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New biotechnologies, allies for food safety in the face of climate change. Where does Europe stand?

The food market is currently marked by soaring prices and shortages due to supply shocks in the wake of the Covid-19 pandemic, but also to repeated extreme weather events linked to climate change; and finally, to geopolitical conflicts, in particular Russia's invasion of Ukraine. All innovations must be used to ensure food security, particularly for the European Union.

THE CHALLENGES AHEAD

Combined with the rise in the cost of inputs (fertilisers and crop protection products) and energy, the increase in agricultural prices is affecting downstream businesses and consumers throughout the value chain. Prices of foodstuffs and fertilisers are still 40% to 80% higher than in 2019 (before the pandemic). The war between Russia and Ukraine is seriously impacting world food trade, exacerbating the global food crisis. Before the Russian invasion, Ukraine was the world's leading exporter of sunflower seeds and one of the world's top five exporters of wheat, rapeseed, barley, and maize. Russia is the world's leading exporter of wheat as well as barley and sunflower seeds and is also a major exporter of energy and fertilisers. For example, 23% of the world's ammonia, 14% of its urea and 21% of its potash come from Russia, and 18% from Belarus; with Canada being the world's largest potash producer (31%) and exporter (38%), ahead of Belarus (20%) and Russia (22%), with the world's largest reserves.

As for the major effects of climate change on the food production system, farming methods are exposed to the increased frequency of extreme weather events and rising temperatures.

One of scientists' main concerns is the impact of climate change on crop yields and quality.

Global food production needs to increase by 70% to meet the growth in the world's population (potentially 10 billion people by 2050)[1]. Land is becoming increasingly unsuitable for cultivation in some regions, due to a lack of water or flooding with salt water.

Agriculture also needs to decarbonise, i.e. reduce its use of fertilisers and pesticides to reduce the greenhouse gases that are contributing to global warming.

SPEEDING UP PLANT BREEDING

Against this backdrop of food instability and to meet the growing demand of the world's population, it is essential to speed up the creation of new varieties by selecting the best combinations of genes: this is called plant breeding.

The aim of plant breeding is to produce crops with improved characteristics by modifying their genes. Genetic modifications can be made to plants to improve photosynthesis and CO2 fixation, increase root mass to capture carbon and water, optimise plant growth, enable cereals to use atmospheric nitrogen and use fewer plant protection products in a sustainable way. Scientists are seeking these new features in plants. Conventional breeding achieves this by crossing plants with the desired characteristics and selecting the offspring with the desired combination of characteristics, using particular combinations of genes inherited from both parents.

New characteristics can be achieved by natural or induced genetic mutations. Mutations induce

[1] *van Dijk M., Morley T., Rau M.L. et al. (2021).* A meta-analysis of projected global food demand and population at risk of hunger for the period 2010–2050.

changes directly in genes to obtain different versions of those genes. Random mutagenesis occurs naturally. It can also be induced in the laboratory by subjecting plant tissues, seeds, etc. to radio-induced or chemical conditions that generate transmissible mutations. Scientists induce mutations using gamma or UV rays (radiation-induced mutagenesis developed since 1920 in the United States) and mutagenic chemicals (chemical mutagenesis used since 1968 in the United States). In the European Union, mutagenesis is a technique exempt from classification as a GMO (directive 2001/18/CE). Scientists can add one or more new genes to the genome of a cultivated plant: this is the technique of transgenesis, and the organism is then classified as a GMO. This technique was discovered in 1983 by Belgian and German scientists. Genes are not added at a specific point in the genome but may come from the same species or related species, or from other species belonging to different kingdoms (this is known as foreign DNA).

NEW GENOMIC TECHNIQUES

These *New Genomic Techniques* (NGT) use precise tools to modify genes (known as gene editing) with promising biotechnological applications. The NGT appellation is that in force since 2021 in the European Union, which previously used the *New Breeding techniques* (NBT).

These techniques use CRISPR-Cas, Talen, ZFN[2], as tools that cause targeted DNA breaks at a precise point in the genome so as to modify a gene, swap one gene with another or add new genes. Amongst the NGTs, the most common is CRISPR-Cas known as "genetic scissors" in everyday language. CRISPR, which occurs naturally in bacteria, is a family of DNA sequences which, when combined with a guide RNA sequence and a CRISPR-associated protein (Cas), a nuclease, is capable of cutting DNA at a targeted point in the genome. CRISPR-Cas is revolutionary and has been a great success with public and private scientists. The Nobel Prize was awarded in 2020 to France's Emmanuelle Charpentier of the Max Planck Institute in Berlin and American Jennifer Doudna of the University of Berkeley, who discovered it in 2012. It is not extremely expensive and is quick to implement.

