is key. However, stakeholders have opposing views, both on the need to continue labelling NGT products as GMOs and on the effectiveness of such labelling in informing consumers.

Overall, the study provides evidence confirming the conclusions of the past evaluations of the GMO legislation, which noted that some of the new techniques create new challenges for the regulatory system. These evaluations also concluded that, as the rate of innovation in the global biotechnology sector is unlikely to slow down, ensuring that legislation remains relevant is likely to be an ongoing challenge, especially if the focus is on the techniques used rather than the characteristics of the final products and the traits they express.

The key question, therefore, is whether legislation that raises implementation challenges and the application of which to new techniques and new applications requires contentious legal interpretation is still fit for purpose or needs updating in light of scientific and technological progress. However, reported views are split on whether the current legislation should be maintained and its implementation reinforced, or rather adapted to take account of scientific and technological progress, the level of risk of NGT products and the benefits to society. The specific characteristics of medicinal products should also be duly considered. The Commission has already announced this will be addressed as part of the pharmaceutical strategy[5].

The follow-up to this study should consider possible policy instruments to make the legislation more resilient, future-proof and uniformly applied. Any further policy action should be aimed at reaping benefits from innovation while addressing concerns. A purely safety-based risk assessment may not be enough to promote sustainability and contribute to the objectives of the European Green Deal and in particular the 'farm to fork' and biodiversity strategies; benefits contributing to sustainability would also need to be evaluated, so an appropriate mechanism to accompany risk assessment may be required.

[5] COM(2020) 761 final.

2. Background and objectives of the Commission study on new genomic techniques

2.1. Council request for a Commission study

Directive 2001/18/EC[6] provides a definition of genetically modified organisms (GMOs), an open list of techniques that result in genetic modification and a closed list of techniques that are not considered to result in genetic modification. Specifically, it defines GMOs as 'an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'. In addition, it includes a closed list of GM techniques yielding organisms to which it does not apply. The definition and lists of techniques in the Directive reflect the scientific and technical knowledge available at the time of its adoption in 2001.

Since then, significant progress in biotechnologies has led to the development of new genomic techniques (NGTs). In some cases, the mode of action and result of these techniques has led to uncertainty as to whether they result in genetic modification and whether their products fall under the definition of a GMO and the scope and obligations of Directive 2001/18/EC.

In Case C-528/16[7], the Court of Justice of the European Union (CJEU) interprets the exemption in Article 3(1) of Directive 2001/18, read in combination with its Annex IB, which provides that certain organisms corresponding to the definition of GMO and produced by mutagenesis techniques can be exempted from the obligations of the Directive (prior authorisation, labelling and traceability rules). The Court held, in light of the clarifications given by the Union legislature in recital 17 of Directive 2001/18, that Article 3(1) read in combination with Annex IB means that "only organisms obtained by means of techniques/methods of mutagenesis which have been conventionally used in a number of applications and have a long safety record are excluded from the scope of that Directive". The Court judgement only concerns mutagenesis techniques and does not concern other NGTs[8] (see also Section 4.2).

The Council of the European Union ('the Council') recognised[1] that, while the ruling clarified the scope of the GMO legislation with respect to mutagenesis techniques, it also raised practical questions with consequences not only for Member States' national competent authorities, but also for the EU industry, in particular the plant breeding sector, research and beyond. These concern, among other things, how to comply with the EU legal framework and to ensure equal treatment for EU products *vis-à-vis* imports, when products obtained with new mutagenesis techniques are not distinguishable from those resulting from natural mutations.

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6 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

7 Judgment of the Court of Justice of 25 July 2018 in Case C-528/16, *Confédération paysanne and Others* v *Premier ministre and Ministre de l'agriculture, de l'agroalimentaire et de la forêt*, ECLI:EU:C:2018:583.

8 Namely cisgenesis/intragenesis, RNA-dependent DNA methylation, reverse breeding and agroinfiltration.

On the basis of the above and in accordance with Article 241 of the Treaty on the Functioning of the European Union[9], the Council asked 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'[10]. In addition, it asked the Commission to 'submit a proposal, if appropriate in view of the outcomes of the study, or otherwise to inform the Council on other measures required as a follow-up to the study', ensuring that any proposal is accompanied by an impact assessment. The Commission has agreed to the Council's request[11].

2.2. Scope and objectives of the study

While the CJEU ruling focused on new mutagenesis techniques, the Council's request was broader and referred to new genomic techniques in general. No definition exists for new genomic techniques; for the purposes of this study, NGTs are defined as techniques that are capable of altering the genetic material of an organism and that have emerged or have been mainly developed since 2001[12]. The scope of the study covers the use of NGTs in plants, animals and micro-organisms, in a broad variety of potential applications, including in the agri-food, medicinal and industrial sectors.

For the purposes of this study, beyond the practical questions and consequences raised in the Council's decision, the Commission considered it important to take into account major political objectives under the European Green Deal[13], the 'farm to fork' strategy[14] and the pharmaceutical strategy[15].

The Commission's Communication on the European Green Deal stated that 'the EU needs to develop innovative ways to protect harvests from pests and diseases and to consider the potential role of new innovative techniques to improve the sustainability of the food system, while ensuring that they are safe'.

The Communication on the 'farm to fork' strategy stated that 'new innovative techniques, including biotechnology and the development of bio-based products, may play a role in increasing sustainability, provided they are safe for consumers and the environment while bringing benefits for society as a whole. They can also accelerate the process of reducing dependency on pesticides'. The strategy also mentioned that this study would look at the potential of NGTs to improve sustainability along the food chain.

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9 OJ C 326, 26.10.2012, p. 1.

10 For the purpose of this study, the Commission used the term 'new genomic techniques' as an equivalent to the 'novel genomic techniques' cited in the Council request.

11 Ares(2020)1117880 – 21/02/2020.

12 For example:
1) genome-editing techniques such as CRISPR, TALEN, zinc-finger nucleases, mega nuclease techniques, prime editing;
2) mutagenesis techniques, such as oligonucleotide directed mutagenesis;
3) epigenome-editing techniques, such as RNA-dependent DNA methylation.
Conversely, techniques already in use prior to 2001, such as agrobacterium-mediated techniques or gene gun, are not considered NGTs.

13 *The European Green Deal*, Commission Communication (COM(2019) 640 final).

14 *A Farm to Fork Strategy for a fair, healthy and environmentally-friendly food system*, Commission Communication (COM(2020) 381 final).

15 *Pharmaceutical Strategy for Europe*, Commission Communication (COM(2020) 761 final).

In line with the above, the objective of this study is to provide clarity on NGTs, in the form of updated and comprehensive information, on a broad variety of topics and assist in deciding, if appropriate, any further action in this policy area.

3. Methodology of the study

3.1 General methodology

The study was performed by the Commission and was informed by external contributions via targeted consultations with Member States' competent authorities and EU-level stakeholders.

The study was also supported by technical contributions from the European Food Safety Authority (EFSA) and from the Commission's Joint Research Centre (JRC). In addition, it took account of expert opinions from the Group of Chief Scientific Advisors (formerly known as the Scientific Advice Mechanism High-Level Group (SAM HLG) of Scientific Advisors[16]) and the European Network of GMO Laboratories[17]. The study also reports on the recent Opinion on the Ethics of Genome by the European Group on Ethics in Science and New Technologies (EGE)[18].

The Commission set up a dedicated website[19] to inform the public on the background and objectives of the study, and ongoing developments, including information on the stakeholder consultation. The website included a 'frequently asked questions' section to provide information and replies to recurring queries on NGTs.

Further information can be found in the accompanying annexes (Section 7) and supplementary material (Section 8). A glossary of the scientific terminology used in this study can be found in Annex A.

3.2 Targeted consultations

Stakeholder consultations are an important instrument for evidence-based policymaking; in this study, the Commission sought to collect technical information, practical experiences and views on NGTs from Member States and relevant EU-level stakeholders via targeted consultations.

The Member States consultation involved all national GMO competent authorities from the 27 Member States[20]; the authorities were invited to consult further at national level where necessary to complement their replies.

The stakeholder consultation targeted EU-level stakeholder organisations and associations that could be directly or indirectly affected or have a potential interest in NGTs. Where there was no adequate EU-level representation, national stakeholders that were interested in participating were invited to

[16] https://ec.europa.eu/info/research-and-innovation/strategy/support-policy-making/scientific-support-eu-policies/group-chief-scientific-advisors/new-techniques-agricultural-biotechnology_en

[17] European Network of GMO Laboratories (ENGL), *Detection of food and feed plant products obtained by new mutagenesis techniques*, 26 March 2019 (JRC116289). https://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf

[18] https://ec.europa.eu/info/files/ethics-genome-editing_en

[19] https://ec.europa.eu/food/plant/gmo/modern_biotech/new-genomic-techniques_en

[20] Malta did not reply to the consultation questionnaire. Norway provided a spontaneous contribution, also included in the supplementary material.

liaise with counterparts in other Member States and to participate together as a group. The initial selection of EU-level stakeholders was based on the members and observers of DG SANTE's Advisory Group on Food Chain and Animal and Plant Health[21]. To cover all fields of interest, stakeholders from the pharmaceuticals, cosmetics and environmental sectors were also invited. The stakeholder group was expanded following spontaneous expressions of interest from other parties that fulfilled the above criteria. In total, 107 stakeholders were invited to participate (Table 6, Annex B); 71 confirmed their interest and received the questionnaire, of which 58 provided replies.

The consultations were carried out via online questionnaire in EUSurvey. The draft questionnaires were shared with the Member States and stakeholders, and discussed in dedicated meetings.

The Member States questionnaire was finalised by a Joint Working Group of GMO competent authorities in Brussels on 15 January 2020[22]. The consultation ended on 30 April 2020; where needed, clarifications were sought on replies bilaterally. The EU-level stakeholder questionnaire was finalised during a dedicated meeting in Brussels on 10 February 2020 and the consultation ended on 15 May 2020[23]. The two finalised questionnaires can be found in Annex B. Also, as required under the Council Decision, the Member States' competent authorities were given an update at a Joint Working Group meeting on 18 September 2020[24].

All views collected from the consultation have been analysed in this study on their own merit; no conclusions are drawn on the basis of the number of respondents in support of a given view. In several cases, the views reported in this study, especially those relating to benefits or concerns for a sector or for society in general, rest on reasoning and assumptions, sometimes extrapolated from past experience with GMOs from EGTs. This is likely due to limited historical data in the EU or its trade partners on the use of NGTs and their impacts across different sectors, as these are very recent technologies.

All replies to the questionnaires can be found as online supplementary material (Section 8)[25]. The consultation replies are summarised in Section 4.

3.3 Overview of NGT legislation in non-EU countries

This analysis covers non-EU countries that have already addressed NGTs in their legislation or are considering how to do so, groups of non-EU countries that share (to various extents) assessment procedures, and selected EU neighbourhood countries. The list also includes the EU's main trading partners in GM commodities. Information was collected via the websites of the relevant authorities in each country; in addition, public search engines and databases were used where needed.

3.4 State of the art on NGTs

The biotechnology sector and NGTs in particular are in constant and rapid development. Various NGT applications in plants, animals and micro-organisms are currently in development, while some are

[21] https://ec.europa.eu/food/expert-groups/ag-ap/adv-grp_fchaph_en
[22] https://ec.europa.eu/food/sites/food/files/plant/docs/gmo_mod-bio_stake-cons_sum-rep-joint-wg.pdf
[23] http://ec.europa.eu/food/sites/food/files/plant/docs/gmo_mod-bio_stake-cons_sum-rep-stakeholder.pdf
[24] https://ec.europa.eu/food/sites/food/files/plant/docs/gmo_modern-biotech_wg_20200918_sum.pdf
[25] https://ec.europa.eu/food/plant/gmo/modern_biotech/stakeholder-consultation_en

already marketed in non-EU countries. In the past, the JRC produced a report on the scientific and commercial landscape of NTGs in plant breeding[26]. Therefore, in order to assess how NGTs have evolved and have a clear understanding of the current scientific state of the art, it analysed the latest scientific developments and market applications relating to NGTs. The following is a brief overview of the objectives and methodology of the JRC reviews.

Scientific and technological developments

The review focused on the range of NGTs developed, including information on mechanisms of action and types of genetic, chemical or other potential modifications induced. In addition, it addressed technical limitations and knowledge gaps and the main differences between NGTs and EGTs.

The JRC carried out a systematic literature review using online scientific databases. For further information on scope and methodology, please refer to the complete review[27]. The key findings can be found in Section 4.1.2.

Market applications

The JRC reviewed current market applications of NGTs around the globe, focusing on products that are marketed in non-EU countries, in near-market development or in the pipeline stage, describing (among other things) the type of techniques involved and the nature and characteristics of traits introduced.

The JRC's data collection involved searches of publicly available online information and consultation of experts through videoconferences, written communication and targeted surveys of public and private technology developers. For further information on scope and methodology, please refer to the complete review[28]. The key findings can be found in Section 4.1.3.

3.5 Overview of EU NGT research funding

DG RTD conducted an analysis of EU funding for NGT-related projects. The analysis covered the 7th framework programme, FP7 (2007-2014), and the 8th framework programme, Horizon 2020 (2014-2020), thus encompassing a period of 13 years up to June 2020[29].

DG RTD used the Community Research and Development Information Service (CORDIS)[30] public repository and the internal Common Research Data Warehouse (CORDA), searching with NGT-related keywords using the CORTEX search tool. The results were manually screened for relevance and scientific publications acknowledging EU funding were also checked. A limitation of the search strategy was that the identification of NGT-related projects relied on beneficiaries having included the keywords in one of the project-related documents submitted to the Commission. The key findings of the analysis are reported in Section 4.5.1.

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[26] *Scientific and technical report on new plant breeding techniques: state of the art and prospects for commercial development*, JRC (2011); https://publications.jrc.ec.europa.eu/repository/bitstream/JRC63971/jrc63971.pdf

[27] New Genomic Techniques: State-of-the-Art Review https://data.europa.eu/doi/10.2760/710056

[28] Current and future market applications of New Genomic Techniques https://doi.org/10.2760/02472

[29] Marie Skłodowska-Curie (individual postgraduate grants) actions were excluded, as their main goal is researcher mobility and research content is not the primary basis of the award.

[30] https://cordis.europa.eu/

3.6 Risk assessment opinions on plants developed using NGTs

The Commission asked EFSA to provide an overview[31] on the risk assessment of plants developed using NGTs, taking into account its own scientific opinions and those from Member State competent authorities and national institutions, as published since 2012 (date when the first EFSA opinions on NGTs have been published). It provided EFSA with 16 scientific opinions relevant to the request (Table 7, Annex C), submitted by eight Member States[32]. EFSA was not asked to conduct a critical appraisal of the Member State scientific opinions, but it commissioned an evaluation and summary of them.

In addition, EFSA also considered three EFSA GMO Panel scientific opinions on NGTs: two opinions from 2012 on cisgenesis/intragenesis[33] and SDN-3-type techniques[34], and the recently adopted opinion on SDN-1, SDN-2 and oligonucleotide-directed mutagenesis (ODM) techniques[35].

Relevant information on each technique and on the risk assessment of plants developed using one or a combination of the techniques was extracted and summarised. The types of NGTs to be included in the overview were based on the JRC's 2011 report on new plant breeding techniques (NPBTs)[36] and on the SAM HLG explanatory note for some more recently developed NGTs.

[31] https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2021.6314

[32] AT, BE, DE, DK, ES, FR, LT and NL.

[33] EFSA Panel on Genetically Modified Organisms (GMO), 'Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis', *EFSA Journal* 2012;10(2):2561. doi:10.2903/j.efsa.2012.2561

[34] EFSA Panel on Genetically Modified Organisms (GMO), 'Scientific opinion addressing the safety assessment of plants developed using ZFN-3 and other SDNs with similar function', *EFSA Journal* 2012;10(10):2943. doi:10.2903/j.efsa.2012.2943

[35] EFSA Panel on Genetically Modified Organisms (GMO), 'Applicability of the EFSA Opinion on SDNs type 3 for the safety assessment of plants developed using SDNs type 1 and 2 and oligonucleotide-directed mutagenesis', *EFSA Journal* 2020;18(11):6299. doi:10.2903/j.efsa.2020.6299

[36] https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/new-plant-breeding-techniques-state-art-and-prospects-commercial-development

4. Status of new genomic techniques under EU law

4.1 State of the art on NGTs

4.1.1 SAM explanatory note on new techniques in agricultural biotechnology

In 2017, the SAM HLG issued an explanatory note on new techniques in agricultural biotechnology applied to plants, animals and micro-organisms[16]. The note describes the nature and characteristics of NGTs and their similarities and differences compared to conventional breeding techniques and established genomic techniques, in particular as regards precision, efficiency, detectability, cost and speed of product development.

The SAM HLG recognised the heterogeneity among NGTs and the fact that this was reflected in the variety of NGT products; consequently, it may not be ideal (for scientific or other reasons) to group NGTs in a single category. There are also similarities between some NGTs and some conventional breeding and established genomic techniques.

The SAM HLG noted that NGT products may or may not contain exogenous DNA, depending largely on the technique(s) used. In addition, exogenous nucleic acids may be present in intermediate products, but not necessarily in the final product.

The note considers that conventional breeding techniques, established genomic techniques and NGTs differ in the extent to which they produce 'off-target' effects. Random insertion of nucleic acids is characteristic of established genomic techniques in plants and animals, and multiple insertions can occur at untargeted genetic locations. By contrast, genome editing makes it possible to target insertions, resulting in comparatively fewer unintended effects on the expression of other genes or their disruption. It also enables small, precise and specific changes, such as point mutations, which can also be observed in nature. The SAM HLG concluded that, while genome editing may produce 'off-target' effects, their frequency is generally much lower than in the context of conventional breeding techniques and established genomic techniques.

The SAM HLG considered that, due to the precision and efficiency of use of certain NGTs, they are the only realistic means of obtaining certain products.

The SAM HLG concluded that safety can be assessed only case by case and depends on the characteristics of the product, its intended use and the receiving environment. Genetically and phenotypically similar products deriving from the use of different techniques are not expected to present significantly different risks.

The SAM HLG observed that prior information on an NGT product enables detection with a variety of analytical techniques. Detection is more challenging in the absence of information on the changes introduced, but a significant attempt can be made through the application of whole genome sequencing in combination with bio-informatics; in such cases, detection depends on the availability of a suitable reference genome. Nevertheless, it is generally not possible to determine whether the changes are the result of natural causes or the use of any breeding technique.

The SAM HLG made only qualitative statements as to the relative cost and speed of product development, as publicly available data were scarce. Development speed depends largely on the specific trait and the species into which the genetic alteration is introduced. However, mutations can often be introduced more quickly using NGTs than with conventional breeding or established genomic techniques, in particular when using the CRISPR[37]-Cas genome editing system, mainly due to the reduced need for time-consuming screening procedures and/or back-crossing. Also, the costs are correspondingly lower.

4.1.2 JRC review on scientific and technological developments – key findings

Scientific advances in molecular biology in the past 20 years have deciphered the molecular mechanisms of many functional properties in various organisms and their genetic basis. Whereas several established GM techniques generate random sequence alterations in the genome, new technological developments mean that changes can be directed to a selected genomic location, thus enabling more precise editing of the genome. Sequence variations to the genome may be entirely novel or may occur already in other individuals of the species. NGTs may also introduce into an organism new sequences derived from other species. Genome editing has rapidly revolutionised plant and animal breeding, and the molecular engineering of micro-organisms; it provides new opportunities for gene therapy in humans.

Types of NGT

The JRC classified NGTs in four groups based on interactions with the genome:

1. NGTs creating a double-strand break (DSB) in the DNA;
2. NGTs achieving genome editing without breaking the DNA double helix or generating only a single-strand DNA break;
3. NGTs inducing epigenomic changes; and
4. NGTs acting specifically on ribonucleic acid (RNA).

While the first two groups target the DNA sequence, new developments have shifted the focus to the epigenome (Group 3 NGTs) and RNA transcribed from DNA (Group 4). The latter two groups provide alternative approaches for achieving certain effects without changing the heritable DNA sequence itself.

Some techniques, such as those based on the use of SDNs, only induce a DSB at a selected site in the genome. The actual genome editing is then a result of the repair of these DSBs by one of several endogenous cellular mechanisms, which occasionally create mutations. These techniques can be used with or without an added donor sequence that may function as a template during the repair processes. Other techniques use either catalytically impaired SDNs that generate only a single-strand break in the DNA or SDNs with completely abolished cleavage activity that only recognise and bind a target sequence, or involve oligonucleotides for DNA editing.

The most prominent set of NGTs is based on the CRISPR-Cas SDN technology that exponentially expanded the opportunities for the modification of many genomic targets in diverse organisms. This

[37] Clustered regularly interspaced short palindromic repeats.

technology is versatile, relatively easy to implement for genome editing and usable for simultaneous editing at multiple sites. With different functionalities added, it has been used as a platform for many of the other NGTs. CRISPR-Cas-based techniques are still evolving and the list of NGTs is expected to expand further in the coming years.

Delivery systems

For an NGT to be functional, its active components (if not already present) have to be delivered to the cell to be treated. The delivery systems for the active components are often similar to those used for transgene delivery by recombinant DNA technology involving biolistic, bacterial or viral delivery systems, leading to transient vector expression or stable transgene integration. However, in most cases, stable integration of the transgenes into the host genome is not a pre-requisite and alternative approaches to DNA delivery (i.e. RNA and/or protein) may be equally effective for inducing genome alterations. Some other NGTs require the administration of only a short (DNA or RNA) oligonucleotide to the targeted cells to obtain a short genome edit. The need for different types of active component and delivery approaches reflects the diversity of NGTs.

Characteristics of NGT genetic modifications

A NGT may generate different genome alterations depending on how it is used. Moreover, similar alterations, e.g. a single nucleotide substitution, can often be generated by different NGTs. Not every desired alteration can be readily achieved at any sequence, because some NGTs may be restricted as to the recognition and binding of their targets. Therefore, the technique itself cannot always be directly linked with the type of alteration that could be obtained.

NGT-targeted alterations are increasingly precise, in terms both of being localised to a specific target site and of the specific DNA alteration that is intended. The alterations are generally more subtle than with established genomic techniques, although insertions of long sequences may be achieved by some NGTs when used in combination with a suitable donor template. Consequently, products obtained by NGTs or hybridisation techniques, or occurring naturally are becoming indistinguishable from each other.

The efficiency of creating a desired genomic alteration has to be weighed against the probability of generating unintended effects at off-target sites. Off-target alterations following the use of NGTs have been reported in the literature. Diverse optimisation strategies are employed for enhancing the specificity of the technique and for minimising off-target effects. Because the targeted sequence is known, the probability of off-target effects can be predicted in some cases via bioinformatic analyses and then experimentally assessed. Various bioinformatic tools have been developed to screen for potential off-target sites in a particular genome and predict the probability of off-target alterations. For some species, individual organisms can be selected that do not contain off-target changes, or the unintended modification may be removed in a subsequent generation by sexual crossing.

NGTs make it possible to create genome alterations directly in elite germplasm or differentiated cells, and thus shorten the development time for organisms with desired phenotypes. As the changes are often small and instructed by similar changes identified in other organisms, the resulting products containing the genome alterations display more predictable phenotypes and further testing requires less time.

Future outlook

We can therefore expect that the technology will be increasingly deployed across the various biological kingdoms; further improvements to current and next-generation NGTs in the coming years in various organisms will probably expand the opportunities for agricultural breeding, industrial biotechnology and human gene therapies and vaccines.

4.1.3 JRC review on market applications – key findings

The review covered applications in plants, mushrooms, animals, micro-organisms or human cells in the agri-food, industrial and medicinal sectors. NGT applications were classified in four development stages:

1. commercial stage – applications currently marketed in at least one country;
2. pre-commercial stage – applications ready to be commercialised in at least one country but not yet on the market (commercialisation mainly depends on the developer's decision and a 5-year horizon is estimated);
3. advanced R&D stage – applications at late stages of development (field trials for plants, clinical trials in medicinal applications) and likely to reach the market in the medium term (pipeline up to 2030); and
4. early R&D stage – applications at 'proof of concept' stage (i.e. gene targets being tested for trait enhancement of commercial interest).

Overview of techniques and applications

NGTs creating a DSB in the DNA (JRC's Group 1; see Section 4.2.1) are currently the most used (almost 91% of applications). Within Group 1, CRISPR-based techniques clearly dominate. In most applications, CRISPR-Cas and other SDN systems are used to obtain small mutations/insertions through non-homologous end-joining without a DNA template (SDN-1); to date, they have been used far less with a DNA template (SDN-2 and SDN-3).

NGTs achieving genome editing without breaking the DNA double helix or generating only a single-strand DNA break (JRC's Group 2) were used in about 7% of the applications. At R&D level, very few applications were identified that used NGTs inducing epigenomic changes or acting specifically on RNA (JRC's Groups 3 and 4 respectively).

Most NGT applications have been developed in the United States or China. In the EU, Germany produced the biggest number of applications. Due to the flexibility and affordability of NGTs (especially CRISPR), several developing countries are also active in the field.

Both private and public/academic entities are actively developing NGT products. Available data indicates that commercial and pre-commercial applications from private companies are more numerous, while public/academic organisations dominate R&D, contributing to a rich pipeline in terms of variety of organisms and traits.

Plants and mushrooms

The review identified two marketed plant applications: a high-oleic soybean variety with healthier fatty acid profile, modified with transcription activator-like effector nucleases (TALENs), and a

tomato variety fortified with gamma-aminobutyric acid[38], modified with CRISPR/Cas. The pre-commercial stage includes 15 plant applications, some of which correspond to plant/trait combinations that have already been developed with established genomic techniques, e.g. maize, soybean, rice and potato with traits such as herbicide tolerance, fungal resistance, modified oil or starch composition and non-browning properties. However, other applications have not been reported before, e.g. herbicide-tolerant pigeon peas and flax, and pennycress and camelina with modified oil content.

Numerous advanced (117) and early (292) R&D stage applications show the potential of NGTs in the medium term (by 2030) and the diversity of applications in terms of traits and targeted plants. Disease resistance is targeted to many types of pathogens and pests. Abiotic stress tolerance is widely applied, including tolerance of drought, salinity and heat. Modified composition goes beyond starch and oil content; examples include crops with other nutrition profile improvements (e.g. fibres, vitamins) or reduced content of harmful substances (e.g. toxins, allergens, acrylamide precursors, etc.) and gluten. Several applications are designed to obtain higher and more stable yields in terms of plant production and/or size of fruits and grains.

In mushrooms, only one NGT application was identified: non-browning white button (*Agaricus bisporus*); this is obtained with CRISPR-Cas9 and is in the pre-commercial stage.

Tables 1 and 2 give an overview of plants in which NGTs are used, and their traits.

Table 1: Overview of plants in which NGTs are used (from early R&D to commercial stage)[28]

Plant groups	Plants included (not exhaustive)
Cereals	Maize, wheat, rice, barley, sorghum, millet
Forage and grasses	Alfalfa, ryegrass, switchgrass, *Setaria viridis*
Fruits	Apple, banana, orange, groundcherry, grapefruit, grapevine, kiwifruit, melon, watermelon, berries, stone fruits, avocado
Legumes	Beans, chickpea, peanut, pea, pigeon pea
Oil and fibre crops	Soybean, rapeseed, cotton, camelina, flax, pennycress, sunflower, mustard, strawberry
Ornamentals	Chrysanthemum, dandelion, orchid, petunia, poinsettia, poppy, Japanese morning glory, wishbone flower (*Torenia fournieri)*, jasmine tobacco
Sugar crops	Sugar beet, sugar cane
Trees	Poplar, softwood trees
Tubers and root vegetables	Potato, sweet potato, cassava, beetroot
Vegetable crops	Tomato, broccoli, cabbage, cucumber, aubergine, lettuce, pepper, chicory
Plants (aggregated)	Only 'plants' or a list of diverse plants were identified
Other plants	Cocoa, coffee, tobacco, sage

[38] Gamma-aminobutyric acid is commonly sold as a dietary supplement.

Table 2: Types of trait introduced in NGT plants (from early R&D to commercial stage)[28]

Trait category	Description
Biotic stress tolerance	Resistance to biotic stressors such as nematodes, fungi, bacteria, viruses and other pests, pathogens or parasites
Abiotic stress tolerance	Resistance to abiotic stressors such as drought, heat, salt, rain and UV radiation
Herbicide tolerance	Tolerance to different types of herbicide
Modified colour/flavour	Modified colour or flavour
Modified composition	Modified content of substances such as starch, oil, proteins, vitamins, fibres, toxic substances, allergens, etc. to improve food/feed quality for better industrial use. This includes seedless fruits as a quality characteristic.
Plant yield and architecture	Yield increase (or stability) related to higher number of flowers/seeds/fruits to fruit size/weight and to photosynthetic efficiency. This includes other changes in plant architecture, e.g. plant height and shape, fruit shape and growth pattern.
Storage performance	Improvement of characteristics such as shelf-life and storage requirements (e.g. cold storage), including non-browning and reduced black spot
Other traits	Remaining traits (not previously classified), e.g. production of molecules of industrial interest, flowering time for agronomic purposes and nitrogen use
Breeding tools	Reproductive/flowering characteristics, e.g. induction of sterility, early flowering and haploid techniques

Animals

The development of NGTs for animal applications is focusing on the livestock sector for food production purposes, especially in cattle, pigs, chickens and various fish species (salmon, tilapia, tuna and red sea bream). Insects (especially mosquitos) and invasive species are the subjects of NGT-based gene drive applications. No NGT animals are yet commercialised, but there are four examples in the pre-commercial stage: yield-enhanced/fast-growing tilapia, disease-resistant pigs, hornless cattle and heat-resistant cattle. The advanced and early R&D stages include 59 identified NGT applications, with a predominance of food production-related traits, followed by gene drive applications.

One particular use of NGTs in animals is in the field of advanced and early R&D on human diseases, using animals as disease models for gene therapy studies or to produce organs for transplantation. To date, most NGT animal models have used mice and focused on human gene therapy studies, especially for cancer and genetic diseases. NGT rats and monkeys are also used to model human diseases, but still in early R&D stages only. Pigs are especially important for the production of organs that do not cause transplant rejection in humans.

Tables 3 and 4 give an overview of animals in which NGTs are used, and their traits.

Table 3: Overview of animals in which NGTs are used (from early R&D to commercial stage)[28]

Organism	Species
Aquatic animals	Salmon, tilapia, tuna, carp, red sea bream, fugu, coral
Domestic animals	Cattle, pig, chicken, sheep, horse, dog
Rodents and primates	Mouse, rat, monkey
Insects	Mosquito, fly, moth
Other animals	Cane toad, feral cat

Table 4: Types of trait introduced in NGT animals (from early R&D to commercial stage)[28]

Trait category	Description
Biotic stress tolerance	Resistance to biotic stressors such as bacteria, virus and other pathogens
Improved meat yield/quality	This includes higher and faster meat production, modification in meat quality and muscle-related performance
Abiotic stress tolerance	Resistance to abiotic stressors such as high or low temperature
Hypoallergenic properties	Hypoallergenic properties of food derived from animals
Reproductive characteristics	This includes changes in sexual characteristics such as sterility or the ratio between male and female offspring
Other traits	Remaining traits (not previously classified), e.g. management of herds, reduced toxin levels and modification of behavioural characteristics
Gene drive	Gene drive technology to pass a genetic modification to the whole offspring, usually to eliminate pathogen-carrying insects or control invasive species
Human therapy applications	Animals used as models to investigate gene therapies for human diseases (especially cancer and genetic diseases) or used to produce organs that can be used in human transplants

Micro-organisms

In industrial micro-organism applications, it appears that NGTs are already a reality, facilitated by the contained use of micro-organisms as bio-factories and the fact that the final product is usually not the target of the modification. In these cases, the industrial biotechnology sector is quick to apply technological innovation; NGTs are therefore used alone or in combination with established genetic techniques in order to improve specific strains, making it difficult to single out NGT applications. Most commonly, this concerns NGTs from Group 1, especially CRISPR, which are used to knock out undesirable gene encoding e.g. for toxins, intrinsic antibiotic resistance or unwanted metabolism by-products.

As regards the commercialisation of NGT micro-organisms as final products for release in the environment, only one marketed application has been identified: soil bacteria for fertilising agricultural soils.

Table 5 gives an overview of NGT applications in micro-organisms.

Table 5: Types of NGT application in micro-organisms (from early R&D to commercial stage)[28]

Applications	Contained use	Deliberate release
Food/feed-related	Production of: • food enzymes (for baking, starch products, plant-based proteins, vegetable oil, diary, meat processing) • feed enzymes (to increase nutritional value) • food/feed ingredients	• probiotics for animal and human health • micro-organisms in feed (improve nutrition and feed conversion ratio) • inoculants (substitutes for fertilisers) • bio-control (substitutes for pesticides)
Non-food/feed	• enzymes (for use in detergents, textiles, leather, pulp and paper) • biofuels • cosmetics • pharmaceuticals • other bio-based chemicals	• soil bio-remediation

Human health

NGTs are employed widely in the development of medicinal products for human use. NGT applications were identified in 64 clinical trials, which are in Phase I or Phase I/II. There is extensive activity at early R&D stage.

Cancer is the main target of 56 therapeutic NGT applications (of which 8 specifically address virus-induced cancers), followed by hereditary diseases (31), including haematological (16), eye (5) and neurodegenerative (2) diseases, and viral diseases (23). The biggest group of medicinal products in development is based on the genetic modification of T-cells (mostly autologous, but in some cases allogenic), followed by stem cells and cancer cells.

Conclusions and future outlook

Group 1 NGTs, especially those based on CRISPR, are increasingly being used in all analysed sectors. Due to its flexibility, affordability and ease of use, CRISPR is opening the doors to several new possibilities in terms of target organisms and traits. In the short term, about 30 applications in plants, animals and micro-organisms are at pre-commercial stage and could reach the market in the next 5 years. In the medium term, over 100 plants, several dozen animals and medicinal applications that are now in the advanced R&D stage could reach the market by 2030. It is likely that the uptake of NGTs will be faster in micro-organisms for the industrial production of bio-based molecules. Most commercial applications by 2030 will be based on Group 1 techniques (mainly CRISPR) and some on Group 2. The maturity of Group 3 and 4 applications, in terms of commercial release, is lower.

4.2 Legal status of organisms developed through NGTs

4.2.1. The EU GMO legislation

EU legislation on GMOs has two main objectives: to protect human and animal health and the environment in accordance with the precautionary principle and to ensure the effective functioning of the internal market. Accordingly, it establishes harmonised and centralised procedures requiring an authorisation for placing a GMO on the market or for its deliberate release into the environment. The EU's GMO authorisation system is based on an assessment of the risks to human and animal health and the environment, and includes requirements for post-authorisation monitoring, labelling and traceability. The legislation also has an important international dimension, embodied in the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, to which the EU is party.

EU law on GMOs is enshrined in five main pieces of legislation:

- **Directive 2001/18/EC** on the deliberate release into the environment of genetically modified organisms[39];
- **Directive 2009/41/EC** on the contained use of genetically modified micro-organisms[40];
- **Regulation (EC) No 1829/2003** on genetically modified food and feed[41];
- **Regulation (EC) No 1830/2003** concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms[42]; and
- **Regulation (EC) No 1946/2003** on transboundary movements of genetically modified organisms[43].

Overall, the legislation covers:

- GMOs intended for deliberate release into the environment for purposes other than being placed on the market;
- GMOs to be placed on the market;
- GM food or feed; and
- genetically modified micro-organisms (GMMs) to be used under containment conditions.

A brief summary of the main EU legislative acts on GMOs can be found in Annex E.

The EU GMO legislation applies to GMOs as defined in Article 2(2) of Directive 2001/18/EC, i.e. *'an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'*. The GMO definition is further refined by a non-exhaustive list of GM techniques (set out in Part 1 of Annex IA to the Directive) and by excluding certain techniques (listed in Part 2 of Annex IA) that are not considered to result in genetic modification under certain conditions. Also, the Directive does not apply to GMOs

[39] OJ L 106, 17.4.2001, p. 1.
[40] OJ L 125, 21.5.2009, p. 75.
[41] OJ L 268, 18.10.2003, p. 1.
[42] OJ L 268, 18.10.2003, p. 24.
[43] OJ L 287, 5.11.2003, p. 1.

that result from certain GM techniques/methods (mutagenesis and cell fusion of plant cells of certain organisms), subject to various conditions.

4.2.2. Application of the EU GMO legislation to new mutagenesis techniques

Article 3(1) of Directive 2001/18/EC provides that the Directive does not apply to *'organisms obtained through the techniques of genetic modification listed in Annex IB'*. These techniques are:

(1) mutagenesis; and

(2) cell fusion of plant cells of organisms that can exchange genetic material through traditional breeding methods.

Organisms obtained through these techniques are GMOs, but they are exempted from the application of the Directive's provisions under certain conditions[44].

In its judgment in *Confédération paysanne and Others*[45], the CJEU ruled that '*Article 3(1) of Directive 2001/18/EC, read in conjunction with point 1 of Annex IB to that Directive and in the light of recital 17 thereof, must be interpreted as meaning that only organisms obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of that Directive*' (paragraph 54).

The ruling clarifies that organisms obtained by means of new mutagenesis techniques that have appeared or have been mostly developed since the adoption of Directive 2001/18/EC are GMOs subject to the provisions of the Directive.

Regulations (EC) 1829/2003, 1830/2003 and 1946/2003 provide the following definition: '"*genetically modified organism" […] means a genetically modified organism as defined in Article 2(2) of Directive 2001/18/EC, excluding organisms obtained through the techniques of genetic modification listed in Annex IB to Directive 2001/18/EC*'.

According to the *Confédération paysanne and Others* ruling, organisms produced with new mutagenesis techniques are not excluded from the scope of Directive 2001/18/EC in accordance with its Article 3(1) and Annex IB.

Therefore, organisms obtained by means of new mutagenesis techniques that have appeared or have been mostly developed since the adoption of Directive 2001/18/EC are GMOs under Regulations (EC) 1829/2003, 1830/2003 and 1946/2003, and subject to their provisions.

Directives 2001/18/EC and 2009/41/EC share very similar aims (protection of health and the environment, application of the precautionary principle). They have a similar and comprehensive definition of GMO/GMM, an article providing for the exemption of organisms produced by certain techniques and an annex listing these techniques (the lists are similar but not identical).

[44] Organisms obtained through these techniques are exempted on condition that they do not involve the use of recombinant nucleic acid molecules or GMOs other than those produced by one or more of those techniques/methods.

[45] Case C-528/16, *Confédération paysanne and Others* (ECLI:EU:C:2018:583).

Part A of Annex II to Directive 2009/41/EC lists techniques[46] producing micro-organisms that are excluded from the scope of the Directive. These techniques had a safe history of use at the time the Directive was adopted. In particular, Annex II, Part A excludes micro-organisms produced through self-cloning using recombinant vectors, provided that those vectors have an extended history of safe use in the micro-organisms in question.

Therefore, for a GMM to be excluded from the application of Directive 2009/41/EC, an essential criterion is that the technique used to develop it had a safe history of use when the Directive was adopted. Based on the CJEU judgment, new mutagenesis techniques do not satisfy this criterion.

Therefore, micro-organisms developed through new mutagenesis techniques that have appeared or have been mostly developed since the adoption of Directive 2001/18/EC are GMMs subject to the provisions of Directive 2009/41/EC if used under containment, and of Directive 2001/18/EC if deliberately released or placed on the market.

4.2.3. Application of EU GMO legislation to organisms produced through cisgenesis and intragenesis

As stated above, the CJEU confirmed that organisms whose genetic material is altered by techniques/methods of mutagenesis fall within the definition of GMO in Directive 2001/18/EC[47].

The fact that mutagenesis is a phenomenon that can also occur in nature and that organisms similar to those obtained from mutagenesis techniques can also be obtained naturally did not lead the CJEU to consider that all organisms in which the genetic material has been altered by mutagenesis are outside the scope of the Directive. Furthermore, the fact that this technique is exempted under Article 3(1) of the Directive implies that, without the exemption, organisms produced through it would otherwise be subject to the requirements of the Directive.

Therefore, since cisgenesis and intragenesis techniques alter the genetic material in a way that does not occur naturally by mating and/or natural recombination, the resulting organisms are GMOs, even if both techniques constitute phenomena that can also occur in nature. Since neither cisgenesis nor intragenesis are listed in Annex IB to the directive, the resulting GMOs are subject to the requirements of the GMO legislation.

4.2.4. Application of EU GMO legislation to organisms in which the genetic material is altered without changes in the nucleic acid sequence

Certain techniques (e.g. epigenome editing) introduce alterations of the genetic material without alteration of the organism's nucleic acid sequence.

The definition of GMO in the legislation refers to an alteration of the genetic material, without further defining the term 'alteration'. There are no elements in the legislation supporting a restrictive

[46] e.g. cell fusion of prokaryotic species that exchange genetic material by known physiological processes, cell fusion of cells of eukaryotic species, including production of hybridomas and plant cell fusions, self-cloning under certain conditions.

[47] Paragraph 38.

interpretation of this term as referring only to the alteration of the nucleic acid sequence of the genetic material.

Annex IA to Directive 2001/18/EC provides indications that are useful for interpreting the definition of GMO: Part 1 lists techniques in which genetic modification occurs and Part 2 lists the techniques that are not considered to result in genetic modification. The list in Part 2, which is exhaustive, does not refer to techniques that introduce chemical alteration in the genetic material of the organism. In addition, the list in Part 1 is non-exhaustive (as the word '*inter alia*' shows).

As regards the objectives of the legislation, the reasoning followed by the CJEU to justify its restrictive interpretation of mutagenesis in the context of the exemption (i.e. the protection of health and the environment and the application of the precautionary principle as being the essential purpose of the system of prior authorisation of GMOs in the Directive) supports a restrictive interpretation of the term 'altered' in the GMO definition.

In view of the above, organisms in which the genetic material has been altered without change of the nucleic acid sequence, in a way that does not occur naturally by mating and/or natural recombination, are GMOs subject to the provisions of the GMO legislation.

4.2.5 Past evaluations of the EU GMO legislation as regards NGTs

The Commission has carried out two evaluations of the GMO legislation in the past. The first, in 2010[48], was in the field of GM food and feed and concerned the traceability and labelling of GMOs and food and feed products derived from them. The second, in 2011[49], was in the field of GMO cultivation and placing GMOs on the market. The evaluations provided general and specific observations and conclusions on the overall GMO legal framework, some of which are pertinent to NGTs.

In the 2010 evaluation, the Commission services commented on new genetic modification technologies, especially techniques inducing modification that cannot be detected in the product. They noted that, while modifications introducing new DNA sequences can be easily detected, the problem with targeted mutagenesis is that there is not the same degree of 'molecular novelty' and the end product might not differ from those obtained via traditional breeding or random mutagenesis. Also, even if it were possible to detect the modification, it would be impossible in certain cases to determine whether it was based on 'old' or 'new' techniques. Similarly, epigenetic techniques, which alter the level of expression of specific genes, also escape detection by routine methodologies, so detection may not be possible at an affordable price.

Food and feed chain operators considered that, overall, the legislation was not appropriate for managing new developments and realising their benefits.

The 2010 evaluation also mentioned concerns that the legislative framework was not suited to ensuring that the EU could take advantage of new developments. In addition, there were concerns that it was too focused on risk and that EU citizens may therefore be denied a range of benefits

[48] https://ec.europa.eu/food/sites/food/files/plant/docs/gmo_rep-stud_2010_report_eval-gm.pdf
[49] https://ec.europa.eu/food/sites/food/files/plant/docs/gmo_rep-stud_2011_report_cultivation.pdf

emerging from future developments. However, these concerns were not shared by all (e.g. NGOs) and it may have been too early to draw clear conclusions given the uncertain timing of new developments.

The 2011 evaluation concluded that researchers' and industry's adoption of innovations in biotechnology was giving rise to pressure to update the scope of the GMO legislation. It was also noted that some of the new techniques created new challenges for the regulatory system, as there was no recombinant DNA in the product. Furthermore, extending the scope of the legislation to new techniques without improving its efficiency would effectively bar any products produced with those techniques from the EU market.

Finally, as the rate of innovation in the global biotechnology sector was unlikely to slow down, ensuring that legislation remained relevant was likely to be an ongoing challenge, especially if the focus was on the techniques used rather than the characteristics and the traits of the final products.

4.2.6 Regulation of NGTs in non-EU countries

For the purposes of this study, the legislative framework in 31 non-EU countries was screened for specific legal acts on GMOs and NGTs.

Legislation on GMOs and NGTs varies significantly across jurisdictions, but a number of key features can be identified:

i) the product-based or process-based exemption (deregulation) of NGT products;

ii) the coverage of NGT products under the GMO legislation; and

iii) the case-by-case determination of NGT products' regulatory status via pre-submission consultations.

NGTs addressed under an adapted GMO legal framework or a specific NGT framework

Around a third of the jurisdictions have adapted their legislation to cover NGTs and/or NGT products[50]. The changes often include exemptions, which can be product-based, process-based or a combination of the two. All the countries have addressed NGT plants; some have also addressed micro-organisms and/or animals.

In product-based exemptions, product characteristics determine whether an NGT product would fall under the legislation (regulated) or not (deregulated). Characteristics leading to exemption include the absence of a new combination of genetic material, the absence of recombinant DNA/RNA in the final product and the presence of only small deletions and substitutions or targeted single base pair substitutions.

Process-based exemptions exclude NGT products obtained through specific techniques (e.g. certain transient RNA interference techniques) and endogenous repair mechanisms without using templates in the process e.g. SDN-1, ODM and RNA-dependent DNA methylation (RdDM).

[50] Argentina, Australia, Brazil, Chile, Colombia, Honduras, Israel, Japan, Paraguay, United States.

Product-based and process-based exemption schemes can be combined, e.g. to exempt only NGT products that are obtained using specific techniques and for which the changes in the final product are limited to single base pair substitutions or deletions.

Both types of exemption scheme often include references to 'natural occurrence', e.g. exempting the introduction of genes, alleles or structural variations known to occur in the plant's gene pool, or changes that could also have occurred in nature or have been obtained by conventional breeding.

Some product-based exemptions can apply only if the applicants demonstrate that certain criteria are fulfilled, e.g. the absence of foreign material in the final product. In some cases, the scope of the exemption is limited to specific organisms, e.g. plants.

NGTs addressed under a general legal framework (GMO or other)

Around two thirds of the reviewed countries[51] have no specific legislation for NGTs and/or their products; they are regulated in the same way as conventional GMOs. However, half of these countries are debating whether to adapt their legislation specifically to NGTs.

In Canada, regulatory oversight is triggered only where a novel trait is introduced, regardless of the technique used (conventional breeding, random mutagenesis, modern biotechnology or gene editing). The 'novelty' of the trait is compared to existing traits in products regarded as safe and on the market at a certain moment in time.

Case-by-case determination via pre-submission consultations

In many jurisdictions, national authorities offer pre-submission consultations for applicants, to clarify the regulatory status of an NGT product and to ensure that the application file is complete.

In the majority of cases, the regulatory status of NGT products is determined by a national authority. This can take between 20 working days and 12 months.

Two jurisdictions apply 'self-determination' of the status of an NGT product. In one, applicants who are unsure of the regulatory status of their products can ask the national authority to determine their status.

Approval procedures

Where an authorisation is required, the procedure can take 3-25 months, or longer if additional information is required. Certain jurisdictions provide for shorter authorisation procedures for NGT products, consisting of a plant-trait mechanism that has already been assessed for another product.

In addition to safety, some countries take additional factors into account in the final assessment/authorisation of GMOs; these also apply to NGT products and include ethical aspects, social acceptance, sustainable development, commercial and production impact, and perspectives and benefits for indigenous people.

[51] Canada, China, Egypt, Guatemala, India, Kenya, Mexico, New Zealand, Nigeria, Norway, Philippines, Russian Federation, South Africa, South Korea, Switzerland, Turkey, Uganda, United Kingdom of Great Britain and Northern Ireland, Ukraine, Uruguay, Vietnam.

As transparency and confidentiality requirements vary, the accessibility of detailed information on an NGT product can differ significantly across jurisdictions.

4.3 Implementation and enforcement of EU GMO legislation with regard to NGTs

4.3.1 EURL/ENGL report on the detection of new mutagenesis products

Following the July 2018 CJEU ruling, diverging views emerged on the detectability of products obtained by new mutagenesis techniques, both among Member States and stakeholders. In October 2018, the Commission asked the EU Reference Laboratory (EURL) to draw up, together with the European Network of GM Laboratories (ENGL), a report on the possibilities and limitations of analytical detection methods, in particular:

- whether and under what conditions current analytical possibilities allow detection and quantification of all types of mutagenesis events and other new breeding techniques (NBTs); and
- if not, what possibilities exist to overcome any issues identified.

The EURL and ENGL would produce three reports, on plants, micro-organisms and animals.

The first report[17], issued in March 2019, addressed the analytical challenges for genome-edited food and feed products of plant origin, with a focus on products of genome editing that contain no inserted recombinant DNA in the final plant. The report covered compliance with the GM food and feed legislation (including requirements for method validation as part of the GMO authorisation procedures) and routine testing of food and feed by the enforcement laboratories in line with the Official Controls Regulation[52].

As regards the use of analytical methods for market control and considering current knowledge and the state of the art of GMO testing, the report considered that it is highly improbable that enforcement laboratories would be able to detect the presence of unauthorised genome-edited plant products in food or feed entering the EU market without prior information on the altered DNA sequences. The polymerase chain reaction (PCR) based screening methods that are commonly used to detect conventional GMOs cannot be applied to, nor could they be developed for, genome-edited plant products, because they target common sequences generally present in transgenic organisms, but that do not occur in genome-edited plants. DNA sequencing may be able to detect specific DNA alterations in a product, but this would not necessarily confirm genome-editing, as the same alteration could have been obtained by conventional breeding or random mutagenesis techniques (which result in organisms being exempted from the GMO legislation).

As regards the availability of validated event-specific and quantitative detection methods, which are a pre-requisite for GMO market authorisation, the report considers that it is questionable whether such methods can be developed readily for all genome-edited plant products. For instance, detection methods for plant products bearing a non-unique DNA alteration will probably lack the specificity

[52] Regulation (EU) 2017/625 of the European Parliament and of the Council on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products (OJ L 95, 7.4.2017, p. 1).

required to identify the genome-edited plant. Moreover, accurate quantification may be challenging if just one or a few base pairs are changed.

The report concludes that validation of an event-specific detection method and its implementation for market control will be feasible only for genome-edited plant products carrying a known DNA alteration that has been shown to be unique. Under the current circumstances, market control will fail to detect unknown genome-edited plant products. The report notes that several issues regarding the detection, identification and quantification of genome-edited products will require further consideration, as its findings are currently based on theoretical assessments.

The other reports, covering micro-organisms and animals (including animal products) obtained by new mutagenesis techniques, will follow.

4.3.2 Member States' and stakeholders' views on implementation and enforcement

Implementation and enforcement of the GMO legislation as regards NGTs

Since the CJEU ruling, most Member States have not adapted their GMO enforcement system to cover NGT products. They have invoked a variety of reasons for this, of which the most common is the absence of reliable detection methods for NGT products. Some Member States consider that the significant increase of human, capital and material resources needed to develop such methods hinders further efforts. In addition, the limited chances of success in developing a reliable detection method are a disincentive to investing large sums of money. Some Member States noted that, as it currently seems unlikely that new NGT product-specific detection methods would comply with the required method performance criteria, the analytical results would not stand up in court; this legal uncertainty refrains them from adapting their current GMO enforcement system.

Some Member States invoked legal reasons for not adapting their GMO enforcement system. For example, some already had, at national level, a definition for NGTs in general. Others argue that, as the CJEU ruled that NGT products are GMOs and thus subject to EU GMO legislation and the legislator did not amend the GMO enforcement provisions following the ruling, existing GMO enforcement should be sufficient to cover NGTs.

Another reported reason for not adapting enforcement systems is the absence, so far, of any evidence that NGT products are present on the EU market. Some Member States consider there is therefore no justification for amending the existing GMO enforcement.

Finally, some Member States reported that they would prefer to wait for a harmonised approach at EU level before adapting their legislation.

A few Member States did report adaptation of their enforcement systems. Some efforts involved including NGT products in the scope of inspections, e.g. by adding new questions. However, Member States reported difficulties with implementation in practice. Other efforts consisted of providing the supervision bodies and GM laboratories with extra information; however, this required additional analytical equipment, chemicals, human resources and access to bioinformatics data.

Most stakeholders share the Member States' concerns on analytical issues, but their perceptions differ on this issue. Almost all stakeholder organisations representing food business operators or researchers/academics point to the analytical limitations and the resulting impossibility of enforcing

GMO legislation in respect of NGT products, either now or in the future. Some stakeholders are concerned that analytical solutions require considerable time and money, with no guarantee of success, and do not help where the genetic alterations can occur naturally or through conventional breeding. NGOs refer mainly to the CJEU ruling, the obligation (under the current GMO legislation) to provide an analytical method and the need for more research to develop suitable methods. Most stakeholders assume the absence of NGT products on the EU market, although some NGOs are less convinced or mention the possible presence of specific NGT products in non-EU countries.

Possible solutions mentioned by stakeholders to overcome the analytical limitations include expanding analytical tests to –omics techniques, the use of whole genome sequencing and the establishment of a global database containing all necessary information on NGTs and related patents.

Challenges for current and alternative traceability systems

For non-transgenic NGT products, all Member States that replied considered there is no valid traceability without a valid analytical strategy and recalled that no enforcement is possible without the necessary legal certainty. In practice, both traceability and analytical detection face difficulties in testing complex matrices (as opposed to detection from pure samples from a single origin with sufficient DNA) and in looking for unauthorised NGT products, where the target is unknown. A number of Member States considered that NGTs in contained use cause no additional problems compared to other products in contained use.

Some Member States mentioned ongoing work on the development of alternative analytical control strategies, which require the collection of sequencing information at EU level and from all trading partners, as well as NGT-specific sampling. They noted that such strategies entail a high logistical and financial burden, and significantly more human and technical resources, to the point that future routine enforcement of current GMO legislation in respect of NGT products could result in disproportionate costs and administrative burden. Another caveat is the ever-increasing complexity of analytical controls jeopardising the shelf-life of perishable products.

A few Member States proposed using alternative traceability systems. One option could be to use existing document-based traceability systems, such as those used in oil obtained from GMOs, organic farming or beef origin, or using digital tools such as block chain. However, they noted that additional paper traceability could distort competition and put EU producers at a disadvantage *vis-à-vis* those from non-EU countries. Another proposal was to use a system of NGT-free certificates, but the feasibility of that approach is hampered by the substantial financial and human resources required to set it up and operate it. Stakeholders expressed various degrees of support for the option of paper traceability for authorised non-transgenic NGT products. However, this approach is weakened by the absence of solid analytical backup.

Other alternative traceability systems suggested by Member States and stakeholders include end-to-end transparency (including block chain), mass balance and sustainability/identity preservation schemes. Some stakeholders consider that these solutions are practicable only for small volumes and rely fully on trust in the suppliers. In addition, they require segregated supply chains. Other suggested solutions include exempting NGT products from traceability requirements and keeping NGT traceability schemes voluntary for interested market segments (e.g. organic). However, existing sustainability schemes/labels may not be the correct vehicle for NGT traceability.