NEW FORMS OF PATENTABILITY TO PROTECT INNOVATION

This is why so many patents are registered worldwide: China, the United States and South Korea are far ahead of the European Union[3]. Within the latter, in order, we find Germany, the Netherlands, Sweden, Denmark, Belgium, Italy, France and Poland filing patents using CRISPR and, outside the EU, the United Kingdom.

Universities hold most of the key patents using CRISPR technology for applications ranging from agriculture to human therapy. NGT biotechnology is already being used by numerous teams in public laboratories[4]. The role of the public sector is important when it comes to holding the key patents for CRISPR technology. The key patents have no economically viable substitutes; some of them require a licence to use the intellectual property right. It is possible to make multisite modifications using NGTs in the same genome, such as transgene pyramiding.

Biotechnology with NGTs, especially in agriculture, is a lucrative industry and will continue to grow. More than 11,000 patent applications relating to CRISPR-Cas have already been filed worldwide[5], which has led some EU Member States to express concern about the complexity of the patent landscape for NGTs. Initiatives are being developed such as the new collaborative patentability platform, *Agricultural Crop Licensing Platform (ACLP)*. Based in Brussels, this licensing platform for agricultural crops is open to all private or public sector organisations involved in plant breeding or trait research and development, from the 39 States of the European Patent Office (including Russia and Ukraine). The initiative is currently led by nine European plant breeding and trait development companies, representing a wide range of agricultural crops and including small, medium and large companies. ACLP is funded by membership fees.

The plant variety certificate (PVC) in force in the European Union and in many countries around the world protects the variety for twenty-five or thirty years under the UPOV Convention. As this protection is not a patent, it allows breeders to exchange varieties to improve them. This is the "breeding exception", which allows breeders to use a variety - protected by

[2] CRISPR (clustered regularly interspaced short palindromic repeats; Talen (transcription activator-like effector nuclease), ZFN (zinc-finger nuclease)

[3] Ricroch A., Martin-Laffon J., B. Rault, V. C. Pallares & Kuntz M. (2021). Next biotech plants: new traits, crops, developers, and technologies for addressing global challenges.

[4] The Crop Transformation and Genome Editing platform (Biotechnology Resources for Arable Crop Transformation) at the John Innes Centre (UK); at the Heinrich-Heine University (DE); Vlaams Instituut voor Biotechnologie of the University of Gent (BE): to name but a few of the pioneering institutes in Europe.

[5] Ricroch A., CRISPR Processes Patents in Green Biotechnology: Collaborative Licensing Models.

COV - to freely create their own new variety, without any authorisation by or remuneration of the owner of the protected variety; such a system encourages research and incremental progress while maintaining the protection of the initial variety. If the variety - protected by COV - contains a patented gene, the breeder must pay a royalty to the patent holder. If the variety contains ten or so patented genes, payment of the royalties can get complicated.

NGT APPLICATIONS

The low laboratory costs of NGTs (especially CRISPR-Cas) and their rapid production mean that not only private companies and multinationals, but also public-private consortia and small and medium-sized enterprises can develop new applications,

Innovations in plant breeding using NGTs are proceeding apace, leading to new solutions such as plants that are resistant to pests or diseases, tolerant to abiotic sources of stress (drought), of nutritional quality (modified starches and fats for food and non-food purposes), with improved conversion of biomass for biofuels.

Gene editing considerably speeds up breeding programmes compared with conventional breeding. Two varieties are currently on the market: a tomato enriched with GABA (an amino acid that reduces hypertension) by Sanatech Seed and the University of Tsukuba in Japan, and a soya bean with reduced trans-fatty acid content by Calyxt in the United States (a subsidiary of the French company Cellectis).

In animal breeding, CRISPR-Cas is mainly used for disease resistance in pigs in China (African swine fever) and for the well-being of farmers and animals with hornless cows from the University of Davis in the United States. In 2020, the US Food and Drug Administration (FDA) authorised the first intentional genomic modification of domestic pigs for human food and potential therapeutic purposes; the modification aims to eliminate alpha-gal sugar from the surface of pig cells (people suffering from alpha-gal syndrome can have allergic reactions to this sugar present in meat). In the UK, the University of Edinburgh is using CRIPSR-Cas9 to study the role of specific genes in influenza virus infection and in infection by other major pathogens in the chicken and pig genomes. In human therapy, trials are underway to treat certain cancers and neurodegenerative diseases; these promising avenues of research are subject to ethical scrutiny, as the modification of transmissible heredity (germ cell modification) is banned worldwide.