As regards the cost of NGT traceability, some stakeholders reported that record-keeping carries a financial and human resource cost, which is often passed on to the primary producer. Other stakeholders expressed concern as to whether the costs are proportionate in view of the benefits and value for the supply chain, consumers, society and the environment. Others consider that the sectors developing and/or using NGT products should bear the additional costs entirely or that past experience from handling the unauthorised presence of GMOs in the food chain could be used to assist NGT traceability.

Finally, stakeholders involved in pharmaceutical applications of NGT products point out that, given the comprehensive regulation applicable to medicines (including on traceability and labelling), there is no need for additional traceability and labelling requirements under GMO legislation.

Information on field and clinical trials and national catalogues of plant varieties

For agricultural applications, a number of Member States reported ongoing or planned field trials with NGT products. Depending on national provisions, these had either been notified in line with the current legislation prior to the CJEU ruling or were regularised following the ruling. Some Member States consider that the current GMO legislation raises concerns for the application of NGTs in the development of new plant varieties, forcing breeders to use other, less efficient methods. The resulting administrative burden and costs have a strong obstructive effect: some field trials were even withdrawn or cancelled following the CJEU ruling. One Member State mentioned a ban on NGT plant field trials until 2023. All Member States replied that no NGT plant varieties were registered in their national catalogues, although a third of them do not actually enquire, during registration, as to the technique used to develop plant varieties.

Some Member States reported that more research is being done for medicinal and industrial applications under contained use and numerous tests are ongoing for such applications. It was also noted that, for the medicinal sector, the current GM legislation reflects the situation in 1990 and has been overtaken by developments.

Stakeholders' views on national and EU-level support relating to NGTs

Most Member States reported that they have been consulted for regulatory advice or have organised information sessions on various NGT-related issues. These include the interpretation and consequences of the CJEU ruling, the legal status of NGT products, questions on the detection of specific products, regulatory advice on field trials, questions on intentions to regulate random mutagenesis techniques, questions on intentions to revise Directive 2001/18/EC, data requirements for risk assessment for NGT products, enforcement of the legislation for NGT products, coexistence with organic agriculture, impact on pharma biotech and patent-related issues.

Most agri-food business operators and academics/researchers mentioned a lack of support from relevant national or EU authorities. The issues on which most stakeholders would have wanted more support are the analytical aspects (e.g. reliable detection methods), followed by the lack of legal certainty.

Some stakeholders consider that the Commission had shown a lack of leadership and ownership on the topic of NGTs over the past decade and that they had not received sufficient support. In addition, some believe that dialogue with the EU institutions was non-existent or of limited benefit; in

contrast, others considered that the dialogue had been useful and that high-quality information had been passed on.

4.4. Safety of new genomic techniques

4.4.1 EFSA's overview on risk assessment opinions of plants developed through NGTs

EFSA provided an overview[31] of the risk assessment of plants developed using NGTs, based on its scientific opinions on SDN-based techniques, ODM and cisgenesis/intragenesis, and on opinions published by Member States' competent authorities and national institutions since 2012. EFSA was not asked to carry out any critical appraisal of the reviewed scientific opinions.

In their opinions, Member States covered cisgenesis and intragenesis, SDN technologies and base editing, ODM, RNA-dependent DNA methylation, grafting (on GM rootstock), reverse breeding and agro-infiltration. In addition, two discussed how various combinations of NGTs can be used.

The EFSA scientific opinions focused on:

i) addressing the risks for humans, animals and the environment by comparing plants developed using NGTs with plants obtained by conventional breeding methods and established genomic techniques; and

ii) evaluating the applicability of the EFSA's GM plant risk assessment guidance documents to the assessment of plants developed using NGTs.

The Member States' opinions were produced at different times since 2012, as advice to a ministry, technical reports or scientific publications.

The different scopes and objectives of the opinions covered in this overview make it difficult to compare them directly and to draw general conclusions. However, a number of observations can be made, in particular regarding SDN-based techniques and cisgenesis/intragenesis.

SDN-based NGTs were discussed in 14 of the 16 Member State opinions and in two EFSA opinions. The other techniques appear to have received less attention from Member States.

SDN techniques and ODM

There is a general understanding that each type of technique can be used for different purposes. For example, SDN-1 techniques can be used to knock out genes, modify regulatory elements and perform genetic deletions, inversions, duplications or translocations (in the case of double breaks in the genome); SDN-2 techniques may introduce mutations from one or more pairs of nucleotides, or small insertions or deletions; SDN-3 techniques can be used to introduce transgenes, cisgenes or intragenes.

EFSA did not identify new hazards specifically linked to the genomic modification produced via SDN-1, SDN-2 or ODM, compared with conventional breeding and techniques introducing new genetic material.

In terms of specificity, there is general agreement among Member States and EFSA that SDN technology is a substantial improvement over random genetic modifications and that several approaches have been developed to improve method specificity. Nonetheless, the Member State

opinions put forward different considerations on off-target modifications, e.g. concerning their type, extent, effect and need for assessment. However, direct comparison is difficult due to the varied nature of the opinions (see above).

EFSA noted that recently published experimental evidence confirmed that the off-target mutations potentially induced by SDNs are of the same type as, and fewer than, mutations in conventional breeding, including spontaneous mutations and those produced by physical and chemical mutagenesis.

As regards ODM, it was generally recognised that less information is available in the literature, in particular on its molecular mechanism and off-target modifications.

Cisgenesis and intragenesis

EFSA noted that cisgenesis and intragenesis use genes derived from the same gene pools as those used for conventional plant breeding. However, unlike conventional breeding, cisgenesis and intragenesis do not introduce the range of other genes and sequences that can be associated with linkage drag (the introduction of undesirable genes along with the intended gene during backcrossing), so the introduction of unwanted traits and hazards associated with these other genes or sequences can be avoided. As regards the hazards associated with the introduced genes, the risks arising from the use of a related plant-derived gene by cisgenesis are similar to those from conventional plant breeding. However, when a related plant-derived gene is used in intragenesis, some new combinations of genetic elements may arise that are not found in cisgenic and conventionally bred plants; these may present, as for transgenic plants, novel traits with novel hazards.

There is general agreement that cisgenesis might result in plants that are not substantially different, in terms of phenotypic characteristics and risks for human and animal health, from traditionally bred plants. One Member State noted that this could be ascertained only through comprehensive comparative analyses between the cisgenic plant and its conventional counterpart.

EFSA stated that cisgenesis, like conventional plant breeding, covers the use of genes from tertiary gene pools, i.e. from species that can only be crossbred using advanced techniques. One Member State disagreed with this, arguing that it invalidated the basic definition of a cisgene (i.e. a gene from a cross-compatible species). EFSA observed that the potential for random changes to the genome caused by the insertion event is not limited to cisgenesis, intragenesis and transgenesis; in fact, it is independent of the breeding methodology. Mutational processes, such as insertions, deletions or rearrangements of endogenous genes and regulatory sequences, are also known to occur in conventional breeding. New open reading frames are created at random during conventional breeding, cisgenesis, intragenesis and transgenesis, potentially giving rise to new proteins.

However, EFSA noted that transgenesis involves exogenous, non-host (and even non-plant) DNA, possibly leading to the formation of sequence combinations and open reading frames that would normally not occur with conventional breeding or cisgenesis. Similarly, intragenesis could give rise to new combinations in open reading frames, due to reconfiguration of the host sequences.

EFSA also observed that, in cisgenesis, the transferred genes are derived from sexually crossable species and are flanked by their native promoters. Although it might be expected that the use of a

native promoter is more likely to result in an expression pattern similar to the donor plant, this is not guaranteed. For example, the length of the cis regulatory elements transferred as part of the cisgene to the recipient plant will probably affect the expression pattern.

On the same topic, EFSA also noted that intragenesis offers considerably more options for modifying gene expression and trait development than cisgenesis, since genes and their promoters and regulatory elements are interchangeable within the intragenes.

Other considerations on risk assessment

There is general agreement that the risk assessment may benefit from any knowledge on the history of safe use of the modification(s) and trait(s) introduced. Therefore, some flexibility in the risk assessment is warranted; data requirements may be reduced and only parts of the risk assessment may be implemented on a case-by-case basis, thus enabling the simplification of the risk assessment process. Overall, there is agreement that existing risk assessment guidance is adequate for the assessment of plants obtained through SDN-based and cisgenesis/intragenesis techniques.

EFSA noted that, in order for the final product to be considered non-transgenic, molecular characterisation should be performed to demonstrate that no exogenous DNA is retained.

4.4.2. Member States' and stakeholders' views regarding safety

Most stakeholders noted that the safety of NGTs and NGT products is of the utmost importance for their placing on the market. However, views are divided, as there is no consensus on their safety, nor on the need and requirements for their risk assessment.

Most stakeholders focused on the safety and risk assessment of products produced by targeted mutagenesis (SDN-1, SDN-2 and ODM), often compared to the safety of products that could be obtained by conventional breeding. Only a few expressed views on other types of NGT. Some volunteered views on gene drive modified organisms.

General views on the safety of NGTs and specific considerations for plant applications

Some Member States are concerned about the possibility of off-target, unintended effects in the genome of the edited organism and their potential negative consequences for human, animal and plant health, and the environment. Some noted the uncertainty as to long-term safety risks in the use of NGTs.

Some stakeholders (mainly NGOs and organic/GM-free food business operators) raised concerns regarding the safety of NGT products, while others (mainly food business operators, NGT developers and academics) consider that NGT products are safe.

The main safety concern raised was the risk of unintended effects linked to the intended genetic modification, e.g. the production of new toxins or allergens. Another concern was the risk of on-target effects, where the intended change occurs at the intended location, but the outcome differs from what was expected. In addition, the risk of off-target effects was mentioned. Some stakeholders also commented that NGTs do not have a long safety record and that there is currently not enough scientific knowledge to evaluate their safety.

Stakeholders highlighted potential negative consequences for the environment, such as the introduction of new traits, interactions with wild species and gene flows, impact on food webs, influence on interaction between plants and pollinators, impacts on microbiomes, and the potential uncontrolled spread of the GMO into the environment. Some stakeholders noted concerns about the potential irretrievability of NGT organisms once released, while others mentioned concerns on persistence in the environment and impact on entire wild populations due to the release of gene drive modified organisms.

For the stakeholders that consider NGT products to be safe, the main argument is that NGTs are more precise (and thus create less risk) than conventional breeding techniques, which are already considered safe and not subject to mandatory safety assessment. Some food business operators and most academics noted that NGT plants are at least as safe as GMOs developed by established genomic techniques, if not safer due to the higher precision of NGTs. A few stakeholders pointed out that no risk assessment anywhere in the world had substantiated the concerns as to the safety of GMOs produced by established genomic techniques and that most regulatory bodies concluded that those GMOs are safe, implying that GMOs developed by NGTs are also safe.

The same stakeholders also mentioned that, for NGT products that could have been obtained by conventional breeding techniques, or random mutagenesis via chemical or irradiation treatment, either there is no safety issue or the issues are no different from those applying to products of the other techniques mentioned above. Some referred to the conclusions of the EFSA scientific opinion on SDN-1, SDN-2 and ODM, stating that no new hazards have been identified compared to SDN-3 and conventional breeding techniques.

A few stakeholders mentioned that the debate on off-target effects of NGTs is irrelevant, as newer NGTs are even more precise, reducing the risk of off-target effects even further, and off-target mutations in plants also occur in conventional breeding. A few also mentioned that unsafe plants are eliminated during the plant breeding process.

Some stakeholders mentioned that current genome sequencing technology allows greater understanding of the genetic modification, confirming that the intended change occurs at the desired site.

Specific considerations for animal applications

Most of the NGOs are particularly concerned about NGT animals and their welfare. Some mentioned the potential risk of increasing the rate of cancer in animals, linked to the mechanism of repair of DSBs in the DNA. Others mentioned that experimenting on animals often causes unnecessary animal suffering and death, and that GM animals often have health issues at birth.

A commonly cited example of unintended consequences of gene editing in animals is the case of genome-edited cattle, in which an unintended plasmid sequence with an antibiotic resistance gene was found at the targeted site in the genome.

Food business operators involved in animal breeding said that the technology should be improved further in order to avoid off-target effects. They are also concerned about epigenetic and epistatic effects, and about animal integrity. It was proposed that NGT animals should be tagged, so that

responsibility and liability can be assigned in the event of damage. Their position is that the use of food products from NGT animals raises no safety or nutrition concerns.

A few stakeholders commented on gene drive modified organisms, particularly in animals, raising concerns as to their safety, in particular their impact on the environment, ecosystem functioning and biodiversity preservation. However, their comments referred to gene drives in general and not specifically to those using NGTs. Stakeholders mentioned that eradicating a species could have a negative impact on the whole ecosystem and that gene drives might inadvertently eradicate another species or expose it to undesirable developments.

Specific considerations for micro-organism applications

Stakeholders active in the field of industrial microbiology stated that the increasing precision of NGTs, combined with recent developments in genomics and sequencing, is helpful for understanding and increasing the safety of the products, also facilitating risk assessment.

Specific considerations for medicinal applications

While it was acknowledged that the technology is not without risk and that good characterisation of products (including safety characteristics) is necessary, it was noted that this was addressed sufficiently under the medicines legislation. In this regard, some healthcare stakeholders specifically expressed trust in the ability of the European Medicines Agency to assess and ensure the safety of NGT products.

Stakeholders' and Member States' views regarding the need for risk assessment

Several Member States consider that the current risk assessment procedures and guidelines need to be adapted for NGTs. Some mentioned the need to adapt the guidelines in various areas (e.g. medicinal products, molecular characterisation and environmental monitoring, particularly as regards gene drive off-target effects) or argued that they should focus on products rather than the GM technology used. One noted the issue of potential environmental hazards, such as the emergence of pest resistance or secondary pests, while another considers that there is no specific need for risk evaluation of NGT products.

Several stakeholders stated that the safety of products developed by NGTs should be risk assessed. However, their views diverged as regards what type of risk assessment was needed.

Most NGOs and organic/GM-free food business operators stated that NGT products require risk assessment under the current GMO legislation or that they require more stringent risk assessment.

Some stakeholders from various sectors, including a few NGOs, are of the opinion that risk assessment is necessary, but that the requirements should be decided on a case-by-case basis. Most are of the opinion that risk assessment should be science-based and proportional to the risk of specific products, not based on a generic standard applying to all products. Some said that risk assessment should not be process-based, but product-based, and that the safety of a product depends on what has been modified or the trait that has been obtained, not on the technique used.

Others are of the opinion that the case-by-case approach should be at least as stringent as current GMO risk assessment and should require more information to assess the safety of an NGT product.

A few stakeholders, representing mostly the agricultural and plant breeding sectors, argued that no additional risk assessment should be required for NGT products that could also have been obtained by conventional breeding. It was also mentioned that plants are subject to a range of rules (e.g. under the General Food Law, Regulation (EC) No 178/2002), which guarantee their safety, and even if not subject to risk assessment under the GMO legislation, they are still tested against various criteria before being marketed; in addition, the agricultural production chain is responsible for ensuring the safety of products that are placed on the market.

Stakeholders from the medicinal sector noted that the current system hinders the development of medicinal products and that the pharmaceutical legislation contains sufficient provisions for risk assessment.

Finally, some stakeholders commented on the limitations of risk-assessing gene drive modified organisms, as we do not know enough about their potential impacts on the environment; the only way to assess the risk is to release the organisms into the environment.

4.5 New genomic techniques research and innovation

4.5.1. EU funding for NGT research

EU research and innovation (R&I) funding for NGT-related projects under FP7 (2007-2014) and Horizon 2020 (2014-2020[53]) amounted to €3.2 billion, distributed among 1 021 projects. Health and medical-oriented research accounted for most of the funding (€2.5 billion; 802 projects). The rest was for bioeconomy research (€685.5 million; 219 projects), which includes agri-food applications.

Health- and medical-oriented research

Genome editing was predominantly used as a research tool either in cultured cells or in laboratory organisms to understand the role of genes in health and disease. Research involving NGTs includes approaches to treat or cure diseases.

Basic research projects (€1.8 billion; 783 projects) focused on changes to the genetic material of cells *in vitro*. Animal studies (€1.2 billion; 359 projects) examined changes to the genetic material of whole organisms, e.g. in mice and zebrafish. Research on medicinal product development (€238 million; 51 projects) focused on changes to the genetic material of cells for cell therapy or gene therapy, while clinical trial research (€75 million; 10 projects) involved testing in human subjects with GM cells or gene therapies. Finally, research on pathogens (€70.7 million; 16 projects) focused on changes to genetic material in order to understand pathogenicity. A large proportion of projects included applications in more than one of the above fields, demonstrating the cross-cutting use of NGTs in biomedical research.

Overall, there was an approximately four-fold increase in citations of NGTs in relevant project documents from the H2020 portfolio, as compared to FP7. In the FP7 period, submitted project documents cited zinc finger nucleases (ZFNs) and TALENs as often as CRISPR. However, in the context of H2020, CRISPR was the dominant NGT cited (in 27% of FP7 but 87% of H2020 documents). This

[53] Up to June 2020.

demonstrates not only a greater use of NGTs in research projects (€700 million in FP7 vs €1.8 billion in H2020), but also a shift in the techniques applied.

The scientific community at large has embraced CRISPR as the NGT of choice for biomedical research, due to its higher targeting efficiency, easy use and affordability as compared to previous nuclease-based technologies. With CRISPR becoming such a mainstream research tool, more new clinical applications and increased support for the development of novel techniques such as prime or base editing can be expected under the 2021-2027 framework programme (Horizon Europe).

Bioeconomy-oriented research

Plant biotechnology research (€271 million; 78 projects) accounted for most of the funding in bioeconomy. Projects focused primarily on increasing plant growth and crop yields, and on resistance to biotic (plant disease) and abiotic (environmental) stresses. Several projects dealt specifically with cereals, in particular wheat, while others focused on crops such as chicory, legumes, potatoes, stevia and fruits. In addition, several focused on plant metabolite biosynthesis and the production of metabolites such as fibres, fatty acids, oils and rubber, or other substances used in pharmaceuticals. Others focused on tree improvement for forestry applications (e.g. in poplar trees). Other plant breeding topics included plant nutrient management, cell signalling, improved root traits and microalgae breeding.

NGT synthetic biology research (€189 million; 75 projects) studied applications in microbial biotechnology and focused on the development of new techniques, tools and methods. Several NGT-related projects dealt with nanotechnologies and smart chips and circuits, such as biomolecular models for synthetic biology, hybrid cells using lab-on-chip technologies, biological computers from bacterial populations and engineering synthetic multicellular signalling biocircuits. A number of projects investigated ethical aspects of synthetic biology, while others focused on novel CO_2-fixing enzymes and carbon fixation pathways.

NGT-related research on micro-organisms (€135.5 million; 47 projects) was mainly basic, addressing bioprocessing issues or metabolic engineering, e.g. understanding and developing cell factories for the production of a range of renewable bioproducts, such as fluorochemicals and synthetic nanomaterials. Several projects were aimed at improving production of renewable and sustainable biofuels.

Animal-related NGT research (€90 million; 19 projects) focused on understanding molecular genetic make-up and gene regulation mechanisms. Project topics included adaptive immunity, cell differentiation, desiccation tolerance, evolutionary adaptation, genetic networks and genetic individuality. Other projects focused specifically on genome editing techniques for small livestock ruminants and better genomic understanding of insects and pests that cause disease in agricultural livestock, including models for the better understanding of animal diseases.

Finally, some projects addressed public communication strategies and methodologies as regards GMOs, NGTs and synthetic biology, and regulatory and risk assessment aspects.

Overall, in bioeconomy NGT projects, 58% of the coordinating institutes were universities or educational entities, 35% were public institutes and 7% were private or industrial entities.

4.5.2. Member States' and stakeholders' activities in NGT-related research

The considerable interest in NGT-related research is reflected in the activities reported by several stakeholders and the level of Member State funding in this area. Many Member States reported that their national funding for NGT-related research amounted to around €356 million in the last 5 years.

The majority of the funding (76%) was dedicated to medicinal (44%) and agri-food (32%) NGT applications, followed by basic research (19%). Other areas include industrial (micro-organism) applications (2%), detection methods, risk assessment and monitoring (1.6%), and regulatory, ethical and communication-related issues (1%). Many Member States consider that NGT research will continue evolving, with some pointing to specific fields such as medicinal or technology optimisation.

In addition, many stakeholders reported that their members are carrying out NGT-related research in the agri-food, industrial, medicinal and biotechnology development sectors, and on risk assessment and ethical issues.

4.5.3. Member States' and stakeholders' views on research and innovation

Benefits and concerns relating to NGT research

All Member States that replied consider that NGT research will bring benefits in medicine (development of new medicinal products, in particular against genetic diseases, and immunotherapies and vaccines). Most also consider that it will contribute to more resilient and sustainable agriculture and many see benefits in healthier and safer foods, e.g. fewer allergens or contaminants, improved nutrient profiles. Several consider that NGTs directly benefit research on basic scientific/biological questions. The industrial sector (bioenergy, bioeconomy, fermentation procedures) will also benefit, according to some Member States.

Many Member States reported that NGT research activities could raise general ethical concerns. Of these, several point to a need to address the responsible use of NGTs (who performs research? for what purpose? how to avoid abuse?), while some consider that ethical issues should be tackled in specific cases, such as the editing of embryos, modification of the human germline or humanisation in animals or gene drives. For further details on ethical concerns associated with NGTs, please refer to Section 4.10.4.

Some Member States consider that research should be subject to open public discussion or that scientific communities or scientific and government agencies should communicate on scientific matters.

Stakeholders' views on the benefits of NGT research are polarised. Some (mainly food business operators and academics) consider that it will bring benefits in their respective fields of agriculture, food and feed, academia and research, industry, the environment, and the medicinal and biotechnology sectors. Others (mainly NGOs and non-GM food business operators) consider that it will not bring any benefits in the agri-food sector. Some are concerned that NGT-related research will hinder participatory and decentralised innovation pathways.

The benefits of and concerns relating to NGT applications in general are further detailed in Section 4.6.

Impact of the CJEU ruling and the GMO regulatory framework on NGT research

Many Member States mentioned that the current regulatory framework brings challenges for NGT research activities: R&D is negatively affected, putting EU academics and public and private research institutions at a competitive disadvantage internationally. In addition, there is a risk of NGT research moving outside the EU.

On the other hand, some Member States report no specific challenges when funding or supporting NGT research.

Stakeholders (food business operators, academics and researchers, biotechnology industry) reported that the CJEU ruling has had some sort of direct or indirect impact on research activities. Most reported negative impacts (projects stopped or postponed, reduced private funding interest, research moving outside the EU) and highlight this as a serious challenge for NGT research in the agri-food and industrial sectors, affecting private companies, public institutions and academics.

Other stakeholders (NGOs) consider that the CJEU ruling has had positive effects on agri-food research, as it allows research into less risky innovation and into alternative conventional and non-NGT strategies. Some NGOs noted that political advocacy and lobbying (e.g. by scientific groups and industrial agriculture) against the CJEU judgment have increased and that such activities are sometimes disguised as research initiatives. One scientific research stakeholder reported that, since the ruling, it had extended its research focus to new risk assessment procedures and unintended effects of NGTs. Other stakeholders (GMO-free/organic operators and NGOs) reported no impact on research activities following the CJEU ruling.

Stakeholders from the medicinal sector indicated that the application of the GMO legislation hinders the development of gene therapies and significantly delays the conduct of clinical trials with these products in the EU.

Research needs

Many Member States pointed to a need to develop reliable detection and traceability methods. Several pointed to a need to develop specific risk assessment procedures for NGTs. Some specified that new risk assessment guidelines should focus on molecular characterisation and assessing unintended effects, rather than the technology used.

Stakeholders often cite a need for research into the safety and environmental risks linked to adverse and unintended effects and the interaction of NGT products with the environment. Some argued that research on potential risks should be independent and free from conflicts of interest. Another oft-mentioned research need is the development of reliable detection methods and traceability strategies. Other topics identified as needing further research include public perception, understanding and awareness of NGTs, ethical issues, socio-economic impacts, regulatory burden impact, farmers' rights, intellectual property (IP), the loss of biodiversity, and animal health and welfare. A number of stakeholders called for more publicly funded research on sustainable alternatives to NGTs.

Some stakeholders reported the need for basic research to increase knowledge of genome functions or improve NGT technology. In addition, stakeholders reported a variety of NGT-related needs for specific sectors, such as the development of specific traits in plants and livestock.

4.6. Member States' and stakeholders' views on potential NGT-related opportunities and benefits

4.6.1 Member States' views

Many Member States recognise potential benefits from NGTs and NGT products. In the agri-food sector, the examples cited most relate to plants with improved tolerance or resistance to biotic stress (plant diseases and pests) and plants with improved tolerance or resistance to climate change effects in general and abiotic stresses (environmental, e.g. temperature, drought) in particular. Other oft-cited benefits include faster, more precise and more efficient plant variety breeding, improved nutrients and water-use efficiency in plants and micro-organisms, and plants with improved agronomic characteristics (e.g. higher yields and harvest resilience) and quality characteristics (e.g. nutrient content for food and feed). Examples of potential benefits include reduced use of plant protection products, the development of plants containing fewer allergens, toxins or other harmful substances, and reduced development costs compared with other breeding methods.

In the medicinal sector, the most-cited examples of benefits include NGTs' contribution to the development of advanced therapies, including gene therapies for the treatment of genetic disorders, the development of immunotherapies, and the faster development of vaccines. Other benefits include the control and prevention of zoonoses, and improved treatments and pharmaceutical products due to a better understanding of gene functions and disease models.

In the industrial biotechnology sector, benefits cited by Member States include the use of NGT plants (including trees) for the production of speciality chemicals in the bio-based industries, e.g. paper, biofuels and plastics. Benefits in microbial biotechnology are also mentioned, e.g. for strain improvement, production of a broad array of substances and fields of application (including alternative use of substrates such as by-products or waste products) and use in the bioremediation of polluted soils.

Further examples of benefits and opportunities reported by Member States are listed in Table 8 in Annex D.

4.6.2 Stakeholders that see benefit in NGTs

A number of stakeholders (mostly food business operators, biotechnology and pharmaceutical industry actors and academic/scientific organisations) state that NGTs can bring benefits to their sector and society in general, similar to those mentioned by Member States. In addition, they argue that NGTs can contribute to and are in line with the Green Deal and 'farm to fork' strategy objectives.

Among the benefits of NGTs mentioned by stakeholders, the examples cited most relate to the agri-food sector. This includes plants with improved tolerance or resistance to biotic and abiotic stresses (including climate change effects), plants with increased yields and plants with reduced content of harmful substances such as allergens, chemicals, contaminants and toxins. Other reported benefits are the reduced use of plant protection products and fertilisers, the reduced use of other agricultural inputs or resources, and reduced costs and time of development and selection in breeding compared to other methods. Some stakeholders said that it would not be possible to achieve the EU's pesticide reduction targets without using alternatives such as NGT plants.

Medicinal sector stakeholders stressed the benefits for patients and society linked to the products' potential to cure conditions for which there is currently unmet medical need. Benefits cited include the significant impact that NGTs can have in terms of the faster, more affordable development of medicinal products, and benefits for patients and society linked to the products' potential to cure, rather than just treating symptoms. The possibility of single curative interventions for certain disorders, instead of multiple interventions, was also mentioned. Other benefits include more robust pre-clinical assessment of candidate drugs.

In the sector of micro-organisms and industrial biotechnology, NGT benefits include the use of safer micro-organisms in food and feed applications thanks to greater efficiency in targeting and eliminating antibiotic resistance and other virulence factors, greater accuracy and efficiency in introducing genome changes, and the introduction of multiple beneficial traits in a single micro-organism.

In animal NGT applications, the benefits mentioned include improved welfare of livestock animals, reduced use of antibiotics or other medicines due to improved disease resistance, less need for experimentation in animals and a smaller environmental footprint from livestock.

Stakeholders that see benefits in NGTs claim that these are NGT-specific; they argued that other methods are less precise and efficient, and more expensive and time-consuming, and that in certain cases the products resulting from NGTs can simply not be obtained by other methods.

Those stakeholders consider that the materialisation of such benefits depends on certain pre-requisites, in particular adapting the regulatory framework to make it fit for purpose for NGTs, as long as NGT products are safe for human and animal health, and the environment. Other conditions include greater public acceptance, transparent authorisation procedures, increased political acceptance and treating NGTs as one tool in an integrated, holistic approach, rather than a solution by themselves.

Further examples of opportunities and benefits reported by stakeholders are listed in Table 10 in Annex D.

4.6.3 Stakeholders that do not see benefits in NGTs

A number of stakeholders (mostly NGOs and GM-free/organic operators) do not believe that NGTs will bring particular benefits in the agri-food sector. They claimed that any benefits can also be obtained via other forms of agriculture and that only a few players gain from NGTs, rather than society in general.

They argue that the benefits of NGTs are largely hypothetical, that, to date, there is neither proof nor substantiation of their potential to contribute to the sustainability of the agri-food system, and that we do not know enough about their health, environmental, economic and social impacts. In addition, the complex environmental, economic and societal challenges in agriculture cannot be resolved by solely technical interventions or a single variant/trait. Some stakeholders compared the potential benefits of NGTs with the earlier (in their view, unfulfilled) promises of transgenic GMOs.

They also stated that NGTs can modify only relatively simple traits such as herbicide or pathogen resistance, which are quickly overcome by new mutations in pathogens and weeds, but will not be able to achieve more complex traits such as drought resistance, which result from the interaction of

many genes and environmental conditions. Some stakeholders noted that multinational corporations behind NGT development prefer uniform seeds, monocultures and narrow genetic resources that may benefit one farming model, but will not support genetic diversity, crop resilience and local solutions. They also mentioned that only large corporations would enjoy economic benefits. Other reasons provided as to why NGTs will not bring benefits largely reflect the concerns that these stakeholders have about NGTs and their products, and are reported in Section 4.7.2.

The benefits of NGTs in the medical field were not questioned by any stakeholder. Further reasons why certain stakeholders do not see benefits in NGTs are listed in Table 11 in Annex D.

4.7. Member States' and stakeholders' views on potential NGT-related challenges and concerns

4.7.1 Member States' views

Many Member States think that the use of NGTs could face challenges or raise concerns in agri-food, the medicinal sector, the industrial sector and society in general.

The concerns mentioned most relate to public acceptance and the negative public perception of NGTs and their applications in the agri-food sector, the difficulties with effective detection, identification and traceability systems for some NGT products, and issues relating to safety. Member States see a challenge relating to the mechanisms that are in place to ensure the risk assessment and risk management of NGTs in all their applications. Many are also concerned about potential negative environmental impacts of NGTs on biodiversity and ecosystems in general.

Many Member States expressed concerns on the EU's and its trade partners' diverging legal and administrative requirements for NGTs and their potential consequences. They believe that this may lead to the presence of unauthorised products in the EU and an uneven playing field, with detrimental impacts for EU farmers' and businesses' competitiveness. Several Member States are also concerned about the difficulties (including high authorisation costs) that the industry will face in developing and commercialising NGT products as a result of the current EU regulatory requirements.

Several Member States expressed concerns on ethical aspects of the use of NGTs; the topic is further discussed in Section 4.11.1.

Several Member States expressed concerns on the co-existence of different types of agricultural production. They draw particular attention to the organic and GM-free premium segment markets and their supply chains (farmers, operators of certification schemes), which may face a severe threat from certain NGT products. These operators could face difficulties in implementing the traceability and labelling requirements for certification and consequently in maintaining consumer trust. Some Member States were concerned about a possible displacement of traditional varieties and loss of agricultural diversity due to the massive use of improved NGT varieties.

Several Member States highlighted the need to ensure consumers' freedom of choice and noted that the labelling of NGT products could be an issue.

Concerns on the use of NGTs in the medicinal sector were less marked and related mainly to scientific unknowns and risks of off-target effects that could have an impact on patient safety. A number of Member States referred to problems relating to the application of the current GMO legislation to medicinal products. In particular for clinical trials, some Member States reported that there are doubts as to which techniques and products are subject to the GMO legislation.

Further examples of challenges and concerns reported by Member States are listed in Table 9 in Annex D.

4.7.2 Stakeholders' views

The lack of international harmonisation on NGT regulatory approaches and, more specifically, differences between the EU and its major trade partners in the regulation of NGTs and their products are a major concern for several stakeholders (food business operators, scientific and research associations, and academics), as they could lead to trade disruption and block access to resources. Several stakeholders are concerned about EU academics and agri-food operators being at a competitive disadvantage. The lack of reliable detection methods is also a major concern, as it affects agri-food business operators' ability to verify compliance with the EU legislative framework. This has potential implications for legal liability, compliance costs, the risk of fraud and consumer trust. Finally, some stakeholders are concerned about the potential regulatory burden on NGTs and their products; others argued that herbicide-tolerant traits should not be rejected just on principle.

Several stakeholders (mainly NGOs) have safety-related concerns; these are further detailed in Section 4.4.2. Similarly, ethical concerns are reported in Section 4.10.4.

In addition, several stakeholders (organic/GM-free operators and NGOs), see NGTs and their products as a major threat to the viability of the organic and GM-free sectors, due to increased compliance and segregation costs, difficulties with controls and certification, the potentially unavoidable presence of NGT products in their supply chains (including contamination of breeding stocks), higher final product prices and a potential loss of consumer trust.

Another challenge mentioned by some stakeholders (mainly business associations) is that the current negative public perception of conventional GMOs could extend to NGTs and NGT products, preventing their market uptake. They also claim that prohibiting the use of NGTs will effectively prevent the EU from accessing much-needed tools for the agri-food sector.

Loss of freedom of choice for consumers due to potential deregulation in the EU and/or undetected NGT products is another stakeholder concern.

Stakeholders from the medicinal sector are concerned about the application of the GMO legislation to medicines. They consider that the GMO legislation is not specifically designed for medicinal products and hinders the conduct of clinical trials, delaying patient access to them and affecting the EU's competitiveness as a place to develop advanced therapy medicinal products and conduct clinical trials. They ask for reconsideration of the application of the GMO legislation to medicinal products consisting of or containing GMOs. More specifically, they believe that there are no environmental and biosafety risks for non-replicating viral vectors or GM human cells, as these do not duplicate and cannot survive in the environment. Specific problems mentioned in relation to the application of the

GMO legislation include the lack of harmonisation, the duplication of assessments (under both GMO and pharmaceutical frameworks) and insufficient expertise among GMO authorities on gene therapies, in view of the rising number of applications. A more streamlined and harmonised approach was proposed, which fully integrates GMO aspects into the clinical trial application process. They further highlighted that the R&D costs of these advanced therapies will require a new financing model, including pricing and reimbursement, due to the products' different mode of action (single administration that is expected to have long-term effects). Finally, the ethical concerns on the genetic modification of embryos or modification of human germline are acknowledged; the developers' associations that responded to the consultation indicate their opposition to such practices.

Some stakeholders (food business operators and NGOs) are concerned that the high business concentration and monopolies observed previously in the GMO sector will be repeated in respect of NGTs. However, the conditions in which they see this occurring are different. Food business operators see this happening if NGTs remain under the current GMO legal framework, while NGOs believe that the NGT business model will lead to monopolies in any case. In addition, some NGOs noted that NGT development is linked to intensive farming models and is patent-driven, resulting in restricted access to plant genetic material and affecting farmers' and breeders' rights.

Food business operators, industry, academics and scientific stakeholders specify that their concerns (see above) will materialise if NGTs continue to be regulated under the current GMO framework; in their view, a more appropriate and fit-for-purpose framework is needed for the regulation of certain NGTs. On the other hand, NGOs and organic/GMO-free operators believe that their concerns will materialise if NGTs are regulated differently from conventional GMOs, or if they are completely unregulated.

Some stakeholders (NGOs and food business operators) believe their concerns relate specifically to NGTs and their products, as opposed to conventional GMOs, due to the lack of detection methods, or due to the ease and efficiency of their applications. However, others (food business operators, academics, NGOs) believe that their concerns as regards NGTs are no different from those they have for conventional GMOs. Finally, others noted that this is a case-by-case issue and depends on the NGT used and its intended application.

Further examples of challenges and concerns reported by stakeholders are listed in Table 12 in Annex D.

4.8 Views relating to Small-Medium Enterprises and intellectual property

4.8.1 SMEs

In the agricultural sector, many Member States and stakeholders see opportunities for SMEs and small-scale operators to access the NGT and NGT-product market, due to the lower cost and ease of use of the techniques as compared to EGTs. They also see the techniques as an opportunity for SMEs to develop minor, niche or orphan crops, and special traits in plants, in response to local needs, to move towards more sustainable agri-food production, stress-tolerant and disease-resistant varieties, and a reduced use of plant protection products.

Many Member States and stakeholders also believe that, if NGTs are considered as GMOs and fall under the EU GMO approval arrangements, the regulatory burden from the authorisation procedure will constitute a major barrier to market access for SMEs. Many cite the high cost of preparing an authorisation dossier, the length and legal uncertainty of the process, the complexity and cost of safety testing and the difficulty in obtaining cultivation approvals in the EU as factors in this respect. In addition, many Member States and stakeholders mention the high cost of patenting innovations and the high patent licence fees as a barrier to market entry for SMEs.

Other challenges mentioned as posing particular economic risks for SMEs are the low level of public acceptance of GMOs, and R&D costs for investment in expertise and laboratory equipment.

By contrast, some stakeholders in the pharmaceutical sector noted that the majority of companies developing gene therapies are SMEs, due to the lower complexity and cost of NGTs. However, some Member States and stakeholders also mentioned the regulatory burden of the EU GMO authorisation system and the lack of sufficient manufacturing and distribution capacity as challenges for SMEs in this sector.

Further views of Member States and stakeholders relating to SMEs can be found in Tables 8-12 in Annex D.

4.8.2 Intellectual property

With regard to IP and the patent protection of biotechnological inventions (under Directive 98/44/EC[54]), many Member States and stakeholders in the agricultural sector acknowledged the benefits and opportunities of patenting NGTs and their products. They noted that a strong patent system is necessary to enable innovation (e.g. by incentivising investments in R&D) and promote the dissemination of knowledge, including through licensing, as this is considered vital for the development and commercialisation of new products.

Some Member States and stakeholders pointed to the need to enhance competition further and ensure access to patented NGTs, e.g. again by promoting licensing.

On the other hand, many Member States and stakeholders expressed concerns with regard to patenting or accessing patented NGTs or NGT products, in particular for SMEs. These include the limiting effects of such patents on access to new technologies, and plant breeders' access to the genetic material they need for further innovation in breeding, especially if compared with plant variety rights[55]. Other concerns related to the concentration of players on the seed market, resulting in higher seed prices, a reduced choice in seeds and greater dependency among farmers. Also mentioned were the high costs and complexity of patenting, licensing patented products and other aspects such as 'freedom to operate' analyses, e.g. due to the complex patent landscape of the CRISPR technology.

[54] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions (OJ L 213, 30.7.1998, p. 13).

[55] Plant variety rights are regulated under Council Regulation (EC) No 2100/94 of 27 July 1994 on Community plant variety rights (OJ L 227, 1.9.1994, p. 1).

All responding stakeholders from the pharmaceutical sector and some Member States mentioning this sector see benefits in strong patent protection of NGTs and NGT products as a pre-requisite for innovation due to high R&D costs, but some express concerns about the complex patent landscape for NGTs, with many players holding patents and uncertainty as regards the IP situation. A few Member States expressed concerns about the affordability of gene therapies. One noted that the potential higher prices for such therapies may not be linked to their actual production cost, but result from patents.

Other views of Member States and stakeholders relating to IP can be found in Tables 8-12 in Annex D.

4.9 Stakeholders' views on the labelling of NGT products

All stakeholders recognise the importance of the consumer's right to information and freedom of choice. However, their views diverge when discussing the labelling of NGT products.

Several stakeholders (NGOs, food business operators, including those specialising in non-GM foods, and retailers) believe that NGT product labelling is important to ensure that consumers are informed and have freedom of choice. Some further specified that NGTs should be labelled as GMOs under the current framework, without any distinction.

Others (NGOs and non-GM food business operators) emphasised that NGT labelling is crucial for organic and GMO-free agriculture farmers and value chains, and (see above) that not labelling NGTs products as GMOs may threaten the survival of these sectors, due to significant negative consequences, including economic burdens due to increased costs of traceability and loss of consumer trust.

They further pointed out that the consumer's right to information is enshrined in EU food law and the Treaties, highlighting that one of the aims of the Green Deal is to improve transparency in the agri-food chain; not labelling NGTs would go against that. In addition, consumers do not accept GMOs and retailers do not want to sell them.

On the other hand, several stakeholders (mainly food business operators) noted that, since no reliable detection and differentiation methods exist, labelling NGT products under the existing legal framework creates not only a challenge and a legally untenable situation for operators, but also problems in dealing with imports from countries that regulate NGTs differently or not at all.

As such, they argue that labelling should not apply to NGT products that are indistinguishable from those obtained from conventional breeding; such labelling might mislead consumers, offer no benefits, and constitute discrimination and a non-tariff trade barrier. Some of these stakeholders proposed that, if NGTs are to be labelled, the label should also highlight their benefits. Some argued that labelling should be restricted to information on food safety and sustainability.

Others are concerned that labelling NGTs as GMOs would amount to a quasi-ban, as it might lead consumers to perceive them as potentially dangerous and reject them as a result. Furthermore, they believe that the decision as to whether to label a product should be based on criteria that consumers can understand and that labelling should be based on the products' final characteristics and not on

the technology used to produce them. Others noted that consumers have the right to fact-based, scientific labelling.

Some stakeholders noted that information and traceability on NGTs is important not only for consumers, but also for operators (e.g. for post-market monitoring, recalls) and that the introduction of an NGT-specific labelling scheme, in addition to all other existing labelling schemes, would not add much value (confusing, difficult to enforce, waste of resources and money).

The labelling of NGT products raises different considerations in the medicinal sector. The traceability and labelling provisions in Directive 2001/18/EC do not apply to medicinal products, which have to be labelled in accordance with the medicines legislation. Stakeholders active in the medicinal sector believe that no additional labelling rules are needed for NGTs, beyond what is already required under the medicines framework.

Further stakeholder views on the labelling of NGT products are listed in Table 13 in Annex D.

4.10 Public dialogues and surveys on NGTs

4.10.1 Public dialogues reported by Member States

Many Member States reported on 67 past and ongoing NGT-related events organised by a wide variety of bodies (e.g. government institutions and research institutes). The number of public dialogue initiatives has increased each year from 2016. Target audiences varied according to the event. In some cases, they were open for all citizens; in others, public dialogues and surveys specifically addressed NGT stakeholders or government representatives.

Various formats were used for the dialogues, e.g. seminars, symposiums and workshops. They focused mainly on the use of NGTs in the agri-food and medicinal sectors, while covering a broad range of topics, including policy, ethics, biosafety, risk assessment, socio-economic impact and NGT applications. The reported initiatives are listed in Table 14 in Annex D.

4.10.2 National and EU-wide surveys

Six Member States reported 11 surveys on NGTs, making it difficult to draw general conclusions. However, from the national surveys, it seems that consumers are poorly informed on NGTs and GMOs in general. Most of the surveys primarily targeted consumers, but two covered farmers, food producers and other stakeholders.

The surveys focused on NGT applications in the agri-food and medicinal sectors and on evaluating public knowledge and perceptions of NGTs. Reported national surveys are summarised in Table 15 in Annex D.

In 2019, a special Eurobarometer on food safety in the EU[56] (requested by EFSA) showed that 60% of EU respondents had heard about GM ingredients in food and drinks, and 27% were concerned about them. In the 2010 Eurobarometer on biotechnology[57], a large majority (84%) had heard of GM foods

[56] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/Eurobarometer2019_Food-safety-in-the-EU_Full-report.pdf

[57] https://ec.europa.eu/commfrontoffice/publicopinion/archives/ebs/ebs_341_en.pdf

and 61% felt uneasy about them. This was also reflected in the EFSA 2010 Eurobarometer on food-related risks[58], where 66% of respondents were worried about GMOs in food and drink. Public perception of gene therapy medicinal products is largely positive, as shown in the Eurobarometer on biotechnology, but people feel that strict laws are needed to alleviate concerns on ethical issues[59].

Specifically on NGTs, the 2019 Eurobarometer reported that only 21% of EU consumers had heard of genome editing and 4% were concerned about genome editing in foods. The former demonstrates an overall limited awareness of NGTs, which probably explains the latter. In the 2010 Biotechnology Eurobarometer, the majority of respondents were favourable towards cisgenesis. 63% agreed that cisgenic apples are useful (25% disagreed), 50% disagreed that they harm the environment (30% agreed) and 45% disagreed that they are risky (40% agreed); 39 % disagreed that cisgenic apples are unnatural (52% agreed); 47% would encourage cisgenic apples, while 38% disagreed. Overall, cisgenesis is perceived as a more 'natural' technique, less problematic for the environment, safer and more useful/promising than transgenesis.

4.11 Ethical aspects of NGTs

4.11.1 Member States' views

Some Member States expressed general ethical concerns in relation to human germline gene modifications[60], the modification of human embryos and the development of 'humanised' animals. Possible off-target effects in human gene modification were also mentioned under ethical considerations and are addressed in Section 4.4.2. One Member State reported concerns as to the compatibility of somatic cell therapeutic applications with the universal and public nature of the healthcare system; the concerns relate to the monopolisation of IP rights and patents, limitations in accessibility and possible higher costs of therapies. One Member State noted that clinical trials in the medicinal product field are subject to ethical review.

Some Member States raised ethical concerns relating to the welfare of gene-edited animals and the environmental release of NGT products, when combined with a lack of traceability. In addition, some ethical concerns about the impact of synthetic biology and gene drives on biodiversity and ecosystems were highlighted.

On the other hand, some Member States believe it is ethically problematic to reject genome-edited plants if they have beneficial traits, while another considers that the impact of the EU GMO legislation on international trade and other countries raises ethical issues, particularly for the developing world. It argued that the failure to adopt more effective breeding methods in the EU could lead to higher production prices, a brain drain, environmental damage and (in less developed countries) crop failures, endemic malnutrition and potentially migration pressure and war.

58 https://ec.europa.eu/commfrontoffice/publicopinion/archives/ebs/ebs_354_en.pdf
59 https://ec.europa.eu/commfrontoffice/publicopinion/archives/ebs/ebs_341_en.pdf
60 Modification of the human germline is prohibited in the EU.

4.11.2 Public dialogue initiatives and Member State expert opinions

Member States also provided information on various events (annual meetings, conferences, symposiums), reports and expert body opinions relating to ethical aspects of NGTs, mainly in the agri-food and medicinal sectors (Table 16, Annex D). These are summarised below.

Agri-food applications

Several Member States stated that NGT applications could be part of the solution to challenges such as the preservation of biodiversity, resilience to climate change and improving animal welfare. One concluded that it would be unethical to reject GMO varieties, including NGTs, if they can contribute to solving problems in agriculture and food production, and if there are no good arguments for rejecting them. As regards animal welfare, one mentioned that genome editing facilitates not only the use of GM laboratory animals, but also the use of other animal species as laboratory animals, which may stoke the debate on the use of laboratory animals. Genome editing opens up (still theoretical) possibilities for reintroducing extinct animal species.

Two expert body opinions reported that innovation should always be based on the precautionary principle, which should inform careful assessment and a broader approach. Another noted that genome-editing policies should take account not only of risk assessment, but also broader considerations, including the societal value of genome-editing applications.

As regards cultivation, two Member States argued that GMOs in general should not be prohibited without justification and that Member States that ban GMOs for cultivation should give reasons for doing so.

Medicinal applications and other potential uses in humans

The reported opinions on ethical aspects of medicinal applications relate primarily to gene editing in humans. The main concerns relate to the therapeutic, enhancement or optimising gene modification of the somatic or germinal human genome.

On the one hand, the opinions broadly recognised the potential of the technology to develop medicinal products to treat/cure life-threatening conditions or develop vaccines. Some of the concerns they noted relate to potential side-effects due to current scientific unknowns (e.g. off-target effects). One opinion was concerned that acceptance of using NGTs in somatic cell modifications could lead to easier acceptance of germline modifications in humans. In addition, a couple of expert opinions mentioned that it could become difficult in the future to differentiate between a therapeutic and an enhancement intervention.

Some opinions noted that, before considering therapeutic or enhancement modification of germline genome in humans, certain issues should be addressed, such as technical risk uncertainties, social consequences of germline genome editing (e.g. stigmatisation, inequality and changing norms) and values concerning health, sickness and solidarity. One national body called for the lifting, under strict conditions and for certain purposes only, of the prohibition on scientific research on specially created embryos, in order to enable further research on cultured embryos. This includes fundamental research into the use of CRISPR for germline genetic modification. The same body warned that the first applications of germline gene editing, including for xenotransplantation, are expected to take place outside the EU, so medical tourism for genome editing could become a real possibility.

Finally, some expert opinions concluded that the release of gene drives into the environment poses ethical and environmental problems that should be addressed. Some stated that research is needed into the management of gene drive reversibility.

4.11.3 Stakeholders' views

Some stakeholders (especially NGOs and GM-free/organic food business operators) mentioned ethical concerns relating to seed producers', breeders' and farmers' freedom of choice on types of seeds, breeding methods and farming techniques, the potential misuse of techniques (e.g. for biological warfare), negative impacts on the ecosystem and biodiversity (e.g. in relation to gene drives), and the concept of 'naturalness'. Animal welfare was another frequently mentioned ethical concern, as, in their view, NGTs have the potential to damage the health and welfare of farm animals, since the main objective of animal NGT research is to increase productivity.

Other stakeholders (food business operators, academics) argued that it would be unethical to prevent, slow down or delay scientific progress and its potential benefits to society, referring specifically to the UN's SDGs. They believe that NGT applications in plant and animal breeding can be part of a sustainable solution to address challenges such as preserving biodiversity or adapting to climate change, and stated that NGTs did not pose any threat to the natural order. For these reasons, some stakeholders consider the current EU legislation unethical.

Some stakeholders (NGOs) were of the view that the precautionary principle is a moral action-guiding principle for regulating new biotechnology. However, others (academics and food business operators) think that, particularly in plant breeding, it has to be taken together with the proportionality principle to strengthen the use of scientific evidence and tackle future uncertainties.

Referring to decision-making, some stakeholders (NGOs) noted that other legitimate factors, such as ethical considerations, should be taken into account in addition to scientific data. Others (food business operators, academics) believe that ethical aspects of innovation in biotechnology should be viewed in light of the resulting organisms and intended uses, rather than the technology used. Some food business operators are concerned that science is overlooked when decisions are made to authorise products and consider that this is highly problematic from an ethical perspective.

As reported in Section 4.7, some stakeholders (NGOs) noted that GM technology has led to increased concentration of ownership and power in agri-food systems through patents, contracts and licence agreements. They consider that the dominance of a handful of firms in the global food chain is dangerous and undemocratic. In their view, the situation would be no different for NGTs.

Finally, as regards medicinal applications, stakeholders see benefits in therapeutic modifications to somatic cells, but note serious ethical concerns on the gene editing of the germline (sperm, eggs, fertilised embryos).

4.11.4 Opinion of the European Group on Ethics

The European Group on Ethics in Science and New Technologies (EGE) has very recently published an Opinion on the Ethics of Genome Editing, which focuses on applications in the human, animal and plant domains. EGE recognised that diversity, human diversity and overall biodiversity can be impacted by genome editing in different ways and questioned common understandings of

naturalness, humanness and humanisation. It highlighted the importance of a responsible use of words, narratives and framings to ensure that the public is well informed, and recommended resisting the 'safe enough' narrative. The opinion addressed topics identified also in this study; certain issues are not specific to genome editing but refer to technology use and agricultural practices in general.

EGE made a series of recommendations. In the human domain, EGE recommended to create a European Platform for information sharing and inclusive debate on germline genome editing and engage in global governance initiatives to establish a public registry for germline research, to protect social justice, diversity and equality when considering applications for prevention, therapy and enhancement, and to ensure adequate competencies in expert bodies.

In animals, EGE considered the instrumental use of genome-editing for human benefit (from health to food) and the welfare of animals with respect to their intrinsic value. EGE called for strengthening oversight for scientific experiments, investing in alternatives to experiment on non-human primates, limiting the humanisation of animals, and regulating the banking and farming on animals carrying human organs for transplantation. Moreover, EGE recommended strengthening ethical oversight of practices involving reductions of animals' natural abilities and ensuring the wellbeing of genome edited livestock animals

In plants, EGE recognised that the introduction of genome edited plants could have a positive or negative impacts on product availability (notably food), human and animal health, socio-economic conditions, and the environment; care must be taken to minimise harm and maximise benefits. Companies introducing new varieties, regardless of method or provenance, should be required to identify the impact of their use on both biodiversity and environment.

EGE recommended a systems approach to evaluate costs and benefits (including the impact of continuing current agricultural practices) in any future use. It also recommended that regulation should be proportional to the risk; light touch regulation should be used where the change in the plant could have been achieved naturally, or where genetic material from sexually compatible plants was introduced. Where genes from non-sexually compatible organisms or multiple changes are introduced, there should be a comprehensive risk assessment. Traceability and labelling should only be required where the modification could not have occurred naturally through mutation or natural recombination with sexually compatible plants.

Finally, EGE called for developing measures to support small actors and paying more attention to public debates about genome edited agricultural products. The impact of increased prices and availability where strong regulation is required should also be considered.

4.12 Other comments by Member States and stakeholders

The consultation allowed Member States and stakeholders to provide other comments in addition to their replies to specific questions. In most cases, respondents used this opportunity to reiterate and reinforce views already presented in other sections of the questionnaire.

Several comments related to the EU legislative framework for NGTs.

Stakeholders made a variety of general comments and final remarks, reflecting diverse views. Some stated their general opposition to GMOs and NGTs, and explained why, in their view, they are not needed in the EU. Others explained why NGTs *are* necessary in the EU, especially for the agri-food and medicinal sectors.

Member States made a variety of comments and final remarks in relation to NGTs and established GMO techniques. They highlighted current problems in the GMO legislation and/or argued that it is obsolete, and called on the Commission to clarify and/or define terminology and to clarify the legal status of NGTs in the current framework. They highlighted the need to develop detection methods for NGTs. One Member State stated that regulation should protect the environment from the impact of uncontrolled wild editing.

Some Member States mentioned the need to streamline procedures by designing criteria for risk management, harmonising some of the current legislative framework and introducing a risk/benefit evaluation of products taking account of sustainability criteria.

Several Member States[61] and stakeholders (mainly food business operators, researchers/academics and biotechnology developers) argued that the EU's current legal framework for GMOs is neither science-based nor fit-for-purpose for NGTs, and proposed (with some specific suggestions) that it be adapted in line with the risk. Other stakeholders (mainly NGOs and organic/GM-free food operators) stress the need to implement the CJEU ruling in full and enforce the existing legal framework, and are concerned about any potential deregulation of NGTs outside the current framework. They made suggestions on how to strengthen the current framework, e.g. more comprehensive risk assessment, a GMO transparency register and new detection methods.

[61] Although not asked for views on the current legal framework, 10 Member States made spontaneous comments in this regard.