HOW ARE NEW GENOMIC TECHNIQUES REGULATED WORLDWIDE?

At present, most countries do not explicitly regulate GMOs. In the European Union, transgenic plants are classified as GMOs under the aforementioned 2001 directive. Several countries are introducing flexible regulations for plants derived from NGTs on the basis of the Cartagena Protocol 2000 which defines a living modified organism as "*any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology*", emphasising the novelty of a (re)combined sequence. Most countries with regulations currently in place base their classification on the absence of added foreign DNA in the final product derived from NGTs.

Organisms without foreign DNA (but with a modification of one gene or a replacement of one gene by another) are not considered GMOs. Countries that already have regulations on NGTs based on the absence of foreign DNA are Argentina in 2015, Chile in 2017, Brazil and Colombia in 2018, Paraguay, Honduras, Guatemala and El Salvador in 2019, Japan in 2019, the United States in 2021, China in 2022, India in 2023 and the United Kingdom in 2023.

Since 2015, Canada has taken a different approach to regulating NGTs; its system uses the concept of "novelty" to assess whether it is necessary to regulate new crops, regardless of the breeding method used. Canada has indicated that "genetic modification" is not limited to recombinant DNA technologies, but can also include conventional breeding, mutagenesis and emerging genetic engineering technologies such as genome editing.

IN THE EUROPEAN UNION, SOME MEMBER STATES ARE ALREADY CONDUCTING TRIALS WITH NBTS

It is virtually impossible to obtain authorisation from the European Commission to cultivate a GMO product (except in Spain and Portugal, where GMO cultivation of maize resistant to an insect, the European corn borer, is authorised), but the Commission does authorise the import of GMOs. Five Member States, including major agricultural countries, prohibit public or private researchers from conducting field trials of GMO or NGT-edited plants: France, Germany, Greece, Cyprus and Estonia. In June 2023, Italy decided to conduct trials with NGTs, whereas until then it had banned trials with GMOs and plants derived from NGTs. For political reasons, France (in 2008) and Germany (in 2009) have banned the cultivation of GMOs in the field, although laboratory experiments are authorised. There are no field trials with either transgenesis or NGTs.

In the European Union, six Member States will be conducting transgenesis or NGT trials in 2023: Sweden (five GMO trials and five NGT trials), Belgium (two GMO trials and four NGT trials), the Czech Republic (three GMO trials), the Netherlands (two GMO trials), Denmark (two NGT trials) and Romania (one GMO trial). Spain, although in favour of trials (it has launched many in previous years), is not conducting any. So only three Member States are conducting field trials on NGT-edited plants: Sweden (five trials), Belgium (four) and Denmark (two).

Outside the European Union, in 2023, three countries will be conducting trials: the United Kingdom (two GMO trials and three NGT trials), Switzerland (three GMO trials) and Iceland (one GMO trial). The UK passed its NGT legislation in March 2023 (entitled *Precision Breeding*) to facilitate the marketing of products modified by NGT and has always conducted trials of transgenic plants.

THE STEPS TAKEN BY THE EUROPEAN COMMISSION TO ADOPT A REGULATORY TEXT

In 2018, the Court of Justice of the European Union, following the judgment in the case of C-528/16, ruled that NGT editing fell within the scope of Directive 2001/18/EC covering GMOs (the judges ruled that edited plants must be regulated as transgenic organisms). The following year, the Council asked the Commission to look into the matter. On 29 April 2021, it published a study on status of NGTs which defines them as "*techniques capable of modifying the genetic material of an organism that have appeared or have been developed since 2001*", i.e. after the adoption of the existing European legislation on GMOs. NGTs include CRISPR-Cas and other techniques. The study concluded that existing GMO legislation was not adapted to gene editing with NGTs and was holding back the development of innovative crops. In September 2021, the Commission published a roadmap on the initiative aimed at establishing a new legal framework for plants obtained by targeted mutagenesis and cisgenesis and for their food and feed products. Cisgenesis is a technique for the artificial transfer of genes between organisms of the same species. This roadmap is based on the conclusions of the Commission's study on NGTs under EU law, particularly in the light of the judgment of the Court of Justice of the European Union. From April to July 2022, the Commission organised a public consultation (80 % of responses were in favour of regulation change and 17% against by NGOs known for their hostile stance to GMOs and new biotechnologies), following which it tabled a proposal for a regulation published on 5 July 2023. The aim is to enable innovation in the agri-food system while maintaining a high level of protection for human and animal health and the environment, and to contribute to the objectives of the European Green Deal and the "Farm to Fork Strategy" as well as biodiversity strategies and the United Nations' sustainable development objectives for a sustainable agri-food system.