5. Discussion

Directive 2001/18/EC (the basis of the EU's legislative framework for GMOs) was adopted in 2001 and reflects the state of scientific knowledge in the 1990s. Since then, the science of biotechnology has evolved rapidly, with the landmark introduction of the first NGTs such as TALENs, ZFNs and ODM. The true game-changer came in 2012, when CRISPR-Cas technology was discovered. In 2020, only 8 years later, its inventors received the Nobel Prize for chemistry.

With such leaps, reviewing and assessing the full spectrum of NGTs is akin to trying to hit a moving target. Currently, CRISPR-Cas SDN technologies dominate research and funding interest, and have become a platform for the development of many other NGTs. When the JRC last reviewed NGTs (in 2011), CRISPR-Cas was not even known. Likewise, some of the NGTs described in the 2020 JRC review are still in exploratory phase and not yet mature enough to be considered for commercial applications. However, this may change in the near future, as the field is evolving fast, and the list of NGTs is expected to expand in the coming years.

This study confirms that there is considerable interest in NGT-related research in the EU and that the research will continue to evolve at both EU level and worldwide. Nevertheless, many Member States and stakeholders reported that the EU's current regulatory framework (as interpreted in the CJEU ruling) has had, or will have, a negative impact on both public and private R&I on NGTs. Reported consequences include a competitive disadvantage compared with non-EU countries, reduced funding interest and the risk of a brain and technology drain. In contrast, some Member States did not report any difficulties (e.g. in funding NGT research) following the CJEU ruling. Similarly, some business stakeholders (mainly in the organic/GMO-free sectors) and some NGOs reported no negative impacts in their research activities.

As NGT-related research is increasing, so too are its potential applications in plants, animals and micro-organisms for the agri-food, industrial and medicinal sectors, with tens of applications potentially reaching market stage in the next 5 years and even hundreds in the next 10 years. Despite the interest in and funding dedicated to NGT research in the EU, by far the majority of NGT applications are being developed elsewhere, including in several developing countries.

In industrial biotechnology, NGT micro-organisms appear already to be a reality, producing compounds of interest as micro-organism cell factories. Their application in the EU is somewhat facilitated by regulation under contained use and the fact that the final product contains no modified genetic material and consequently does not require authorisation under the GMO legislation.

In agri-food biotechnology, the first gene-edited plants (a soybean with healthier fatty acid profile and a tomato fortified with gamma-aminobutyric acid) has already been marketed in North America, while new opportunities are emerging as breeding portfolios are extended to new trait/plant combinations. Especially in the R&D stage, most traits under development relate to modified composition, biotic and abiotic stress tolerance, and plant yield. Similarly, beyond cereals and oil crops, there is a greater focus on vegetables, fruits and legumes. Many Member States and stakeholders note that NGTs allow for faster and more precise plant breeding and see opportunities

in the use of NGTs (especially by SMEs) to develop minor crops or special traits in response to local needs. However, some stakeholders express doubts, arguing that these kinds of application are not in the interests of large corporations, which they believe will dominate NGT product development.

Although not as developed as those for plants, livestock animal applications are following suit, with genome-edited fish, pigs and cattle in the pre-commercial stage. However, Member States and stakeholders reported concerns on the safety and ethical aspects of NGT use in animals.

The European Green Deal calls for innovative ways to protect harvests from pests and for consideration to be given to the role of safe innovative techniques in improving the sustainability of the agri-food system. Similarly, the 'farm to fork' strategy highlights climate change challenges and their impact on agriculture, and notes that biotechnology may play a role in reducing dependency on pesticides and increasing sustainability, if it is safe for consumers and the environment and it benefits the society as a whole. Both Green Deal and 'farm to fork' strategy, and in particular the biodiversity strategy, aim to halt biodiversity loss linked, among others, to chemical pesticide and fertiliser use; the 'farm to fork' strategy calls for action to reduce the overall use and risk of chemical pesticides by 50% by 2030. Several plant NGT products identified in the JRC review, from R&D to the market stage, could contribute to the Green Deal, and more specifically to the 'farm to fork' and biodiversity strategy objectives of a more resilient and sustainable agri-food system, and to the UN SDGs. Examples of benefits include plants that are more resistant to diseases and environmental conditions or climate change effects in general, improved agronomic or nutritional traits, reduced use of agricultural inputs, including plant protection products, adaptation of varieties to local needs, or preservation of traditional or niche varieties.

In contrast, it has been claimed that the proposed benefits of NGTs in agriculture are hypothetical and that they could be achieved by means other than biotechnology. Particularly strong concerns were expressed by several Member States, operators in the organic/GM-free premium market sector and NGOs. They argued that the organic/GM-free value chain could face severe threats from certain NGTs, which runs counter to the Green Deal and 'farm to fork' objective of increasing organic farming in the EU. To date, organic and GM-free agriculture has grown in the EU and has co-existed with GMOs. Organic and GM-free operators argue that dealing with NGT products outside the scope of Directive 2001/18/EC would irrevocably damage consumer trust in their sector. Nonetheless, the organic sector uses seeds that may also result from conventional mutagenesis and are hence GMOs not subject to the obligations of the Directive.

Sustainability in the food system goes beyond the environment and can involve seed and food security, safety, nutrition, competitiveness and social aspects. Therefore, any assessment of NGTs' impact on the agri-food system should look beyond the immediate intended effect. A Commission's upcoming legislative initiative under the 'farm to fork' strategy is expected to provide a framework for assessing the sustainability of food systems. This framework would apply to all products linked to the food system, including NGT products, which could then contribute to a more sustainable food chain.

As noted in the 'farm to fork' strategy, the safety of NGTs is a key prerequisite when addressing their potential role in increasing the sustainability of the agri-food system. However, as demonstrated in this study, NGTs and NGT products vary considerably (the same technique can be used in various

ways to achieve various results and products), so it is not possible to draw generalised conclusions as to their safety.

In this study, most of the expert opinions and views on safety and risk assessment relate to SDN-based techniques used in plant applications; less information is currently available on other NGTs and micro-organism or animal applications.

There is consensus that NGT products must be safe for human and animal health and for the environment in order to be placed on the market. However, Member States and stakeholders express divergent, at times opposite, views on the safety of NGTs and their products, and on the need and requirements for their risk assessment.

Case-by-case assessment is widely recognised as the appropriate approach. EFSA and the Member State opinions agree on the need for flexibility and proportionality in risk assessment methodologies and data requirements, to take account of available knowledge on the history of use of the modification(s) and the trait(s) introduced. On these points, not all stakeholders share the expert body opinions. Several Member States and stakeholders see a need to develop specific risk-assessment procedures for NGTs. Some stakeholders called for research on safety and environmental risks linked to unintended adverse effects and NGT products' interaction with the environment.

Some expert opinions consider that genetically and phenotypically similar products deriving from the use of different techniques are not expected to present significantly different risks. In particular, EFSA did not identify new hazards linked to SDN-1, SDN-2 or ODM, as compared with conventional breeding and established genomic techniques.

One key aspect relating to the safety of genome-editing techniques is their specificity. There is general agreement among Member States and EFSA that SDN technology is a substantial improvement compared to random genetic modifications and that several approaches have been developed to improve method specificity in recent years. This is also supported by the SAM HLG note and the recent JRC review.

In the consultation, Member States and stakeholders presented various views and some concerns on off-target modifications. On the other hand, EFSA concluded, on the basis of recent experimental evidence, that the off-target mutations potentially induced by SDNs are of the same type as, and fewer than, those in conventional breeding, including spontaneous mutations and those produced by physical and chemical mutagenesis. The SAM HLG and the JRC made similar observations.

EFSA noted similarities between cisgenesis and conventional plant breeding, as did other Member State expert opinions. At the same time, EFSA observed that the introduction of unwanted traits and hazards associated with unintended sequences can be minimised more easily with the former than with the latter. On the other hand, intragenesis introduces new combinations of genetic elements that are not found in cisgenic or conventionally bred plants and that may present novel hazards, as for transgenic plants.

EFSA noted that random changes to the genome occur independently of the breeding methodology. Insertions, deletions or rearrangements of genetic material also arise in conventional breeding and

potential new proteins are created at random during conventional breeding, cisgenesis, intragenesis and transgenesis.

The above conclusion (i.e. that SDN-1, SDN-2 and cisgenesis techniques present similar hazards to conventional plant breeding) assumes that no exogenous genetic material is present in the product derived from these techniques. It is widely recognised that this absence must be demonstrated through molecular characterisation. Pharmaceutical stakeholders consider that the technology is not without risk and that products should undergo risk assessment.

Ensuring safety for human and animal health and the environment, and the effective functioning of the single market are the main objectives of the EU legislation on GMOs. In its request for a study on the status of NGTs under EU law, the Council acknowledged that the definition of a GMO and the lists of techniques supporting it in Directive 2001/18/EC had been drafted in the light of the genomic techniques available and used at the time of its adoption.

The Council recognised that the substantial progress made since then has led to uncertainty as to whether NGT products fall within the scope of the Directive.

As explained in Section 4.2, the GMO legislation applies to organisms obtained through new mutagenesis techniques, cisgenesis and intragenesis, and organisms in which the genetic material is altered without changing the nucleic acid sequence.

While the CJEU has provided important elements of legal clarity, there are still open questions. Developments in biotechnology, combined with a lack of definitions (or clarity as to the meaning) of key terms in the legislation, have given rise to ambiguity in the interpretation of some concepts, potentially leading to regulatory uncertainty; for example:

- 'mutagenesis' – the lack of a definition of this term meant that the CJEU had to use other elements in the legislation to determine whether it covers all mutagenesis techniques or only conventional ones;
- 'conventionally used in a number of applications' and 'long safety record' – on the basis of these formulations, the CJEU clarified that new mutagenesis techniques fall within the scope of the GMO legislation. However, there is no definition of 'conventional use', 'a number of applications' or a 'long safety record'. In addition, technological advances take the form not only of steps (emergence of completely new techniques), but also of linear progress (gradual changes and developments of existing techniques);
- 'altered' genetic material – the term 'altered' does not seem to cover *de novo* artificial synthesis of genetic material/organisms; certain future products of synthetic biology may therefore not be covered by the current GMO legislation;
- 'alteration of the genetic material' – the JRC's review of scientific and technological developments identified a group of NGTs targeting RNA transcribed from DNA (Group 4, section 4.1.2). The legal status of products deriving from these techniques depends on whether or not this RNA is considered genetic material;
- 'recombinant nucleic acid molecules' – certain GMOs are excluded from the scope of the GMO legislation, provided they are produced without the use of recombinant nucleic acid

molecules. However, this term is not defined in the legislation and is interpreted differently by different stakeholders, resulting in broader or narrower exemptions;

- 'use of recombinant nucleic acid molecules' – it is not clear whether this wording refers only to the use of recombinant nucleic acid molecules during the genetic modification process or also includes the result of the genetic modification[62]; and
- 'transformation event' – Regulation (EC) No 1829/2003 and Commission implementing Regulation (EU) 503/2013 use this term, but do not define it. Where NGTs produce a GMO without transformation[63], the meaning of 'transformation event' is unclear. Furthermore, EFSA (in its scientific opinion on plants developed through synthetic biology) considers that, in order to cover all technologies (including genome editing), the term 'modification' rather than 'transformation' is more accurate for the molecular characterisation of GMOs in risk assessment. The concepts of 'event', 'junction site' and 'flanking region' may also need to be reconsidered also in view of the event-specific detection methods

In the consultation, some Member States highlighted these types of problem in the GMO legislation, which they described as obsolete, and called on the Commission to clarify terminology and the legal status of NGT products in the current framework. Some Member States mentioned a need for more harmonisation, streamlining procedures by designing risk-management criteria and a risk-benefit evaluation of products taking account of sustainability criteria.

Stakeholders are divided on the need to maintain the current legislation and reinforce its implementation, or to adapt it to scientific and technological progress and the level of risk of NGT products.

Overall, this study has provided evidence confirming the conclusions of the 2010 and 2011 evaluations of the GMO legislation. In particular, it was noted at the time that some new techniques create new challenges for the regulatory system. It was also concluded that, as the rate of innovation in the global biotechnology sector was unlikely to slow down, ensuring that legislation remains relevant is likely to be an ongoing challenge, especially if the focus is on the techniques used rather than the characteristics of the final products and the traits they express.

While some stakeholders call for full enforcement of the GMO legislation in respect of NGT products, the study demonstrated that only a limited number of Member States have adapted their inspection systems accordingly. Member States provided various reasons for not doing so, one of which was the lack of detection methods. For enforcement purposes, a detection method must be able to distinguish products that fall within the scope of the GMO legislation from other products. In addition, methods should be capable of detecting authorised or unauthorised products. Finally, all methods have to comply with performance criteria and be fit for testing complex matrices and processed products, which is the routine situation in enforcement.

The EURL/ENGL report highlighted implementation challenges for certain plant products that contain no foreign genetic material. Although existing detection methods may be able to detect even small

[62] There are situations where no recombinant nucleic acid molecule is used during the process of genetic modification, but the result of the genetic modification is a recombinant nucleic acid molecule.

[63] Transformation is the process consisting in the uptake and incorporation of exogenous genetic material into the cell.

specific DNA alterations, this does not necessarily confirm the presence of a genome-edited plant product. The same DNA alteration could have been obtained by conventional breeding or random mutagenesis techniques, which are exempted from the GMO legislation. With the current state of knowledge, enforcement laboratories are unlikely to be able to detect the presence of unauthorised genome-edited plant products in food or feed entering the EU market without prior information on the altered DNA sequences.

The lack of reliable detection methods is also a concern for stakeholders, as it affects agri-food operators' ability to verify compliance with the EU legislative framework. This has potential implications for legal liability, compliance costs, the risk of fraud and consumer trust. Some stakeholders proposed extending analytical tests to –omics techniques, whole genome sequencing and establishing a global database containing relevant information on NGTs and related patents. However, these complementary approaches have their own limitations.

Many respondents cited the need to develop reliable detection methods as a priority to enable enforcement of the current GMO legislation. However, as explained above, methods must be able to distinguish between regulated and unregulated products. EFSA concluded that mutations introduced by genome editing (SDN-1, SDN-2) are of the same type as those obtained with conventional breeding techniques. As things stand, certain genome-edited products have no unique features that could be the focus of specific methods. There is a need to explore ways of addressing this basic problem.

Some stakeholders referred to experience from past incidents involving the presence of non-authorised GMOs in the food chain. Screening methods targeting genetic elements common to GMOs resulting from established genomic techniques can be used to detect their unauthorised presence. However, this is not the case for genome-edited products; there are no such screening methods providing analytical evidence that demonstrates the presence of NGT products.

This situation presents specific challenges for applicants, whose inability to submit a detection method (as required under the legislation) could have an impact on the authorisation of certain products.

To overcome the analytical limitations, document-based traceability systems could be considered, like that provided for in the GMO legislation or the seed variety certification system. However, these would involve additional costs and could affect the international competitiveness of EU operators. Member States emphasised that there can be no valid traceability without a valid analytical strategy and that no enforcement is possible without the necessary legal certainty and evidence that would stand up in court. Other traceability systems mentioned were all subject to various limitations.

A third of the non-EU jurisdictions examined in this study have already adapted their legislation to address NGTs and their products, e.g. by introducing product- or process-based exceptions. Another third are considering whether/how to do so. Major agricultural trade partners, including in North and South America, do not or will not regulate certain NGT products as GMOs, e.g. in the case of products of targeted mutagenesis. Differences in legislation between the EU and its trade partners are nothing new and not a concern in themselves. However, in the case of NGTs, diverging legal and administrative requirements have consequences that are of concern for many Member States and stakeholders.

In certain cases, it would be difficult to identify or trace the presence of NGT products not authorised in the EU, and to prove in court that it did not result from naturally occurring mutations. Trade disruptions may occur, with economic losses and a lack of access to resources outside the EU; the feed sector in particular is highly dependent on imports of GM plant proteins.

Diverging requirements could also throw up technical barriers to trade, potentially leading to disputes between the EU and its trade partners in international fora such as the World Trade Organization. In addition, many Member States and stakeholders reported that burdensome and divergent legislative requirements contribute to an uneven playing field that affects the international competitiveness of the EU's agri-food, industrial and pharmaceutical sectors.

Similarly, they note the difficulties that operators will face in developing and commercialising NGT products, due to the regulatory burden in general and to the costly EU authorisation requirements in particular. Regulatory barriers are highlighted in the case of SMEs and small-scale operators seeking to gain market access with NGTs, even though many Member States and stakeholders see opportunities for them in this sector. However, some stakeholders note that the high business concentration observed previously in the GMO sector will threaten NGTs too.

Business models in biotechnology are often linked to IP rights, including patents and plant variety rights. Many Member States and stakeholders acknowledged the benefits of patents and licensing in promoting innovation and the development of NGTs and their products. However, many also mentioned that these same aspects can act as a barrier to market entry for SMEs and limit access to new technologies and genetic material, e.g. for breeders and farmers. A key objective of the Commission's 2020 IP action plan[64] is to improve SMEs' uptake of IP.

Business models and IP are among a wide range of issues that stakeholders reported as potentially presenting ethical concerns. In the agri-food sector, most of the concerns relate to how NGTs are used, rather than the techniques themselves. As in other areas examined in this study, there are different and often opposing views as to what is ethically questionable regarding NGTs. For some, it is unethical to use NGTs, while for others it would be unethical not to.

Some respondents referred to the precautionary principle and proportionality as ethical guidelines for EU decision-making. These principles are often cited as a basis for accepting or rejecting novel technologies. However, stakeholders interpret these principles differently. Therefore, any future measures (as requested by the Council) should address how they should be interpreted and implemented in synergy.

In an area in which public opinion has a significant influence on policy and seems to be made up of a wide range of views, it was important to explore what public dialogue initiatives have been taking place in Member States. The interest in discussing NGT-related topics in the agri-food and medicinal sectors has been demonstrated by past and ongoing dialogues and events organised by a variety of (governmental, research) institutions.

64 *Making the most of the EU's innovative potential – an intellectual property action plan to support the EU's recovery and resilience*, Commission Communication (COM(2020) 763 final).

Apart from promoting open debate, public dialogue can also help to raise awareness and understanding. Member States and stakeholders report that people's acceptance of new biotechnologies such as NGTs is of prime importance and depends on their awareness. Public perceptions of new biotechnologies are key to market uptake, but Member States and stakeholders agree that these are currently negative. However, as illustrated in the national survey information provided by the Member States for this study and by the recent EFSA Eurobarometer, the EU public has limited knowledge of NGTs. This apparent paradox should be investigated further.

Understanding and awareness are important in enabling consumers to make informed choices. The provision of information to consumers, including via labelling, is key. However, stakeholders have opposing views, both on the need to continue labelling NGT products as GMOs and how effective labelling is in informing consumers.

Specific consideration should be given to the medicinal sector, where NGTs can be used to develop gene-therapy products for seriously debilitating and life-threatening diseases, vaccines and treatments for the control and prevention of zoonoses. The potential benefits in the medical field are widely recognised by Member States and other stakeholders.

The use of the technology in the medicinal sector is viewed more positively than in other areas; the controversy observed in the agri-food sector was not apparent in the medicinal sector. In general, respondents see benefits in therapeutic modifications of somatic cells, but recognise serious ethical concerns as regards the genome editing of the human germline and embryos.

Medicinal products are heavily regulated within the EU medicines framework and not subject to certain aspects of the GMO legislation (e.g. traceability and labelling). The application of the GMO authorisation procedures to medicines has been identified as a problem that hinders the development of these products in the EU. Member States and stakeholders noted the challenges of applying the current GMO legislation to medicinal products for human use.

The Commission's Communication on the pharmaceutical strategy states that the regulatory requirements for authorising the use of GMOs in medicines for human use should be fit for purpose when it comes to addressing the specificities of medicines and the conduct of clinical trials. The issues identified in this study will be addressed in the context of the pharmaceutical strategy.

6. Conclusions

This study has examined the status of novel genomic techniques under EU law, taking into account state of the art knowledge and the views of Member State and stakeholders. It has found that NGTs have developed rapidly in the past two decades and will continue to do so, while NGT products are becoming a reality in many parts of the world. Their applications are already on the market outside the EU and more applications, across different sectors, are expected in the years to come.

NGT products and their applications could provide benefits for EU society and address major challenges, from resilience and sustainability in the agri-food system to advanced therapies and vaccine development in the medicinal sector. However, safety and environmental concerns have been raised, in parallel with concerns related to negative consequences from not using NGT products. Stakeholders have different and often opposing views on NGTs and their products. Any further policy action should aim to reap the benefits of innovation while addressing concerns; efforts should be made to reconcile opposing views in order to find common ground to address the issues identified in this study.

A more sustainable agri-food system, is a key objective of the European Green Deal and in particular of the 'farm to fork' and biodiversity strategies. To enable NGT products to contribute to sustainability, an appropriate mechanism to evaluate their benefits should be considered. At the same time, NGT applications in the agricultural sector should not undermine other aspects of sustainable food production, e.g. as regards organic agriculture.

Future policy action would also need to address the knowledge gaps and limitations identified in this study. Safety data are mainly available for genome editing in plants, making it difficult to draw relevant conclusions on other techniques and applications in animals and micro-organisms. It would be prudent to generate relevant information in these areas too. In addition, the effects of business models and the patenting system on NGTs and their users should be investigated further. Finally, more effort should be made to inform and engage with the public on NGTs and assess their views.

Due consideration should also be given, as part of the pharmaceutical strategy, to the specific characteristics of medicinal products.

The GMO legislation sets out stringent safety requirements and procedures. Embedding rigid risk-assessment guidance in legislation limits case-by-case assessment and makes it difficult to adapt risk-assessment requirements to scientific progress; this appears to be very much the case for NGTs.

Furthermore, as concluded by EFSA, similar products with similar risk profiles can be obtained with conventional breeding techniques, certain genome editing techniques and cisgenesis. It may not be justified to apply different levels of regulatory oversight to similar products with similar levels of risk.

This study identified a series of challenges relating to the GMO legislation's capacity to keep pace with scientific developments; these affect the feasibility of implementing it.

The GMO legislation has clear implementation challenges and requires contentious legal interpretation to address new techniques and applications. There are strong indications that it is not

fit for purpose for some NGTs and their products, and that it needs to be adapted to scientific and technological progress. The follow-up to this study should confirm whether adaptation is needed and, if so, what form it should take and which policy instruments should be used in order for the legislation to be resilient, future-proof and uniformly applied as well as contribute to a sustainable agri-food system.

7. Annexes

ANNEX A — Glossary of scientific terminology[65]

cisgenesis	Insertion of foreign genetic material (e.g. a gene) into a recipient organism from a donor that is sexually compatible (crossable). The foreign genetic material is introduced without modifications or rearrangements.
clustered regularly interspaced short palindromic repeat associated nucleases (CRISPR/Cas)	A family of SDNs that use an RNA-guiding molecule to recognise specific DNA sequences where the cut will be effected.
conventional GMOs	GMOs resulting from established genomic techniques. Conventional GMOs that have been authorised to date in the EU are transgenic.
conventional or random mutagenesis techniques	An umbrella term used to describe older techniques of mutagenesis that have been used since the 1950s; they involve irradiation or treatment with chemicals in order to produce random mutations, and typically involve screening of a large number of mutants to select one with desirable properties. Organisms obtained with such techniques are GMOs that are exempted from the scope of the EU GMO legislation.
deoxyribonucleic acid (DNA)	DNA is a biological polymer that constitutes the genetic material of all known organisms, some organelles (including mitochondria and chloroplasts) and some viruses. In cells, DNA usually occurs in the form of a double helix formed by very long complementary strands arranged in an antiparallel way.
double-strand break	The mechanical, chemical or enzymatic cut of both strands of the DNA.
epigenetics	The molecular mechanisms (e.g. DNA methylation) controlling expression of a genetically encoded trait. DNA methylation is reversible and, although it can be inherited between generations, its retention will depend on the environment.
epigenomic or epigenetic modifications/changes	Modifications of the genome that affect gene activity and expression without involving a change in the nucleotide sequence. Examples of epigenomic modifications are DNA methylation and histone modification, which alter how genes are expressed without altering the underlying DNA sequence.
established genomic techniques	Genomic techniques developed prior to 2001, when the existing GMO legislation was adopted.
exogenous or foreign DNA	DNA originating outside the organism that can be introduced naturally or by technological intervention.
genome	The entire complement of genetic material (including coding and non-coding sequences) present in a cell of an organism, a virus or an organelle.
genome-editing (gene-editing) techniques	A subset of NGTs that allow precise modification of DNA in the target genome in a variety of ways. Genome editing encompasses a variety of techniques, which may be applied in mutagenesis, cisgenesis, intragenesis or transgenesis.
intragenesis	As for cisgenesis, insertion of foreign genetic material from a crossable organism; however, in this case the genetic material is not introduced as such, but rearranged.

[65] The definitions are for the purpose of this study only.

mutagenesis	Creation of mutation(s) in an organism without insertion of foreign genetic material.
new genomic techniques (NGTs)	An umbrella term used to describe a variety of techniques that can alter the genetic material of an organism and that have emerged or have been developed since 2001, when the existing GMO legislation was adopted.
off-target modifications	DNA modifications occurring at an unintentional location in the genome.
oligonucleotide-directed mutagenesis (ODM)	A targeted mutagenesis technique by which oligonucleotides (short pieces of DNA) are used to introduce small, precise mutations in the genome.
-omics	Analysis of large amounts of data representing an entire set of some kind, especially the entire set of molecules, such as proteins (proteomics), lipids (lipidomics), or metabolites (metabolomics), in a cell, organ, or organism[66]
ribonucleic acid (RNA)	RNA is an essential biological polymer involved in various biological roles in coding, decoding, regulation and expression of genetic information. In cells, RNA (like DNA) is assembled as a chain of nucleotides, but (unlike a typically double-stranded DNA) it usually comprises a single strand. Many viruses encode their genetic information using an RNA genome (which can be single- or double-stranded).
RNA-directed DNA methylation (RdDM)	A technique that uses the effect of small RNA sequences to alter gene expression through methylation of specific DNA sequences without changing the nucleotide sequence itself (epigenetic change). The purpose could be to shut down expression of specific genes. This gene silencing obtained by the methylation can be inherited through some generations, but will eventually disappear.
SDN-1	A targeted mutagenesis technique using SDNs to introduce small mutations in a specific location of the genome. In SDN-1, no DNA template is provided, so the type of mutation is random.
SDN-2	A targeted mutagenesis technique using SDNs to introduce small, precise mutations in a specific location of the genome. In SDN-2, a DNA template is used to obtain a desired mutation.
SDN-3	An application of SDNs that allows the introduction of foreign genetic material in a specific location of the genome. If the inserted material comes from a donor organism that is sexually compatible with the host organism, the process is cisgenesis or intragenesis; if the inserted material comes from a donor organism that is sexually incompatible with the host organism, the process is transgenesis.
single-strand break	The mechanical, chemical or enzymatic cut of one strand of the DNA.
site-directed nucleases (SDNs)	Enzymes that cut the DNA at precise and selected target locations. SDNs use a guiding molecule to target the site to be cut. Various SDNs exist, depending on the nature of the guiding molecule and the type of enzyme, e.g. ZFNs, TALENs, CRISPR/Cas. Depending on their type and application, SDNs can be used for mutagenesis, cisgenesis, intragenesis and transgenesis.
targeted mutagenesis or site-directed mutagenesis techniques	An umbrella term used to describe newer techniques of mutagenesis that induce mutation(s) in selected target locations of the genome without insertion of genetic material. The process usually results in a 'knock-out', i.e. the disruption of the functioning of a gene that is responsible for an unwanted effect, or in modifications of the expressed protein or of regulatory elements of a gene.

[66] adapted from The American Heritage® Medical Dictionary Copyright © 2007, 2004 by Houghton Mifflin Company. Published by Houghton Mifflin Company. All rights reserved.

transcription activator-like effector nucleases (TALENs)	A family of SDNs that use a protein-guiding molecule to recognise specific DNA sequences where the cut will be effected.
transformation	
transgenesis	Insertion of foreign genetic material (e.g. a gene) into a recipient organism from a donor organism that is sexually incompatible. Transgenesis can be effected by a variety of techniques, including NGTs.
zinc finger nucleases (ZFNs)	A family of SDNs that use a protein-guiding molecule to recognise specific DNA sequences where the cut will be effected.

ANNEX B — Targeted consultation

Table 6: EU-level stakeholders invited to the targeted consultation on NGTs (107)

71 expressed an interest in participating, of which 58 (in bold) completed the questionnaire

1. Alliance for Regenerative Medicine (ARM)
2. Animal Health Europe
3. Aquaculture Advisory Council (AAC)
4. *Arbeitsgemeinschaft für Gentechnik-frei erzeugte Lebensmittel* (ARGE) & *Verband Lebensmittel ohne Gentechnik* (VLOG)*
5. ARCHE NOAH*
6. **Association of Manufacturers and Formulators of Enzyme Products (AMFEP**)
7. Bio-based Industry Consortium (BIC)
8. Birdlife international
9. International Community of Breeders of Asexually Reproduced Horticultural Plants (CIOPORA)
10. *Comité Européen des Entreprises Vins* (CEEV)
11. Committee of Professional Agricultural Organisations (COPA)
12. Compassion in World Farming EU (CIWF)
13. Confederation of European Paper Industries (CEPI)
14. Corporate Europe Observatory (CEO)
15. Cosmetics Europe
16. *Dachverband Kulturpflanzen- und Nutztiervielfalt* e.V.*
17. EU association of specialty feed ingredients and their mixtures (FEFANA)
18. EU Fish Processors and Traders Association (AIPCE-CEP)
19. EU Vegetable Oil and Protein Meal Association (FEDIOL)
20. EuroCommerce
21. Eurocoop
22. Eurogroup for Animals
23. EuropaBio
24. European Academies' Science and Advisory Council (EASAC)
25. European Agricultural Machinery Association (CEMA)
26. European Aquaculture Technology and Innovation Platform (EATIP)
27. European Association of cereals, rice, feedstuffs, oilseeds, olive oil, oils and fats and agrosupply trade (COCERAL)
28. European Association of Professional Portside Storekeepers (UNISTOCK Europe)
29. European Association of Sugar Manufacturers (CEFS)
30. European Biopharmaceutical Enterprises (EBE)
31. European Bioplastics
32. European Chemical Industry Council (CEFIC)
33. European Cocoa Association (ECA)
34. European Consortium for Organic Plant Breeding (ECO-PB)
35. European Consumer Organisation (BEUC)
36. European Coordination via Campesina (ECVC)
37. European Council of Young Farmers (CEJA)
38. European Crop Care Association (ECCA)
39. European Crop Protection Association (ECPA)
40. European Environmental Bureau (EEB)
41. European Fat Processors and Renderers Association (EFPRA)
42. European Federation for Cosmetic Ingredients (EFCI)
43. European Federation of Associations of Health Product Manufacturers (EHPM)
44. European Federation of Biotechnology (EFB)
45. European Federation of Pharmaceutical Industries and Associations (EFPIA)

46. European Feed Manufacturers' Federation (FEFAC)
47. European Fermentation Group (EFG)
48. European Flavour Association (EFFA)
49. European Flour Millers (EFM)
50. European Food and Feed Cultures Association (EFFCA)
51. European Former Foodstuff Processors Association (EFFPA)
52. European Forum of Farm Animal Breeders (EFFAB)
53. European Landowners Association (ELO)
54. European Livestock and Meat Traders Union (UECBV)
55. European Mobile Seed Association (EMSA)
56. European Network of Scientists for Social and Environmental Responsibility (ENSSER)
57. European Nurserystock Association (ENA)
58. European Organic Certifiers Council (EOCC)
59. European Organisation of Cosmetic Ingredients, Industries and Services (UNITIS)
60. European Plant Science Organisation (EPSO)
61. European Potato Trade Association (EUROPATAT)
62. European Poultry Meat Sector (AVEC)
63. European Primary Food Processing Industry (PFP)
64. European Professional Beekeepers Association (EPBA)
65. European Renewable Ethanol Producers (ePURE)
66. European Society for Blood and Marrow Transplantation (TBPM)
67. European Society of Gene and Cell Therapy (ESGCT)
68. European Specialist Sport Nutrition Alliance (ESSNA)
69. European Sustainable Agriculture through Genome Editing (EU-SAGE)
70. European Traders in Agri-Food Commodities (CELCAA)
71. European Vegetable Protein Association (EUVEPRO)
72. Euroseeds
73. Farmhouse and Artisan Cheese and Dairy Producers European Network (FACE Network)
74. Federation of European Academies of Medicine (FEAM)
75. Federation of European Aquaculture producers (FEAP)
76. Federation of European Rice Millers (FERM)
77. Federation of Veterinarians of Europe (FVE)
78. Food and Water Action Europe
79. Food Supplements Europe (FSE)
80. FoodDrinkEurope (FDE)
81. FoodFirst International Action Network (FIAN International)
82. FoodServiceEurope
83. Friends of Earth Europe (FoEE)
84. General Committee for Agricultural Cooperation in the European Union (COGECA)
85. Greenpeace Europe
86. Health and Environment Alliance (HEAL)
87. Independent Retail Europe
88. Institute for Independent Impact Assessment of Biotechnology (Testbiotech)
89. *Interessengemeinschaft für gentechnikfreie Saatgutarbeit* (*IG Saatgut*)*
90. International Association of Horticultural Producers (AIPH)
91. International Biocontrol Manufacturers Association (IBPMA)
92. International Confederation of European Beet Growers (CIBE)
93. International Federation of Organic Agriculture Movements Europe (IFOAM EU)
94. International Flower Trade Association (UF)
95. International Fragrance Association (IFRA)
96. International Natural and Organic Cosmetics Association (NATRUE)
97. International Platform of Insects for Food and Feed (IPIFF)
98. International Society for Cell and Gene Therapy (ISCT)
99. Maiz'Europ' (CEPM)
100. Medical Nutrition International Industry (MNI)

101. Pesticide Action Network Europe (PAN)
102. Plants for the Future — European Technology Platform (PlantETP)
103. Pollinis*
104. Slow Food
105. SMEunited
106. Starch Europe
107. Total Diet & Meal Replacements Europe (TDMR Europe)

* coordinating and representing national associations in various Member States

Member States' questionnaire

Member States' 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[67] 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[68].

Unless specified otherwise, the term "NGT-products" used in the questionnaire covers plants, animals, microorganisms 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[69]. Member States have until 30 April 2020 (close of business) to submit the questionnaire via EUsurvey.

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[67] Council Decision (EU) 2019/1904, OJ L 293, 14.11.2019, p. 103–104, https://eurlex.europa.eu/eli/dec/2019/1904/oj .

[68] 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 as RdDM. Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs.

[69] 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.

Questionnaire

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*
    - If yes, please provide details on the request.
2. Have you taken specific measures (other than inspection) related to the application of the GMO legislation to NGT-products? *Yes/no*
    - If yes, please describe the measures and, if possible, their effectiveness.
    - If yes, what best practices can you share? If no, please explain why not.
    - If yes or no, have you encountered any challenges or limitations, including administrative burden or costs? *Yes/no*
        - If yes, please describe.
        - If yes, how could this challenges or limitations be overcome?
        - If no, please explain why not.
3. Have you adapted your inspection practices to cover all NGT-products and to ensure the enforcement of traceability requirements? *Yes/no*
    - If yes, please describe these practices (e.g. adaptation of multiannual control plans) and, if possible, their effectiveness (including of physical checks).
    - If yes, what best practices can you share?
    - If yes, have the adapted inspection practices created additional requirements/burden for operators and/or public authorities? *Yes/no*
        - If yes, please provide concrete examples/data.
        - If no, please explain why not.
        - If yes or no, have you encountered challenges or limitations, including administrative burden or costs? *Yes/no*
            - If yes, please describe.
            - If yes, how could these challenges or limitations be overcome?
            - If no, please explain why not.
4. Do you have experience or information on traceability strategies, which could be used for tracing NGT-products? *Yes/no*
    - If yes, please describe the traceability strategy, including details on the required financial, human resources and technical expertise required.
    - If yes, what best practices can you share?
    - If yes or no, have you encountered challenges or limitations, including administrative burden or costs? *Yes/no*
        - If yes, please describe.
        - If yes, how could these challenges or limitations be overcome?
        - If no, please explain why not.

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
    - agri-food sector;
    - industrial sector;
    - medicinal sector.
6. Have plant varieties obtained by NGTs been registered in national catalogues? *Yes/no*
    - If yes, please specify.
7. Do you require specific information in national catalogue when registering plant varieties obtained by NGTs? *Yes/no*
    - If yes, please specify.

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*
    - If yes, 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.
    - If yes or no, please highlight the potential challenges encountered when supporting/funding NGT-related research and any consequences from these challenges.
9. How do you see NGT-related research evolving?
10. Have you identified any NGT-related research needs from private or public entities? *Yes/no*
    - If yes, please specify which needs and how they could be addressed.
11. Could NGT-related research bring opportunities/benefits to science, to society and to the agri-food, medicinal or industrial sector? *Yes/no*
    - If yes, please provide concrete examples/data.
    - If no, please explain why not.
12. Could NGT-related research bring challenges/concerns to science, to society and to the agri-food, medicinal or industrial sector? *Yes/no*
    - If yes, please provide concrete examples/data.
    - If no, please explain why not.

Information on public dialogues and national surveys:

13. Have you or other institutions/bodies/entities organised national dialogues concerning NGTs? *Yes/no*
    - If yes, please describe briefly the content, methodology and conclusions.
14. Have you or other institutions/bodies/entities organised national surveys, which assessed public opinion on NGTs? *Yes/no*
    - If yes, please describe briefly the content, methodology and conclusions.

Information on ethical aspects:

15. Have any national bodies or expert groups discussed or issued opinion on the ethical aspects of NGTs? *Yes/no*

- If yes, please describe briefly the content, methodology and conclusions.

Information on potential 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 agrifood, medicinal or industrial sector? *Yes/no* o If yes, please provide concrete examples/data.
    - If no, please explain why not.
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* o If yes, please provide concrete examples/data.
    - If yes, under which conditions do you consider this would be the case?
    - If no, please explain why not.
18. Do you see particular opportunities for SMEs on the market access to NGTs? *Yes/no* o If yes, please explain under which conditions o If no, please explain why not.
19. Do you see benefits/opportunities in patenting or accessing patented NGTs or NGTproducts? *Yes/no*
    - If yes, please describe and provide concrete examples/data.
    - If no, please explain why not.

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*
    - If yes, please provide concrete examples/data.
    - If no, please explain why not.
21. Could the use of NGTs and 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, in the short, medium and long term? *Yes/no*
    - If yes, please provide concrete examples/data. o If yes, under which conditions do you consider this would be the case?
    - If no, please explain why not.
22. Do you see particular challenges for SMEs on market access to NGTs? *Yes/no*
    - If yes, please explain under which conditions.
    - If no, please explain why not.
23. Do you see challenges/concerns in patenting or accessing patented NGTs or NGT products? *Yes/no*
    - If yes, please describe and provide concrete examples/data. o If no, please explain why.

Final question:

24. Do you have other comments you would like to make? *Yes/no*
    - If yes, please provide your comments here.

Stakeholders' questionnaire

Stakeholder consultation on new genomic techniques to contribute to a Commission study requested by the Council. Questionnaire Discussed and finalised in the ad-hoc stakeholder meeting on 10 February 2020.

Background

The Council has requested[70] 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.*[71]

Unless specified otherwise, the term "NGT-products" used in the questionnaire covers plants, animals, microorganisms 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.[72] Stakeholders will be invited to reply to the questionnaire via EUsurvey by 15 May 2020 (close of business).

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). Please mention the sectors of activity/fields of interest of your association.
- If applicable, please indicate which member associations (national or EU-level), or individual companies/other entities have contributed to this questionnaire.
- If applicable, indicate if all the replies refer to a specific technique or a specific organism.

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
    - If yes, please provide details.
    - If no, please explain why not.

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70 Council Decision (EU) 2019/1904, OJ L 293 14.11.2019, p. 103-104 https://eur-lex.europa.eu/eli/dec/2019/1904/oj .

71 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 ODM. 3) Epigenetic techniques such as RdDM. Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs. .

72 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–.

2. Have your members taken or planned to take measures to protect themselves from unintentional use of NGT-products? Yes/no/not applicable
    - If yes, please provide details.
    - If no, please explain why not.
    - If yes or no, have you encountered any challenges?
        - If yes, please provide details
3. Are you aware of initiatives in your sector to develop, use, or of plans to use NGTs/NGT-products? Yes/no/not applicable
    - If yes, please provide details.
4. Do you know of any initiatives in your sector to guard against unintentional use of NGT-products? Yes/no/not applicable
    - If yes, please provide details.
    - If yes or no, are you aware of any challenges encountered?
        - If yes, please provide details
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
    - If yes, please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise.
    - If yes, what best practices can you share?
    - If no, please explain why not.
    - If yes or no, what challenges have you encountered?
6. Has your organisation/your members been adequately supported by national and European authorities to conform to the legislation? Yes/no/not applicable
    - If yes, please describe what type of support and what best practices you can share?
    - If not, what challenges have you encountered?
7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products? Yes/no/not applicable
    - If yes, please describe the traceability strategy, including details on the required financial, human resources and technical expertise.
    - If no, do you have suggestions on possible traceability strategies and/or methods? Yes/no
        - If yes, please describe.
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
    - If yes, please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise.
    - If yes, what best practices can you share?
    - If no, please explain why not.
    - If yes or no, what challenges have you encountered?
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
    - If yes, please describe for the:
        - Agri-food sector;
        - Industrial sector
        - Medicinal sector

Information on research on NGTs/NGT-products:

10. Are your members carrying out NGT-related research in your sector? Yes/no/not applicable
    - If yes, please specify including subject, type of research, resources allocated, research location.
    - If no, please explain why not.
11. Are you aware of other NGT-related research in your sector? Yes/no/not applicable
    - If yes, please specify.

12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling[73] on mutagenesis? Yes/no/not applicable

    - If yes, please describe.
    - If no, please explain why not.

13. Could NGT-related research bring benefits/opportunities to your sector/field of interest? Yes/no/not applicable
    - If yes, please provide concrete examples/data.
    - If no, please explain why not.
14. Is NGT- related research facing challenges in your sector/field of interest? Yes/no/not applicable
    - If yes, please provide concrete examples/data.
    - If no, please explain why not.
15. Have you identified any NGT-related research needs/gaps? Yes/no/not applicable o If yes, please specify which needs/gaps, explain the reasoning and how the needs/gaps could be addressed.

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

16. Could NGTs/NGT-products bring benefits/opportunities to your sector/field of interest? Yes/no
    - If yes, please describe and provide concrete examples/data.
    - If yes, are these benefits/opportunities specific to NGTs/NGT-products?
        - If yes, please explain.
        - If no, please explain why not.
    - If no, please explain why not.
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 o If yes, please describe and provide concrete examples/data.
    - If yes, under which conditions do you consider this would be the case?
    - If yes, are these benefits/opportunities specific to NGTs/NGT-products?
        - If yes, please explain.
        - If no, please explain why not.
    - If no, please explain why not.
18. Do you see particular opportunities for SMEs/small scale operators to access markets with their NGTs/NGT-products? Yes/no
    - If yes, please describe and provide concrete examples/data.
    - If no, please explain why not.
19. Do you see benefits/opportunities from patenting or accessing patented NGTs/NGTproducts? Yes/no
    - If yes, please describe and provide concrete examples/data.
    - If no, please explain why not.

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
    - If yes, please describe and provide concrete examples/data.
    - If yes, are these challenges/concerns specific to NGTs/NGT-products?
        - If yes, please explain.
        - If no, please explain why not.
    - If no, please explain why not.
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
    - If yes, please describe and provide concrete examples/data.
    - If yes, under which conditions do you consider this would be the case?
    - If yes, are these challenges/concerns specific to NGTs/NGT-products?

[73] Case C-528/16; http://curia.europa.eu/juris/documents.jsf?num=C-528/16 .

        - If yes, please explain.
        - If no, please explain why not.
    - If no, please explain why not.

22. Do you see particular challenges for SMEs/small scale operators to access markets with their NGTs/NGT-products? Yes/no
    - If yes, please describe and provide concrete examples/data.
    - If no, please explain why not.
23. Do you see challenges/concerns from patenting or accessing patented NGTs/NGTproducts? Yes/no
    - If yes, please describe and provide concrete examples/data.
    - If no, please explain why not.

Safety of NGTs/NGT-products:

24. What is your view on the safety of NGTs/NGT-products? Please substantiate your reply.
25. Do you have specific safety considerations on NGTs/NGT-products? Yes/no
    - If yes, please explain.
    - If no, please explain why not.

Ethical aspects of NGTs/NGT-products:

26. What is your view on ethical aspects related to NGTs/NGT-products? Please substantiate your reply.
27. Do you have specific ethical considerations on NGTs/NGT-products? Yes/no
    - If yes, please explain.
    - If no, please explain why not.

Consumers' right for information/freedom of choice:

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

Final question

29. Do you have other comments you would like to make? Yes/no
    - If yes, please provide your comments here.

ANNEX C — List of Member State national body opinions used in the EFSA overview

Table 7: Overview of the 16 scientific opinions issued by the Member State national bodies and used in the EFSA overview[31]

For each opinion, the type of NGT covered is indicated by a 'yes' in the table. The use of a specific SDN is indicated if applicable.

Member State - Year	Title of report	Author	New Genomic Technique									
			SDN-1	SDN-2	SDN-3	ODM	Cisgenesis intragenesis	RdDM	Grafting	Reverse breeding	Agro-infiltration	Base editing
AT_2012	Cisgenesis - A report on the practical consequences of the application of novel techniques in plant breeding	Bundesministerium für Gesundheit	ZFN	ZFN	ZFN	yes	yes	-	-	-	yes	-
AT_2013	New plant breeding techniques	Bundesministerium für Gesundheit	-	-	-	-	-	yes	yes	yes	-	-
AT_2017	RNAi-based techniques, accelated breeding and CRISPR-Cas: basics and application in plant breeding	Bundesministerium für Gesundheit	yes	yes	yes	-	-	-	-	-	-	-
BE_2016	Advice of the Biosafety and Biotechnology Unit (SBB) concerning genome editing in plants using the CRISPR/Cas system	Wetenschappelijk Instituut Volksgezondheid WIVISP	CRISPR	-	-	-	-	-	-	-	-	-
BE_2019	Advice of the Belgian Biosafety Advisory Council on notification B/BE/19/V1 (maize) from VIB under Directive 2001/18/EC	Biosafety Advisory Council	CRISPR	-	-	-	-	-	-	-	-	-

DK_2019	Induced genetic variation in crop plants by random or targeted mutagenesis: convergence and differences	Dept of Molecular Biology and Genetics, Aarhus University, Denmark	yes	yes	-	yes	-	-	-	-	-	yes
ES_2019	National Biosafety Commission Report on the site directed mutagenesis ("gene editing")	Ministerio Para La Transición Ecolológica	yes	yes	yes	-	-	-	-	-	-	-
FR_2017	Scientific opinion on new plant breeding techniques	Haut Conseil des Biotechnologies	yes	yes	yes	yes	yes	yes	yes	-	yes	-
8_1_DE_2019	Genetic engineering - public hearing	Federal Agency for Nature Conservtion (BfN)	yes	yes	yes	-	-	-	-	-	-	-
9_2_DE_2019	Genome editing	Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit	yes	yes	yes	yes	-	-	-	-	-	yes
10_3_DE_2018	Scientific report on new techniques in plant breeding and animal breeding and their uses in food and agriculture	Federal Office of Consumer Protection and Food Safety (BVL)	yes	yes	yes	yes	-	-	-	-	-	yes
11_DK_2020	Comments from DTU on studies of the risk arising from the new mutagenesis techniques	National Food Institute at the Technical University of Denmark (DTU Food)	yes	yes	yes	yes	-	-	-	-	-	-
14_NL_2014	CRISPR-Cas advisory report - Revolution from the lab	Commissie Genetische Modificatie (COGEM)	CRISPR	CRISPR	CRISPR	-	-	-	-	-	-	-

15_NL_2017	Advisory opinion on CRISPR-Cas and directed mutagenesis in plants	Commissie Genetische Modificatie (COGEM)	CRISPR	CRISPR	-	yes	-	-	-	-	-	-
16_NL_2019	Advisory opinion on the Dutch proposal for the exemption of certain GM plants	Commissie Genetische Modificatie (COGEM)	-	-	-	yes	yes	-	-	yes	yes	-
17_LT_2019	Analysis of new gene modification techniques or methods	UAB Caszyme, Vilnius	yes	yes	yes	yes	yes	yes	yes	-	yes	yes

ANNEX D — Tables with further information

Table 8: Further opportunities and benefits of NGTs reported by Member States (supplementary to Section 4.6.1)

General	• NGTs and NGT products are key enabling life-science technologies and therefore they are seen as necessary to solve societal challenges. • The use of NGTs may effectively help meet the UN Agenda 2030 goals for health, eradicate hunger/poverty and offer realistic and essential solutions for multiple SDGs. • NGTs/NGT products may help to solve the problems of sustainable development. • SMEs could move to a more sustainable agri-food production with the use of NGTs, towards the objectives of the 'farm to fork' strategy. • If the legislation and administration burden for NGTs were to differ from those for conventional GMOs, SMEs could break monopolies in GMOs by using NGTs.
Agri-food sector	• NGTs can help to create GMOs that are much closer to natural analogues and thus have less negative environmental impact. • NGTs/NGT products can minimise growing problems caused by degradation of arable land. • The application of NGTs could also help to support ecological activities. • Modification of plants suited for indoor, vertical farming or aquaculture with LED lighting; growing in saltwater may be possible with NGTs. • Enhanced manufacturing of cultured meat and plant-based imitation meats. • Decrease food and feed imports (e.g. of starch) and increase competitiveness by facilitating domestic production. • Improved quality characteristics, e.g. NGT micro-organisms could improve freeze tolerance, leading to higher quality bakery products. • NGTs may allow domestication of wild plant species. • NGTs can help to improve conservation of the landscape and land-use efficiency. • SMEs play an important role in R&D of NGTs, e.g. the first R&D phases of plant breeding.
Medicinal sector	• NGTs can create cheaper and affordable medicines, especially for orphan diseases and inborn genetic diseases. • NGTs/NGT products bring benefits to the medicinal sector in drug manufacturing. • NGTs could provide the tools that are needed for the development of immunotherapies. • NGTs can help to fight multi-drug resistant bacteria. • NGTs would allow single treatments where currently only chronic or symptomatic therapy is possible. • By decreasing healthcare consumption, NGTs might also reduce the environmental burden of the healthcare sector. • NGTs could bring benefits in the field of epigenetics, e.g. with diagnostics and identification of the cell type/state (e.g. blood test for reliable identification of the type/location of an early-stage cancer), but also with rejuvenation and changing of individual cells into stem cells (replacing embryonic origin). These benefits may also include diagnostics and repair of numerous diseases and aging-related tissue damage types with epigenetic reprogramming. • NGTs may facilitate the use of autologous cells for treatment of malignancies. • NGTs may improve organ transplantation. • NGTs/NGT products can speed up drug discovery. • NGTs could allow the use of animals to produce therapeutic proteins. • SMEs may find opportunities and play an important role in R&D of NGTs, e.g. the first R&D phases of clinical trials

Industrial sector	• NGTs can develop organisms that can eliminate contaminants *in situ*. • NGTs/NGT products can help to develop novel enzymes for detergents. • NGTs enable design of novel and improved cell factories for biotechnology. • Industrial strains could be rapidly engineered to consume alternative feedstock with smaller environmental impact for production of bulk and speciality chemicals. • In enzyme production, NGTs enable extensive bio-informatics data analysis of both production strains and enzyme variants, leading to improved success rate to develop higher-performance products. • Synthetic biology (NGTs and non-NGTs) may be used to create biological macromolecules with entirely new properties. • NGTs/NGT products could help to produce sustainable energy. • NGTs/NGT products could contribute to green mobility. • NGTs/NGT products can bring 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. • NGT micro-organisms can improve fermentation capacities, making fermentation more efficient, leading to less waste and lower greenhouse gas (GHG) emissions per unit of production.

Table 9: Further challenges and concerns reported by Member States (supplementary to Section 4.7.1)

General	• The economic impact of NGTs is a concern. • In contained use, there is a concern about being able to keep NGT organisms under control. • Intensification of technologies that are open to the environment can be achieved only at environmental costs. NGTs are no exception. • Some NGTs may use recombinant nucleic acid molecules, which act as a template to direct sequence changes. This process is different from the sole introduction of DNA DSB by NGTs that are repaired by a natural mechanism of the cell, leading to equal DNA changes, e.g. through the repair of naturally occurring DSB. In contrast, NGTs that use such recombinant nucleic acid molecules (SDN-2, ODM) cause potential modifications beyond the range of natural mutations and pose novel risks in some types of organism. • There are concerns about the ability of NGTs to make voluntary or unintentional modifications of certain aspects that could exacerbate the danger posed by existing pathogens or create and support the emergence of new pathogens. • NGT technology only benefits a handful of large multinational corporations and consumers will have a lack of choice in the end. • Fast development of new technologies brings risk in management of the impact of the technology on society. • Consumers have the right to base their choices on unbiased information. • Use of NGTs in the fight against climate change is a challenge. • The difficulty and complexity of accessing good quality knowledge about what is done, including collateral effects and impossibilities, makes it difficult for the public to take part in the debate and they are vulnerable to poor quality information. • NGT technologies alone cannot solve the problem of how to feed the growing population. • Improving competitiveness is seen as a challenge. • Informing the public on products and techniques will be decisive. • Over-regulation of NGTs/NGT products should be avoided, because it could inhibit orderly progression towards legitimate uses of the technology.

	• No consumer labelling is needed. Labelling and separated production lines through the food chain would also raise food prices. Imported food and commodities would not be labelled reliably anyway. • Use of NGTs to meet ambitious public health objectives is a challenge • SMEs in Europe are moving outside the EU due to the EU GMO legislation. • Some CRISPR IP owners license their patents to companies trained by academic institutions. This could create exclusivity situations, making research unprofitable. • EU and Member States are significantly lagging behind other countries (which are key competitors) in the patenting of techniques and products developed using some NGTs. • The fact that beneficial applications may not be used fully remains a concern. • Novelty in the patent: it is difficult to determine whether a NGT product in a patent application is covered by a prior known technique, i.e. whether it includes organisms that are already present in natural or breeding populations. • To find a balance between social, economic and scientific interests is a challenge.
Agri-food sector	• EU policy should take care that legal security is guaranteed for all stakeholders in agri-food sector. • The ability to secure fair revenues, the profitability, is a concern for NGTs. • In the short term, extensive use of NGTs could provide some challenges for traditional sectors. • NGTs will allow their use in semi-domesticated and/or wild species and this will pose challenges for the environmental risk assessment. • It is not clear how well the public would be able to discriminate between the methods. • Undisclosed GMOs produced by NGTs may contain vector backbone sequences of the plasmids used for transforming eukaryotic cells including antibiotic resistance genes, which may spread in the gut of the transgenic animals or consumers. • Concerns on choice of models that dominate farming and agri-food systems. • Consumer concerns could be raised about the consumption of products derived from animals treated with medicines derived from the use of NGTs. • The challenge is using NGTs to protect the environment and conserve the landscape. • Inclusion of NGT use in an overall concept of good agricultural practice is a challenge.
Regulation	• It is a challenge to find a good balance in applying the precautionary principle while stimulating innovations and economic development. • Technology development, in the case of NGTs, exceeds the pace of updating the legislation. • If some NGTs are to be exempt from GMO regulation, this decision has to be based on scientific evidence concluding that a comprehensive risk assessment as for GMOs is unjustified. • The legal framework due to the CJEU 2018 decision raises challenges, not the NGTs *per se*.