Intellectual property and patent protection for biotechnological inventions (in virtue of the 98/44/EC directive), The Union's 2021 study recognised the advantages of patents and licences in promoting innovation and the development of NGTs and their products. The licensing landscape is developing rapidly with licensing agreements, some exclusive, some non-exclusive, across a diverse range of CRISPR technologies and application areas, from agriculture to therapeutics.

In the European Union, gene editing, such as transgenesis, has until now been regulated under Directive 2001/18/EC on GMOs. The high cost of regulation, as well as the time required to complete the dossier for a GMO, can constitute obstacles to innovation. In Europe, the cost of a GMO approval dossier is between 11 and 17 million€[6]. In North America, the cost of discovering, developing and authorising a new gene-governed trait is $115 million (including $10.3 million in costs for regulatory affairs). An approval dossier contains data provided by the breeder proving that the GMO is harmless to human and animal health and to the environment, and consists of laboratory and field tests at several sites and over several years. Gene editing enables scientists to make targeted changes to DNA and modify a plant much more quickly than with conventional selection or transgenesis. For this reason, it is imperative that the European institutions succeed in drawing up a clear text on the use of NGTs.

DRAFT EUROPEAN LEGISLATION ON NGTS

On 5 July 2023, the European Commission proposed to facilitate the research and marketing of plants published with NGTs. This project aims to speed up research into making crops more resistant to climate change (drought), pests and diseases, and developing plants that require less fertiliser or agrofuels. It is part of a wider package of legal measures to promote the sustainable use of natural resources, which also includes provisions for monitoring soil health and reducing food waste.

The idea is to exempt edited plants from current GMO legislation if they are equivalent to those that could be obtained through conventional plant breeding (cross-breeding between plants, for example). Scientists or companies will have to demonstrate that edited plants are identical to conventional plants. The time and cost required to assess GMOs is excessive; will it be the same for plants derived from NGTs? According to the project, edited plants would not require lengthy and costly assessments of potential risks to human health or the environment, which would help developers to bring them to market much more quickly than GMOs. As a result, many modified crops would reach the market over the next few years.

The draft legislation authorises scientists to use NGTs to add genes, if these genes already exist in what is known as the breeder's gene pool (made up of species that cross-breed with each other; these genes would not be considered as foreign DNA). This flexibility is interesting, because adding genes can lead to more sophisticated effects than simply deleting a gene through mutation. But this flexibility is insufficient, because moving genes from another species outside the pool can have promising applications (resistance to pathogens, for example, as obtained by transgenesis in the case of GMOs).

On the other hand, this draft legislation still bans NGT-edited plants from organic farming and requires these edited seeds to be labelled. As a result, companies and other developers will have to register the crops and their characteristics in a public database. These plants can be grown in integrated farming, which uses few or no inputs. Moreover, sustainable agriculture combined with the use of plants derived from NGTs could prove to be environmentally and climate friendly, while guaranteeing good yields at affordable prices for as many consumers as possible.

Unfortunately, change is still a long way off, as it could take several years for the European Parliament and the Council to approve these new regulations on NGTs.

WHAT WOULD BE THE BEST REGULATION FOR EUROPE?

If Europe wants to reap the benefits of gene editing and rapidly obtain new varieties, these regulations must not hamper the research of plant breeding scientists through prohibitive costs.

Ideally, Europe should have regulations based on the product and not on the technique, as the latter evolves faster than the regulations. Whatever the breeding technique (crossing two plants, grafting, cuttings, radio-induced or chemical mutagenesis, transgenesis or NGT), the end product (the plant and its new trait) would be assessed, as is the case in Canada. The assessment always involves determining the benefits and risks to human or animal health or the environment. Such regulations would make Member States competitive with other countries that already

[6] Menz J., Modrzejewski D., Hartung F., Wilhelm R. and Sprink T. (2020). Genome Edited Crops Touch the Market: A View on the Global Development and Regulatory Environment.

have flexible regulations (USA, Canada, China, etc.) to produce their own plants, adapted to their needs and soil and climate conditions, and to export some of them rather than importing plants or products derived from NGTs.

Pending such effective and flexible product-based regulation, close collaboration should be established between countries conducting field trials and those not allowed to do so, because the freedom of scientists in the public and private sectors must be respected and the originality of their research explored to meet the many challenges. The rules of the game should be the same for all Member States, while protecting research from vandalism. It is imperative to support young innovative companies, keep small and medium-sized enterprises in Europe, ensure that scientists do not relocate their field trials outside Europe and thus avoid a brain drain and job losses in a booming sector.

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