Table 10: Further opportunities and benefits of NGTs reported by stakeholders (supplementary to Section 4.6.2)

Agri-food sector	• NGTs can improve feed conversion, resulting in higher livestock productivity. • NGTs could make it possible to introduce crops in areas in which environmental conditions previously made it impossible to grow. • NGTs/NGT products could offer lower dependency on protein supply from non-EU countries. • NGTs can help to maintain rare alleles in livestock. • NGTs can help in dealing with genetic defects in local/endangered breeds. • NGTs could reduce castration of pigs at farm level, thus improving animal welfare. • NGTs can introduce sterility in farmed fish in order to prevent genetic interaction with wildlife relatives.

	• NGTs/NGT products can improve competitiveness and relevance of plant breeding. • NGTs can bring improvements to food security.
Medicinal sector	• NGTs/NGT products can bring benefits to medicinal products and vaccines for animals. • NGTs/NGT products can bring savings to healthcare budgets due to healthier populations.

Table 11: Further reasons given by stakeholders as to why they see no benefits in NGTs (supplementary to Section 4.6.3)

• Conventional breeding has proven more successful. • The solutions offered by NGTs cannot be sustainable, since their obsolescence is programmed from their conception. • Precautionary principle is not guaranteed with NGTs/NGT products.

Table 12: Further challenges and concerns reported by stakeholders (supplementary to Section 4.7.2)

General	• Genetic engineering techniques purport to offer solutions to problems that can be dealt with in simpler, less high-tech ways. For example, there is the suggestion that gene editing can be used to provide disease resistance and reduce antibiotic use in farming, but this problem is much better addressed by moving away from intensive farming. • Widespread misinformation in Europe on a number of topics, including biotechnology, is a concern. To fight against this misinformation is a challenge. • The benefits of NGTs/NGT products are too little, too late and bring isolated solutions. • It is challenging to foresee the consequences of NGTs/NGT products for the environment, humans and animals. • It is a challenge to educate society in relation to biotechnology. • There are concerns relating to biological weapons and NGTs/NGT products. • Indicating that all genomic alterations or allelic combinations generated by CRISPR/Cas9 generally are identical to naturally occurring variations is a misleading oversimplification. • It is a challenge to prove benefits for society and consumers. • Attention to NGTs diverts funds away from other sustainable solutions. • Loss of genetic sovereignty and diversity due to NGTs/NGT products is a concern. • Public perception on GM animals is a challenge and a concern. • Patentability of genes that are also present naturally is an issue; natural biodiversity should not be patented. • Patents on NGT products threaten the conservation of genetic diversity, its traditional use in local communities and innovation in plant breeding. • NGTs/NGT products bring ethical concerns as regards the dignity of plants. • Concerns about NGTs disturbing the 'one health' balance in humans and animals. • The unintended effects of multiplexing techniques, possible with NGTs, are a concern. • The cumulative effects of different NGT organisms are a concern. • Data are lacking on non-SDN next-generation sequencing. • It is difficult to detect unintended effects or off-targets.
Agri-food sector	• NGTs/NGT products could bring a potential loss of the image of 'naturalness' in wine. • Although the EU is free to approve, restrict or ban certain technological treatments and uses, restricting NGTs will limit the products available to European consumers. • The sampling of NGTs/NGT products is a challenge, because collecting the requisite information on NGTs for all plant products would constitute an enormous task. • There is a concern that patented and specialised varieties (e.g. by favouring NGTs) lead to a loss in plant genetic diversity. • There are concerns relating to the decision as to which NGT applications have positive effects for consumers. For example, apples or mushrooms whose cut surfaces do not turn brown are in reality not a benefit for consumers, who could be misled into believing that such products are fresher than

	they actually are. • Pesticide traits are perceived negatively by consumers. • The business model of NGTs is geared towards return of investment on a large scale and the standardisation of ecosystems; no adaptation capacity and monocultures are concerns. • It is a concern that political and financial support for NGTs removes support from agroecology. • Concerns if NGTs can actually lead to less use of plant protection products. • Commercialisation practices for seeds as a result of NGTs will threaten farmers' autonomy and resilience. • It is a concern that there are no authorised European NGTs and barely any cultivation. • It is a concern that, with the current regulation, field trials for NGTs are as costly as those for GMOs.
Medicinal sector	The increasing number of gene therapy applications is likely to create resource difficulties, which may have knock-on effects on approval timelines and enrolment of patients in clinical trials.
Regulation	• It is not 100% clear which techniques are covered or excluded from the scope of the GMO Directive in practice, which is a source of legal uncertainty. • NGTs/NGT products are a threat to the precautionary principle. • Depending on how national legislation interprets the ECJ ruling, materials such as conventional mutants or tissue-culture derived plants may fall under this regulation. This is a concern that brings challenges for past and current breeding activities. • An absence of coherent regulatory requirements or marketplace transparency will create significant new challenges for commodity and speciality supply chains. • Not applying a specific risk regulatory system to NGT products will not mean that they will not be tested. They can be tested through the 'distinctness, uniformity and stability' (DUS) test for all food crops and 'value for cultivation and use' (VCU) testing for most field crops before they are released on the EU market. They also remain in the scope of the EU's general food law.

Table 13: Further views from stakeholders on the labelling of NGT products (supplementary to Section 4.9)

- The general public would find unacceptable to deregulate labelling for NGTs.
- If NGT products are as convincing and successful as promised, they can convince the public also under the current labelling system.
- Need internationally harmonised framework for specific NGT labelling.
- If NGTs are under GMO labelling, there is no need to specify the technique used.
- Different labelling rules between EU and non-EU products on NGTs will create difficulties, which is not in the consumer's interest.
- Legally binding obligation to disclose the applied breeding method is essential.
- The breeder's exemption is very important. The breeders will not be able to know all methods used by other breeders of materials that have been used in crossing programmes, so they are unable to guarantee their declarations. Therefore, it will be much more transparent towards the public if no NGTs are used in the organic production or chain.
- If NGT products are regulated as GMOs in the EU, the cultivation of such crops is likely to be unprofitable under the current labelling rules.
- Decision to label or not should be based on criteria that are significant and not misleading to consumers.
- Labelling should be accessible to public, without misleading euphemisms such as 'precision/smart breeding'.
- Use extra information such as QR codes or other alternative methods to ensure transparency and access to information on production methods.
- Without central guidance, patchwork of labelling situations may arise in Member States, which is detrimental to the single market.
- Can people trust the technology if it can only succeed if it remains invisible for the public?
- Consumers and companies in the food industry focus more on the knowledge of the origin of the product and how or with which process/techniques it was produced. NGT products should be labelled in accordance with these increasing demands.
- Growers do not see how consumers would benefit from knowing by what method a flower has been produced.
- Perhaps only label in cases of transgenic or with major genome changes, irrespective of method used.
- Existing non-GMO labels are a pragmatic solution under the current framework, but an EU-wide mandatory GMO-free label and NGT-free label may be an option.
- Basing labelling decisions on the technology used, for transparency, is misleading, as it provides no information on safety and quality.
- Future developments must be transparent, with clear product labelling.
- There is no reason why voluntary labelling schemes such as GMO-free/organic cannot continue to be used excluding NGTs, e.g. by sharing information.
- Imports should be labelled the same as EU products.
- Only developers, manufacturers and marketers of NGTs will gain from no labelling.

Table 14: Initiatives related to public dialogues on NGTs, as reported by the Member States in the targeted consultation

MS	Year	Organiser	Methodology	Title/content	Audience	Sector
Belgium	2019	ALLEA and Royal Flemish Academy of Science and Art	Symposium followed by a report published in 2020	Symposium on genome editing for crop improvement http://allea.org/wp-content/uploads/2020/10/ALLEA_Gen_Editing_Crop_2020.pdf	Information not provided	Agri-food
Czechia	2018	NGO Biotrin and the University of Chemistry and Technology in Prague.	International conference	NBTs — hope for agriculture and the food chain. https://www.biotrin.cz/nbt-conference/	Experts	Agri-food
	2019	Research company IPSOS, in cooperation with the scientific centre CEITEC	Public dialogue	Public dialogues on genome editing in Prague to better understand public opinion on disruptive technologies such as the new genome-editing technique CRISPR/Cas9 used in science and research. https://www.orion-openscience.eu/tags/genome-editing	30 random citizens and 3 scientists (as moderators)	Agri-food and medicinal
	2019	Institute of Molecular Genetics of the Czech Academy of Sciences	Public dialogue	The attempt to modify humans (China)	200 attendees	Medicinal
	2020 (every year)	Czech Commission for the Use of GMOs and Genetic Products	Public dialogue	Information about the activities of the Czech Commission and new developments in biotechnology	Open for the public	Agri-food, medicinal and industrial
	Not provided	Crop Research Institute in Prague	Seminars	NBTs	Agri-food specialists	Agri-food

Denmark	2020	Danish Agriculture Agency (DAA) and Danish Council on Ethics	Working group	Regulation of NGT techniques. The large majority of the group found that gene editing (without insertion of foreign DNA) was different from traditional GMOs and could contribute to developing a more sustainable agriculture. This majority also believed that gene editing should be regulated differently from traditional GMOs and that this should be given priority. Other new techniques were clearly creating GMOs and should be regulated as such.	Representation from key stakeholder organisations and institutions, including NGOs and the consumers' organisation	Agri-food
Germany	2017	Federal Government (BMEL)	Dialogue events with presentations and plenary debates	• Applications of genome editing in research and practice; • Criteria for responsible handling of genome editing; • Making innovation responsible	Representatives from academia, politics, business and society	Not specified
	2019	Federal Government (BMBF)	Workshops and conferences	Ethical, legal and socio-economic aspects of genome editing in the agricultural economy https://www.dialog-gea.de/de/service/veranstaltung	Representatives from research, breeding, seed industry, trade, project promotion, NGOs, public authorities, church	Agri-food
	2019	Federal Government (BMEL), Forum NMT	Event with presentations and discussions	Regulatory options for new molecular biological techniques such as CRISPR/Cas	Representatives from academia, politics, business and society	Not specified

	Not provided	Catholic Rural Movement Germany and Commissioner of the German Bishops — Catholic Office in Berlin	Working group	It focuses on the biological and socio-economic impacts of genome editing on agriculture and the environment. The objective is to form a common understanding of genome editing as a technology in agriculture, the development of building blocks of its ethical assessment and the acquisition of ability to speak in this regard, including in non-religious contexts.	Working group with representatives of Catholic associations and organisations from the agricultural, development, youth, environmental, scientific sectors and official church. The group invites speakers from science (biology, social ethics, law), business, development policy and the federal ministries dealing with genome editing.	Agri-food
	Not provided		Public information sessions at universities/ *Länder* ministries, with presentations and discussions	Methodology, opportunities and risks of NGTs	Information not provided	Not specified
	Not provided		Technical meeting with lecturers from public authorities and universities	New molecular biological techniques (genodication, CRISPR/Cas, etc.) and their analytical challenges.	Professionals from academia, authorities and practitioners	Not specified
	Not provided	Federal Government (BMBF)	Interactive workshops, lectures, science slam, final panel discussion with experts	ELSA Dialogue Conference: different application areas of genome editing. The workshops showed through a variety of approaches how a dialogue about dealing with the new genome-editing techniques can succeed.	Students, interested citizens, patients' representatives and representatives of politics and society	Not specified

Estonia	2019	Estonian University of Life Sciences representative	Presentation	Future of plant breeding, explaining the mechanisms of NGTs. Conclusion from farmers was that the new technologies are very useful and they need to be used more and faster in agriculture	Farmers	Agri-food
	2020	Estonian University of Life Sciences representative	Presentation	Precision breeding, explaining the mechanisms of NGTs. Conclusion from the farmers was that the new technologies are very useful and they need to be used more and faster in agriculture.	Farmers	Agri-food
Spain	2019	Ministry for Ecological Transition and Demographic Challenge.	Workshop	On the implementation of GMO legislation in clinical trials	Members of the pharmaceutical industry, research centres and hospitals	Medicinal
	2019	Ministry of Agriculture, Fisheries and Food	Website	Creating a specific section about NGTs on the Ministry's webpage https://www.mapa.gob.es/es/agricultura/temas/biotecnologia/mejora-genetica/	All citizens	Agri-food
	2019	Ministry of Agriculture, Fisheries and Food	Workshop	Dissemination of the conclusions of the ECJ ruling on the regulation of products obtained by NGTs. https://www.mapa.gob.es/es/agricultura/temas/biotecnologia/mejora-genetica/	Rural stakeholders	Agri-food
	2020	Scientific Committee of the Spanish Food Safety Agency	Report	Report on the NGT judgment and regulation.	Spanish Food Safety Agency	Agri-food

France	2016	High Council for Biotechnology (HCB)	Meeting	• Potential opportunities, particularly in new features that could not be obtained by other techniques; • Potential socio-economic and ethical risks; • Considerations for the governance of the development of NPBTs and the marketing of their products http://www.hautconseildesbiotechnologies.fr/fr/system/files/file_fields/2016/03/30/cees_1.pdf	HCB and various stakeholders in the Economic, Ethical and Social Committee (EESC).	Agri-food
	2016	Ministry of Ecological and Inclusive Transition	Seminar	'Evolving ideals for debate and controversies regarding GMOs' http://recherche-riskogm.fr/fr/article/seminaire-riskogm-2016-les-ideaux-participatifs-lepreuve-du-debat-et-des-controverses-sur	Government representation and experts	Agri-food
	2017	Parliamentary Office for evaluation of scientific and technological options (OPECST)	Report	The economic, environmental, health and ethical challenges of the development of new biotechnologies, in particular those of genome editing https://www.senat.fr/rap/r16-507-1/r16-507-11.pdf	All citizens	Agri-food and medicinal
	2017-2018	High Council for Biotechnology was consulted by the Minister for the Environment	Working group	Use of mosquitoes modified by biotechnology for vector control (gene drive) http://www.hautconseildesbiotechnologies.fr/sites/www.hautconseildesbiotechnologies.fr/files/file_fields/2017/06/06/hcbceesmoustiquesrecommandation2juin2017.pdf	High Council for Biotechnology and National Centre for Expertise on Vectors (CNEV)	Medicinal

	2018	French Association for Seeds and Seedlings (GNIS)	Meeting followed by an online consultation	Purposes of varietal research and ethical questions raised by different research techniques depending on the use that can be made of them https://www.gnis.fr/plan-de-filiere-semences-et-plants-consultation-publique/	Stakeholders	Agri-food
	2018	National Advisory Committee on Ethics (CCNE) in association with the Regional Ethical Reflection Spaces (ERER)	Events and debates across the country summarised in a report	• The need to better inform not only the general public, but also healthcare professionals; • The tensions between the fear of eugenics and the desire to reduce suffering, between the risks and benefits; • When the scope for modifying genomes was discussed, many reject any modification of the germline in their therapeutic applications on humans.	61 meetings in the regions, more than 6 000 participants on the website, 36 consultations with associations, institutions and schools of thought, and 11 consultations with learned societies	Medicinal
Italy	2015	Ministry of Agricultural, Food and Forestry Policies and CREA, during the Milan EXPO	Speech	'Agriculture of the future: which biotechnologies to use to guarantee food for everyone?'	EXPO participants	Agri-food
	2018	Ministry of the Environment and the Ministry of Agricultural, Food and Forestry Policies, in collaboration with the National Committee for Biosafety, Biotechnology and Life Sciences, the Ministry of Health and the Ministry of Economic Development	Workshop	Technical-scientific meeting on NBTs in agriculture, with a first session addressing regulation issues, detection and traceability, human and environmental risks, and potential applications. The second session was dedicated to stakeholders' opinions.	Representatives of central and regional administrations, science and academia, trade and environmental associations, civil society	Agri-food

	2018	Ministry of the Environment	Study group	'Study document on new breeding techniques'	Research bodies and institutions	Not specified
Latvia	2019	Nordic/Baltic regional cooperation	Workshop	'Ecological and socio-economic impacts of gene drive organisms': the scientific developments of gene drive organisms, environmental risk assessment management, socio-economic considerations and regulatory frameworks of gene drive organisms	GMO authorities in the Nordic and Baltic countries	Medicinal
	2019	Nordic/Baltic regional cooperation	Workshop	Nordic/Baltic GMO meeting: 'We cannot detect it — what is the way forward? — The ECJ decision on mutagenesis and its implications for GMO control'	Authorities responsible for GMO (food, feed and seed)	Agri-food
	2020	Latvian research centre (BIOR)	Workshop	'GMO in food, feed and plant propagating material — current events, risk assessment'.	Stakeholders (farmers, animal feed producers, experts from control laboratories and state institutions, scientists)	Agri-food
Lithuania	2019	Lithuanian Academy of Sciences, in collaboration with research institutions	Public discussion	The outcome was a signed petition to support European research organisations' call to revise the GMO Directive so as to exclude NGTs.	Information not provided	Not specified
Hungary	2018	Parliamentary Committee on Sustainable Development, the Advocate of Future Generations, the Hungarian Friends of the Earth partner, the Hungarian Bioculture Association and the Central Hungarian Green Circle	Conference	NBTs and genetic modification	Information not provided	Not specified

	2018	The Hungarian Academy of Sciences, in cooperation with the OECD	Symposium	CRISPRing — a new beginning for the genetic improvement of plants and microbes https://crispring.agrar.mta.hu/	Experts	Agri-food and industrial
	2019	Ministry of Agriculture (EAI-CA)	Public discussion	• The national and EU legal environment relating to NGTs; • Human and environmental risks of products obtained by NGTs; • The relevance of the current risk assessment to products obtained by NGTs; • NGT products' socio-economic impact; • Concerns and difficulties of detecting and identifying products obtained by NGTs	More than 50 experts representing Hungarian research institutes, enterprises, universities, plant breeders, licensing and inspection authorities, NGOs, beekeepers and experts in the food and feed industry	Agri-food
The Netherlands	2015	Netherlands Commission on Genetic Modification (COGEM) and Health Council of the Netherlands	Symposium	The implications and applications of human genome editing; their limits and the governance challenges and societal perspectives https://cogem.net/en/publication/editing-human-dna-moral-and-social-implications-of-germline-genetic-modification-2/	Experts	Medicinal
	2017	Netherlands Commission on Genetic Modification (COGEM)	Symposium	The applications and implications of gene editing in animals https://cogem.net/publicatie/event-report-gene-edited-animals-applications-and-implications/	Experts	Medicinal
	2017	NEMO *Kennislink*	Website	Developments in biotechnology https://biotechnologie.nl/	All citizens	Agri-food, medicinal and industrial

	2017 and later years	Netherlands Commission on Genetic Modification (COGEM), Health Council of the Netherlands and Scientific Council for Government Policy (WRR)	Meetings	Biotechnology policy http://www.bureauklb.nl/images/181015_Stand_van_de_gedachtewisseling_modernisering_biotechnologiebeleid_-_eindrapport-min.pdf	Government and national stakeholders	Agri-food, medicinal and industrial
	2019	Netherlands Commission on Genetic Modification (COGEM)	Symposium	Global perspectives and regulation of gene editing in plants https://cogem.net/nieuws/gene-edited-crops-global-perspectives-and-regulation/	More than 100 scientists, policymakers, consultants, regulators and representatives from international breeding companies	Agri-food
	2019-2021	Erfocentrum, Erasmus MC, Rathenau Institute, NPV *Zorg voor leven* and NEMO *Kennislink*	Public dialogue	'*DNA dialoog*': Use of new genomic techniques for germline modification https://dnadialoog.nl/	All citizens	Medicinal
Austria	2015-2019	Federal Ministry of Sustainability and Tourism (BMNT, formerly BMLFUW)	Round tables	Crop cultivation in general https://www.zukunft-pflanzenbau.at/home/	Stakeholders, from industry to NGOs	Agri-food
	2017	Federal Ministry of Social Affairs, Health, Care and Consumer Protection	Meetings	Risk assessment of NPBTs	EU risk assessment experts and authorities	Agri-food
	2018	Federal Ministry of Social Affairs, Health, Care and Consumer Protection	Meetings	Meeting on issues relating to NGT application	National stakeholders	Not specified
	2019	Federal Ministry of Social Affairs, Health, Care and Consumer Protection	Workshop	1st workshop on NGT issues	Representatives of Austrian authorities	Not specified

	2019	Federal Ministry of Social Affairs, Health, Care and Consumer Protection	Workshop	2nd workshop on NGT issues	Representatives of Austrian authorities	Not specified
Poland	2019	Polish Patent Office and the World Intellectual Property Organization (WIPO)	Conference on World Intellectual Property Day in Warsaw	'Whose genome is it? Biotechnology and intellectual property protection'	Experts	Agri-food
	Not provided	Institute of Plant Breeding and Acclimatisation (PIB) in Radzików	Seminar	Possibilities of NGTs	Breeders	Agri-food
	Not provided	National Research Institute of Animal Production	Lectures	Topics regarding NGTs.	Students, researchers and breeding associations	Not specified
	Not provided	Plant Breeding and Biotechnology Department of the Institute of Cultivation of Fertilisation and Soil Science (PIB) in Puławy	Lectures	Open days on unconventional use of tobacco (GMO) as a green bioreactor for obtaining substances useful for humans	Students, researchers and breeding associations	Agri-food
Portugal	Not provided	Information not provided	Seminars	Characteristics and scope of the technologies and their potential. From these seminars, they also concluded that a higher level of communication between researchers and society in general is needed.	Students, farmers, reporters, professors	Agri-food, medicinal and industrial
Romania	2017	Romanian Academy together with Academy of Agricultural and Forestry Sciences, Romanian Seed Industry Alliance and Agrobiotechrom	Symposium	'Innovative alternatives in plant improvement — the foundation of sustainable and efficient agriculture': NPBTs – innovations for a sustainable and responsible growth and regulation of genome edited plants	Information not provided	Agri-food

	2018	Not provided	Workshop	Risk assessment of NPBTs: description, benefits in agriculture and for society, and overview of legal, political and social implications of their use in modern agriculture	Romanian specialists with responsibility in the field of GMOs, NBTs Techniques Platform (Brussels)	Agri-food
	2018	United States Embassy and Academy of Agricultural and Forestry Sciences, in collaboration with AgroBiotechRom, the Alliance of the Romanian Seed Industry and the Corn Producers Association	Conference	'Innovations in plant breeding — a new path to modern agriculture'	Competent authorities and institutes with responsibilities in the field of GMOs	Agri-food
	2019	United States Embassy in Romania	Round table	'Innovations in plant improvement — recent evolutions and future paths'	Competent authorities and institutes with responsibilities in the field of GMOs	Agri-food
Finland	2014	Finnish Advisory Board on Biotechnology (BTNK)	Publication	Current status and future prospects of synthetic biology: opportunities and challenges http://www.btnk.fi/files/pdf/Julkaisu/Synteettinen_biologia.pdf	General public	Agri-food, medicinal and industrial
	2015	Finnish Advisory Board on Biotechnology (BTNK)	Seminar	NPBTs, genetic engineering in medicine, technology trends and regulatory gaps in synthetic biology and regulation of genetic engineering and environmental impact assessment http://www.btnk.fi/files/seminaarit/BTNK_geeni-_ja_genomimuokkaus_kutsuseminaari_13102015.pdf	Experts	Agri-food, medicinal and industrial

	2015	Finnish Advisory Board on Biotechnology (BTNK)	Seminar	Synthetic biology definition, opportunities and risks. http://www.btnk.fi/files/seminaarit/Synteettinen%20biologi%20Chembio%2018.3.pdf	Experts	Agri-food, medicinal and industrial
	2018	Finnish Advisory Board on Biotechnology (BTNK)	Publication	Genome editing with new techniques — plants, animals, microbes http://www.btnk.fi/files/pdf/Julkaisu/261668_Geenien_muokkaus_verkkoversio_uusi.pdf	General public	Agri-food, medicinal and industrial
	2018	Report for the Finnish Parliament's Committee for the Future (TuVK)	Report	Threats and possibilities of genetic engineering. Investment from society is necessary before businesses are prepared to invest in development. Changes to regulation, investment in expertise and support development.	Government and scientific representation	Agri-food, medicinal and industrial
	2020	Finnish Government	Study	Study on NGTs	Stakeholders	Agri-food, medicinal and industrial
Sweden	2018, 2019, 2020	Mistra Biotech (research programme focusing on the use of biotechnology in crop and livestock breeding for sustainable and competitive agriculture)	Lectures, reports, articles	NGTs, NGT applications, policy, opportunities and risks, ethics https://www.slu.se/en/Collaborative-Centres-and-Projects/mistra-biotech/news-mistra-biotech/?page=0	Information not provided	Agri-food

	2019	Royal Swedish Academy of Agriculture and Forestry	Seminar	Will NPBTs have a future in the EU?: consequences of the ECJ ruling for research, plant breeding and agriculture in the EU https://www.ksla.se/aktivitet/will-new-plant-breeding-techniques-have-a-future-in-the-eu/	Seminar available on the internet	Agri-food

Table 15: National surveys related to NGTs, as reported by the Member States in the targeted consultation

MS	Year	Organiser	Participants	Aim	Summarised results
Germany	2019	Federal Institute for Risk Assessment (BfR)	20 consumers	To draw a qualitative consumer vote on the opportunities and risks of genome editing	• The consumer group agreed that genome editing has the potential to deliver on a wide range of issues. • Various demands were specified (e.g. maintaining the precautionary principle, freedom of choice for consumers, patent law reform). • During the event, it became clear that consumers lacked information on the topic.
	2019	Federal Ministry of Education and Research and National History Museum in Berlin	891 visitors of *ErbUndGut* supermarket project	To give a glimpse of the complex and controversial topic of plant breeding, including NGTs	• The stances of those for and against genetic engineering were far less static than is often suggested. • Attitudes towards the use of genetic engineering technologies depended on an understanding of nature and what is 'natural'. • The survey shows the extent to which the reasoning behind this concept of nature is situational and dependent on context. https://www.museumfuernaturkunde.berlin/de/erbundgut-der-supermarkt-im-museum-fuer-naturkunde
	2019	Federal Ministry of the Environment, Nature Conservation and Nuclear Safety (BMU), Federal Agency for Nature Conservation (BfN)	Not provided	To study awareness of nature in the population	• 81% of those surveyed were in favour of banning genetic engineering in agriculture. • 95% said they were in favour of investigating its potential impact on nature.
	Not provided	Federal level	Students (schools, universities, adult education), general public	To promote social debate on genome editing	• The results of the participatory online teaching module on the ethical, legal and social dimensions of genome editing are not yet available.
Estonia	2009	National economic research institute	1 000 consumers	To carry out a public perceptions study	• The main conclusion was that the population is poorly informed on GMOs. The survey did not distinguish between GMOs and NGTs.

France	2016	Institute of Public Opinion (IFOP) on behalf of Alliance VITA	1 007 participants over 18 representing the French population	To evaluate public opinion on CRISPR-Cas9 applications in terms of genetic engineering	• The CRISPR-Cas9 genetic engineering technique is very little known in France: only 9% say that they have heard of it. • Once the technique was explained to the participants, it gave rise to polarised judgments. 76% would be in favour of using CRISPR-Cas9 on adults or children as part of gene therapy in cases of genetic disease, but 76% would be against using it for *in vitro* genetic modification of human embryos. • 67% expressed concern at the increased pace of intervention by scientists in the human genome and 68% would be in favour of France requesting an international framework for this practice. https://www.ifop.com/wp-content/uploads/2018/03/3394-1-study_file.pdf
Italy	2017	National Committee for Biosafety, Biotechnology and Life Sciences of the Presidency of the Council of Ministers	16 stakeholders: scientific associations, research bodies, trade associations and industrial associations	To represent the different positions on NBTs in agriculture and to provide useful elements for interpretation and legislative revision	• The main difference between genome editing and other approaches concerns the greater precision of the new techniques and, therefore, the lower risk of unexpected effects. • With the current state of scientific knowledge, the risks associated with the main applications of NBTs are similar to those deriving from conventional techniques. • The unanimous recommendation of the scientific world and almost unanimous of the other stakeholders is to examine the plant varieties, based on the characteristics of the product. • In light of the rapid evolution and use of NBT technologies, Directive 2001/18/EC is inadequate and should be reviewed on the basis of new knowledge, making it product-oriented. • Strong action is expected in order to reduce the revision time to a minimum. • In the meantime, Directive 2001/18/EC should not be applied to genome editing products when the changes are identical to those obtained by other techniques. If this does not happen, several problems are foreseeable for the agri-food system. • Environmental and economic benefits are foreseeable following the cultivation of varieties produced by NBTs.

Lithuania	2019	Kaunas University of Technology study commissioned by Ministry of Agriculture	251 consumers, 50 farmers and 56 food producers	To compare the opinion of Lithuanian consumers, farmers and producers on conventional GMOs and NGT organisms	• All the groups in the survey are more familiar with GMO than with NGTs and regard GMO food mostly negatively. However, they had more positive views on food produced with raw material obtained from NGTs than from GMOs. • All groups felt it was important to know which method is used to obtain an organism. • NGTs were more likely to be used than GMOs. • Most important factors in food for consumers are food properties, perceived benefits for health and price. • There is a less negative consumer attitude towards NGTs than towards GMOs. • Opportunities for the application of directional mutagenesis and other NGTs in plant breeding. • Advisable to evaluate the NGT plant varieties on case-by-case basis, taking a product-based approach. http://zum.lrv.lt/uploads/zum/documents/files/LT_versija/Veiklos_sritys/Maisto_sauga_ir_kokybe/GMO/NMM%20gaut%C5%B3%20organizm%C5%B3%20panaudojimo%20Lietuvos%20%C5%BEem%C4%97s%20%C5%ABkyje%20perspektyvos.pdf

The Netherlands	2015	Netherlands Commission on Genetic Modification (COGEM)	Representative sample of Dutch population (1208 participants)	To investigate if public opinion on GMOs has changed since the last Eurobarometer (2010)	• Many respondents indicate that they are unfamiliar with the terms 'genetic modification' and 'genetically modified organisms'. • Respondents were asked about three specific GM applications: for making enzymes in detergents; for the development of a new potato variety; and for the production of insulin. From the answers about enzymes, respondents believe that the product offers benefits: cost price and washing at a lower temperature. For the GM potato, a majority agree that farmers can decide for themselves whether to grow it. Half agree that this new variety may be sold for consumption. A large majority agree that sufficient and good medicines must be available, even if they are made with the help of GM. • A large majority agree that civil society organisations should be consulted in decisions about GM. • Researchers at universities and general practitioners are most trusted by respondents when using or providing information about the use of GM and GMOs. https://cogem.net/en/publication/trend-analysis-biotechnology-2016/ https://jcom.sissa.it/archive/17/04/JCOM_1704_2018_A01
	2017	InSites Consulting commissioned by the Netherlands	150 participants over 15	To explore how societal values can be better reflected in the consideration of benefits and risks of biotechnological applications	• The public has mostly nuanced/balanced views. • Developments in biotechnology bring opportunities, especially for health applications. • Biotechnology should not be used solely for monetary reasons or for entertainment. • Safety is very important. https://www.rijksoverheid.nl/onderwerpen/biotechnologie/documenten/rapporten/2017/11/07/publieksopvattingen-over-biotechnologie

	2019	Netherlands Commission on Genetic Modification (COGEM)	Representative sample of Dutch population (1 000 participants)	To gain insight into how citizens perceive genetic modification in relation to plant breeding and medical applications	• More than half of the respondents have difficulties making the distinction between genetic techniques, both in plants and vaccines. • In plant applications, the perceived importance of the technique used is greater than in medical applications. • Respondents want the application of mutagenesis, gene editing, cisgenesis and transgenesis to be subject to stricter safety requirements than traditional breeding. With regard to vaccines, hardly any distinction is made in this area. • Many respondents see opportunities regarding quality of life, food and the environment, although many express concerns as regards concentration of power of companies, unforeseen consequences and upsetting nature's balance. • Supervision of genetic modification must be independent; respondents refer to independent scientific institutes and government agencies. https://cogem.net/publicatie/percepties-van-burgers-over-genetische-modificatie-een-kwalitatieve-en-kwantitatieve-verkenning/

Table 16: Public dialogue initiatives and expert body opinions relating to ethical aspects of NGTs, as reported by Member States in the targeted consultation

MS	Year	Organiser	Methodology	Title/content	Audience	Sector
Belgium	2005	Belgian Advisory Committee on Bioethics	Published opinion	Gene editing in humans: gene therapy, eugenics, somatic and germinal gene modification. https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/opinion_33_web.pdf	Open to the public	Medicinal
Czechia	Not provided	Experts	Discussions in the media (TV, newspapers, journals) and social media	Plant research specialist's opinion: • It is important to shift the focus of discussion from the tools used by breeders (NBT/NGTs, transgenesis, etc.) to goals pursued by breeders. • If anything should be scrutinised from an ethical perspective, it should be specific breeding goals (e.g. breeding for herbicide tolerance vs hypoallergenic crop).	Open to the public	Agri-food
	Not provided	Not provided	Discussions in the media (TV, newspapers, journals) and social media	Ethical aspects of NGTs in medical applications are discussed, including the religious points of view.	Open to the public	Medicinal
Denmark	2019	Danish Council on Ethics	Published opinion	'GMO and ethics in a new era' covering GMOs and NBTs. 15 of 16 members of the Council on Ethics concluded that it would be unethical not to use NGTs in light of the huge challenges, such as climate change. https://www.etiskraad.dk/~/media/Etisk-Raad/en/Publications/DCE_Statement_on_GMO_and_ethics_in_a_new_era_2019.pdf?la=da	16 members of Council on Ethics	Agri-food

Germany	2003	Ecclesiastical Office of the Evangelical Church in Germany/Secretariat of the German Bishops	Catholic social teaching	• Treat animals as creatures rather than just as 'live goods'. • Discussion about consumption behaviour, agriculture, agricultural policy, private animal handling, based on ethical criteria that respect animals' intrinsic value. • Cost-effectiveness and consumer preference are at odds with the recognition of animals as co-creatures. Humans are guardians of the animals, not their engineers. The focus on high-performance breeds threatens their genetic robustness.	Information not provided	Agri-food
	2018	Friedrich-Alexander-University Erlangen-Nuremberg representatives	Analysis using the approach of a modern-sensitive, concrete ethics of responsibility	'Ethical opinion on the use of new molecular biological technologies in agriculture': analysis focusing on the application of: genome editing technologies in plant breeding and possible use in agriculture; development of formal and ethical criteria for the design and management of new molecular biological techniques.	Information not provided	Agri-food
	2018	University of Kiel, University of Tübingen and Federal Agency for Nature Conservation	Multi-day expert discussion with female philosophers, natural, social and human scientists; nature conservation authorities; nature conservation associations	Nature protection implications of synthetic biology, genome editing, gene drives and regenesis relating to nature conservation. As well as a risk assessment, there is a need for a further technical impact assessment of genetic engineering applications with reference to nature conservation. This must include an ethical, conceptual and social assessment.	Experts	Agri-food, medicinal and industrial
	2019	Nature Conservation History Foundation and Federal Agency for Nature Conservation	2-day expert discussion with lawyers, philosophers, nature, culture, social and internal humanities scientists and representatives of nature conservation authorities	'New genetic engineering and nature conservation — a proportional determination': analysis of new genetic engineering procedures' compatibility with the self-image and objectives of nature protection and the adequacy of nature protection instruments.	Experts	Agri-food, medicinal and industrial

	2019		Workshop with ecclesiastical experts in the field of environment/agriculture and development	'Genome editing in agriculture: an interim call on new genetic engineering from an evangelical point of view'. Innovation should always be based on the precautionary principle. This is particularly the case in the area of agriculture and food. We welcome the ECJ judgment of 25 July 2018; the legal certainty thus created gives us time for the necessary social debate and a comprehensive, thorough and timely assessment of the technological consequences of new genetic engineering. http://www.kircheundgesellschaft.de/sustainable	Information not provided	Agri-food
	Not provided	Catholic *Landvolk* Movement Germany (KLB)	Expert consultation and discussion, decision-making, critical assessment of the impact of NGTs	Basic information, classification in the previous genetic engineering system and legal regulations, ethical consideration. The following considerations were raised against NGTs from the members' point of view: genomic editing not only modifies genes in organisms, but also the integrity of animals and plants and their perception by the public. The simplification of genome editing by CRISPR/Cas will strongly affect the equity issue and favour large-scale food production to the detriment of smallholder farmers worldwide. A one-sided industrial understanding dominates other values relating to food, e.g. the question of a culture of food and drink, the relationship of diet to a 'good life' and to tradition, religion and belief.	Information not provided	Agri-food
Estonia	2019	160 European scientists (including Estonians)	Letter to the European Commission and European Parliament	A letter to ask for a change in the legislation (NGTs relating to agriculture; need for such techniques). Call on the Commission to amend legislation was perceived as the ethical choice.	Open to public	Agri-food
	Not provided	European fora in which the University of Tartu and the University of Tallinn participated	Fora	Would allowing foreign GMOs have adverse effects on the availability and use of local varieties? During a public debate about GM food crops, the question was raised as to whether it is ethical to restrict the use of NGTs if they could improve plant resistance.	Information not provided	Agri-food

Greece	2020	National Bioethics Commission (NBC)	Published opinion after three rounds of hearings of experts by the NBC, including from relevant ministries and related directorates (e.g. biotech, plant reproductive material, food safety, feed, detection labs), Greek Food Safety Authority, Greenpeace Greece, Greek seed industry association, Greek organic farmers' association	• GMOs should promote enough safe food, including new technologies, respecting safety, justice and diversity. • Safety doubts can be raised as regards GMOs and conventional food or feed already marketed. The difference is in the uncertainty of the risks that stem from GMO use, while with conventional products, in principle, the risks are known. The GMO risks will be reduced, but today we are not in a position to ensure that there is enough data for a full risk assessment. The crucial question is whether this uncertainty is enough to completely ban GMOs from use in agriculture. NBC believes that the precautionary principle in a broader manner (allowing, but with careful assessment) means that measures should be taken for controlled market circulation. • Financial factors are also involved, including patent protection, monopolies of GM seeds and unfair competition. • For GM trade, it is crucial to ensure consumer information. • In cultivation, MS can ban cultivation also for non-scientific reasons (political, social, etc.). However, such decisions should be substantiated, because apart from completely banning GM technologies it is an exception in the free market. • CJEU decision, detection issues and suitability of current risk assessment were also discussed.	Open to the public	Agri-food
France	2014	High Council of Biotechnologies on Ethics, High Council of Biotechnology (HCB)	Report	The committee's working group on ethics drafted a report entitled *General ethics and assessment of new technologies*. http://www.hautconseildesbiotechnologies.fr/fr/article/publications-hcb	Open to the public	Agri-food and medicinal

	2016	Ethics Committee of the National Institute of Health and Medical Research (Inserm)	Note	Ethical issues relating to the development of CRISPR-Cas9 technology. The note deals with the medical applications of this technology. It looks at gene forcing CRISPR-Cas9, the modification of the genome at the zygous stage in animals, and the modification of the genome of the germline or the zygote stage in humans. https://www.inserm.fr/sites/default/files/2017-10/Inserm_Saisine_ComiteEthique_Crispr-Cas9_Fevrier2016.pdf	Open to the public	Medicinal
	2017	Parliamentary Office for Scientific and Technological Options Assessment (OPESCC)	Report	*The economic, environmental, health and ethical challenges of biotechnology in the light of new avenues of research* https://www.senat.fr/rap/r16-507-1/r16-507-11.pdf	Open to the public	Agri-food and medicinal
	2018	Joint Consultative Committee on Ethics of Inrae, CIRAD, Iremer and IRD	Published opinion	Opinion on new techniques for genetic improvement of plants. The CRISPR-Cas9 system is the focus, as it provides a concrete indication of the deployment of these new techniques. https://www.inrae.fr/sites/default/files/pdf/Avis-11-Comite-Ethique.pdf	Open to the public	Agri-food
	2018	Association for Responsible Research and Innovation in Genome Editing (ARGE)	Not-for-profit association drafting reports, statements, opinions on ethics in biotechnology	It is mainly composed of specialists in medical matters, but intends to promote responsible research across the board, whatever the field of application. This includes research publications calling for international monitoring of genomic publishing, and the conduct of ethical work. https://arrige.org/documents.php	Open to the public	Medicinal
	2019	Joint Consultative Committee on Ethics of Inrae, CIRAD, Iremer and IRD	Published opinion	Opinion on the genetic modification of animals in the testing of genome editing. The opinion is dedicated to the use of genome editing technologies for the modification of the genome of animals by targeted mutagenesis. It follows up on the opinion on the edition of plant genomes. It is of interest as regards farmed animals and animals considered to be pests. https://www.inrae.fr/sites/default/files/pdf/Avis-12-Comite-Ethique-web.pdf	Open to the public	Agri-food, medicinal and industrial

	2020	National Advisory Committee on Ethics for Life and Health Sciences (CCNE)	Published opinion	Ethical challenge of targeted changes in the genome. https://www.ccne-ethique.fr/sites/default/files/avis_133_-_ad_final.pdf	Open to the public	Agri-food, medicinal and industrial
	2020	Ethic committees from France, Germany and the UK	Joint declaration in a scientific journal	Joint declaration of the French, German and UK ethics committees in the *Nature* journal. https://www.ccne-ethique.fr/sites/default/files/declaration_commune.pdf	Open to the public	Medicinal
	2020	French Agricultural Academy	Published opinion	The opinion covers crops, forests and livestock. The Academy claims that it is well founded to use these techniques for objectives of cognitive research and to find solutions to address global challenges (biodiversity, climate change, agroecology, etc.) and calls on key players in the field to publish their ethical commitments. It proposes that limits be set that restrict editing to rewritings of the genome that preserve the identity of the species. https://www.academie-agriculture.fr/publications/publications-academie/avis/reecriture-du-genome-ethique-et-confiance	Open to the public	Agri-food
The Netherlands	2017	Health Council of the Netherlands and Netherland Commission on Genetic Modification (COGEM)	Policy report	The report examines the moral and social implications of germline genetic modification in humans. https://cogem.net/en/publication/editing-human-dna-moral-and-social-implications-of-germline-genetic-modification-2/	Open to the public	Medicinal

	2018	Netherlands Commission on Genetic Modification (COGEM)	Policy report	This report describes the scientific developments and policy implications of genome editing in animals. Potential applications are in farm animals, pets, laboratory animals, medicine (xenotransplantation) and population control (gene drives in insects and animals in the wild, and even bringing back extinct animal species). Given the accelerating pace of technological change, the government and stakeholders should adopt a position on the possible importation of genome-edited animals and products derived from them. For this, they must first consult scientists, breeders, industry and societal stakeholders. https://cogem.net/en/publication/crispr-animals-implications-of-genome-editing-for-policy-and-society/	Open to the public	Agri-food and medicinal
	2019	Netherlands Commission on Genetic Modification (COGEM)	Policy letter	Policy letter update on human genome editing based on the news that a scientist created the first gene-edited (GM) humans. https://cogem.net/en/publication/update-to-policy-report-editing-human-dna/	Open to the public	Medicinal
	2019	Royal Netherlands Academy of Arts and Sciences, Rathenau Instituut	Report	Genome editing in plants and crops. Towards a modern biotechnology policy focused on differences in risks and broader considerations. Advice for a policy option on genome editing in plants and crops. Instead of upholding or exempting genome-editing techniques from the GMO Directive, the report proposes a third policy option that entails a level-based risk assessment in combination with an assessment for the value of applications for society. https://www.rathenau.nl/en/making-perfect-lives/genome-editing-plants-and-crops	Open to the public	Agri-food

	2019	Royal Netherlands Academy of Arts and Sciences, Rathenau Instituut	Report	Discussing the modification of heritable DNA in embryos. Advice for broad societal debate on human germline editing. This report provides guidelines and instruments for conducting national debate on the subject. These lessons are being used in the public debate on the use of NGTs for germline modification. https://www.rathenau.nl/en/making-perfect-lives/discussing-modification-heritable-dna-embryos	Open to the public	Medicinal
Austria	2016	National Bioethics Commission with national ethics commissions from Austria, Germany and Switzerland	Meeting	Genome editing in human medicine. https://www.bundeskanzleramt.gv.at/themen/bioethikkommission/pressemitteilungen-bioethik/bioethik-kommission-diskutiert-zu-gen-chirurgie	Open to the public	Medicinal
	2016	UNESCO Chair for Bioethics (at the Medical University of Vienna)	Conference	Fighting malaria with CRISPR/Cas9: ethical implications. https://www.meduniwien.ac.at/web/internationales/unesco-lehrstuhl-fuer-bioethik/aktivitaeten-auswahl/2016-konferenz-die-bekaempfung-von-malaria-mit-hilfe-von-crisprcas9/	Open to the public	Medicinal
	2017	Research Platform Responsible Research and Innovation in Academic Practice (University of Vienna)	Symposium	It aims to discuss the potential impact and challenges while exploring the scientific, ethical and societal issues inherent in genome-editing research. https://rri.univie.ac.at/workshops-events/crispr-symposium/	Open to the public	Agri-food, medicinal and industrial
	2019	Federal Ministry of Labour, Social Affairs, Health and Consumer Protection (BMSGPK)	Study	A study on ethical aspects of NGTs. Participants were stakeholders and NGOs.	Open to the public	Not specified
	2019	University of Natural Resources and Life Sciences, Vienna	Ethics platform to stimulate systematic and participative debate on ethical questions concerning NGTs	Scientific inputs and public discussion addressing opportunities and risks associated with the use of NGTs in crop development. https://boku.ac.at/en/ethikplattform/genome-editing	All citizens	Agri-food

	2019	University of Natural Resources and Life Sciences, Vienna	Ethics platform to stimulate systematic and participative debate on ethical questions concerning NGTs	Organic farming and genome editing — a potential/impossible match. https://boku.ac.at/ethikplattform/genome-editing/biolandbau-und-gene-editing-eine-un-moegliche-kombination	All citizens	Agri-food
	2020	UNESCO Chair for Bioethics (at the Medical University of Vienna)	Conference	Vector-borne diseases, nature and genome editing: an ethical consultation. https://www.meduniwien.ac.at/web/internationales/unesco-lehrstuhlfuer-bioethik/ https://www.meduniwien.ac.at/web/internationales/unesco-lehrstuhl-fuer-bioethik/aktivitaeten-auswahl/2020-konferenz-vector-borne-diseases-the-nature-and-genome-editing-an-ethical-consultation/	Open to the public	Medicinal
	Not provided	National Bioethics Commission at the Federal Chancellery	Discussions	Ongoing discussions on ethical aspects of NGTs. https://www.bundeskanzleramt.gv.at/themen/bioethikkommission.html	Open to the public	General
Portugal	2018	National Council of Ethics for Life Sciences	Annual seminar	The Council discussed ethical aspects of NGTs, but issued no conclusion or opinion.	Council members	Not specified
Slovenia	Not provided	Not provided	Research project presented in fora	'Procedures for ensuring the safety and social acceptability of new techniques and applications of synthetic biology and modern biotechnology' – the project touched briefly on ethical aspects.	Information not provided	Not specified
Finland	2016	Finnish Academy of Science and Letters	Expert and public seminars	'Genetic modification and the opportunities in genome editing'.	Experts and open to public	Not specified

	2017	Finnish Defence Research Agency and Centre for Military Medicine	Expert and public seminars	Synthetic biology in the context of security and defence.	Experts and open to public	Medicinal
	2017	University of Oulu	Expert and public seminars	Genes and society.	Experts and open to public	Not specified
	2017	Biobio Society	Expert and public seminars	ChemBio Finland seminar 'CRISPR/Cas9 genome editing: holy grail or doomsday for humankind?'	Experts and open to public	Not specified
	2019	Academy of Finland	Expert and public seminars	'Synthetic biology foresight'.	Experts and open to public	Not specified
	Not provided	Academy of Finland Synthetic Biology (FinSynBio) Programme	Research projects and publications	'Synthetic biology and ethics'. One conclusion reached 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. It is mainly concerned with biosafety. This, together with certain developments relating to synthetic biology, provide a strong reason to review and possibly refine the legislation and the supervisory practices as regards biosecurity.	Open to the public	Not specified
	Not provided	Academy of Finland Synthetic Biology (FinSynBio) Programme	Research projects and publications	'Biological knowledge through modelling and engineering: epistemological and social aspects of synthetic biology (SynBioMode)'.	Open to the public	Not specified

ANNEX E — EU legislation on GMOs

Directive 2001/18/EC on the deliberate release of genetically modified organisms

Directive 2001/18/EC defines GMO as *'an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'.* This Directive requires the relevant authorities' prior consent for the deliberate release of GMOs into the environment. In order to obtain consent, an application ('notification') has to be submitted to the national competent authority, accompanied *inter alia* by an environmental risk assessment. The risk assessment must comply with the general principles and the methodology set out in the directive and draw conclusions for each relevant area of risk. The requirements are different for the placing on the market of GMOs as or in products (Part C of the Directive) and for other purposes (Part B). Decisions

The authorisation procedure for the placing on the market of GMOs (as such or in products) is conducted at EU level, whereas the procedure to authorise the deliberate release of GMOs for other purposes is conducted by each Member State. The national competent authority to which the notification has been submitted must deliver an assessment report. In cases where the Commission or another Member State have expressed objections to the assessment report and no agreement has been reached, the Commission adopts a decision after obtaining the scientific opinion of EFSA. The national competent authority that prepared the report then gives written consent for the placing on the market of the GMO as such or in a product. It must set out the conditions for the placing on the market, and labelling and monitoring requirements. It can be valid for a renewable period of up to 10 years.

Directive 2009/41/EC on the contained use of genetically modified micro-organisms

This Directive defines a GMM as '*a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'* (Article 2(b)). It requires a notification to the national competent authorities and in some cases their prior consent for the use of GMMs. To that end, the user has to carry out an assessment of the contained uses as regards risks to human health and the environment.

The requirements of Directives 2001/18/EC and 2009/41/EC apply to all GMOs/GMMs (as such or in products) except GM food and feed, which are subject to Regulation (EC) No 1829/2003.

Regulation (EC) No 1829/2003 on GM food and feed

This Regulation requires authorisation for the placing on the market of food and feed consisting of, containing or produced from GMOs ('GM food and feed'). The authorisation procedure is centralised, providing for a single application to be submitted to a national competent authority for all the intended uses of the GM food or feed in question (including cultivation). It is based on an independent risk assessment carried out by EFSA. Authorisation may be granted only if the risk assessment demonstrates that, under its intended conditions of use, the product has no adverse effects for human and animal health and for the environment, does not mislead the user or the consumer and is not nutritionally disadvantageous compared to the food or feed it is intended to replace. Authorisations are granted by the Commission for a renewable period of 10 years. They may impose conditions or restrictions, including post-market monitoring requirements, and must set out

the method for detecting the transformation event, as provided by the applicant and validated by the EURL. The Regulation also provides for mandatory labelling of authorised food and feed, so that final users can make an informed choice.

Regulation (EC) No 1830/2003 on the traceability and labelling of GMOs and the traceability of food and feed products produced from them

Under this Regulation, operators placing GMOs and GM food and feed on the market must inform the operators receiving the products, in writing, that the products contain or consist of GMOs. They must provide an indication of each ingredient/material produced from GMOs or, for products without an ingredients list, an indication that the product is produced from GMOs. They must keep that information for 5 years and be able to identify the operator(s) by whom and to whom the products have been made available. Traceability requirements allow for close monitoring of potential effects of the product on environment and health, and where necessary for the withdrawal of products if an unexpected risk to human health or to the environment is detected. Furthermore, the Regulation requires that all products consisting of or containing GMOs be labelled as such.

Regulations (EC) No 1830/2003 and (EC) No 1829/2003 (the latter as regards the labelling of food and feed) both exempt from the traceability and labelling requirements products with traces of GMOs in a proportion no greater than 0.9% when their presence is adventitious or technically unavoidable.

Medicinal products containing or consisting of GMOs

Specific mention should be made of medicinal products for human and veterinary use containing or consisting of GMOs. Articles 13 to 24 of Directive 2001/18/EC do not apply to medicinal products containing or consisting of GMOs that are authorised under Regulation (EC) No 726/2004[74]. The authorisation, labelling and public information requirements in Part C of Directive 2001/18/EC do not apply. However, the application for marketing authorisation must include a copy of the competent authorities' written consent for the deliberate release into the environment of the GMO for R&D purposes, as provided for in Part B of the Directive. It must also include a technical dossier, in compliance with Annex III of Directive 2001/18/EC, and an environmental risk assessment, in accordance with Annexes II-IV to the same Directive. The assessment is carried out by the competent committee (for human or veterinary medicines) of the European Medicines Agency, in consultation with Union and Member States' competent authorities for GMOs. The results of the assessment are included in the opinion of the competent committee.

Furthermore, as regards clinical trials with medicines for human use containing or consisting of GMOs, Directive 2001/20/EC[75] on the conduct of clinical trials is without prejudice to the application of Directive 2009/41/EC (on the contained use of GMMs) or Directive 2001/18/EC (on the deliberate release of GMOs), if the investigational product to be used in clinical trial contains or consists of GMOs.

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[74] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

[75] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

Regulation (EC) No 1946/2003 on transboundary movements of GMOs

At international level, the EU is a party to the Cartagena Protocol on Biosafety to the UN Convention on Biological Diversity[76]. The purpose of the Protocol, in line with the precautionary approach, is to ensure an adequate level of protection in the safe transfer, handling and use of GMOs that may have adverse effects on biodiversity and human health. To that end, it sets out common rules to be followed in transboundary movements of GMOs and provides for a central database (Biosafety Clearing House) to allow parties to exchange information on GMOs and help them to comply with their obligations under the Protocol. Those obligations are reflected in the EU GMO legislation. The Protocol's procedures concerning exports of GMOs are implemented in the EU by Regulation (EC) No 1946/2003 on transboundary movements of GMOs. In particular, the Regulation requires EU operators to notify the competent authorities of importing countries of exports of GMOs intended for deliberate release into the environment and to seek their consent prior to the first export. It also requires the Commission and Member States to inform the Biosafety Clearing House of relevant legislation and decisions on GMOs.

[76] Cartagena Protocol on Biosafety to the Convention on Biological Diversity, adopted on 29 January 2000, concluded on behalf of the EU by Council Decision 2002/628/EC of 25 June 2002 concerning the conclusion, on behalf of the European Community, of the Cartagena Protocol on Biosafety, OJ L 201, 31.7.2002, p. 48.

8. Supplementary material

This section provides links to online supplementary material produced for and used in the study:

Member States and stakeholders replies to the targeted consultation

https://ec.europa.eu/food/plant/gmo/modern_biotech/stakeholder-consultation_en

Overview of EFSA and national authorities' scientific opinions on the risk assessment of plants developed through New Genomic Techniques

https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2021.631

JRC Science for Policy Report - Current and future market applications of New Genomic Techniques

https://doi.org/10.2760/02472

link to web dashboard:
https://datam.jrc.ec.europa.eu/datam/mashup/NEW_GENOMIC_TECHNIQUES

JRC Technical Report - New Genomic Techniques: State-of-the-art Review

https://data.europa.eu/doi/10.2760/710056