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Towards a new European Union regulation for certain NGT plant products

Vers une nouvelle réglementation de l'Union européenne pour certains produits végétaux issus d'édition génomique

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Résumé

Les biotechnologies ont connu une rupture technologique il y a dix ans avec les nouvelles techniques de l'édition du génome (particulièrement CRISPR/Cas). Il s'agit d'une révolution technologique qui bouleverse non seulement les perspectives en santé humaine, animale et végétale en ouvrant des champs d'investigation nouveaux avec des outils de génie génétique plus performants, mais aussi qui modifie les critères réglementaires appliqués aux transformations génétiques et la législation dans de nombreux pays. Dans ce contexte, l'Union européenne s'est vue dans l'obligation de revoir la réglementation communautaire concernant ces nouvelles techniques génomiques. Le processus de cette révision réglementaire est long et complexe. Débuté en 2019, où en est-il en 2023 ? Quelles transformations génétiques sont concernées ? La réponse est-elle à la hauteur des enjeux ? Tel est le propos de cet article.

Abstract

Ten years ago, biotechnologies experienced a technological breakthrough with the new genome-editing techniques (particularly

CRISPR/Cas). This technological revolution not only opens up new fields of investigation with more powerful genetic engineering tools for human, animal and plant health, but also changes the regulatory criteria applied to genetic transformations and the legislation in many countries. Considering this new international background, the European Union was obliged to review Community regulations regarding these new genomic techniques (NGTs). The regulatory review process is long and complex. Begun in 2019, where are we in 2023? What genetic transformations are involved? Is the response up to the challenges? This article provides some answers to these questions.

Mots clés:
biotechnologies, édition du génome, nouvelles techniques génomiques, réglementation, initiative européenne

Keywords:
biotechnologies, genome editing, new genomic techniques, regulation, European initiative

Introduction

Ten years ago, biotechnologies knew a real technological breakthrough with the development of new genome-editing techniques. The technique CRISPR/Cas described by Emmanuelle Charpentier and Jennifer Doudna (who were awarded the Nobel Prize in Chemistry in 2020 for this discovery) is in the lead. It is a technological revolution because it not only opens up new fields of investigation with more powerful genetic engineering tools for human, animal and plant health, but also changes the regulatory criteria applied to genetic transformations and the legislation in many countries.
According to this new international context, the European Union (EU) was obliged to review the Community regulations applied to these new genomic techniques (NGTs). But the EU regulatory review is a long and complex process. Begun in 2019, where is it in 2023? Let us examine it.

Biotechnologies: past and present

New genomic techniques have been developed over the last thirty years and have today supplanted in the research field the older techniques of random mutagenesis and transgenesis. These two techniques used for modifying the genome by genetic engineering during the twentieth century constitute now the first-generation biotechnologies. They led to major advances in human medicine (diabetes, for example) and nutritional improvement (golden rice), as well as in plant health (pest control) for several crops of major economic importance, or to help farmers with their work (weed control) (Regnault-Roger et Kunz, 2019; Regnault-Roger, 2020a; 2020b). Typically soybean and rapeseed are herbicide resistant, while maize and cotton are insect resistant, herbicide resistant or often both (ISAAA, 2020).
The NGTs are the second-generation biotechnologies. They open up new prospects in both human and animal health (Regnault-Roger, 2022a). They are expected to lead to major therapeutic developments in the treatment of cancers or rare hereditary genetic diseases that were hitherto incurable, or the development of plant-based nutraceuticals (*e.g.,* GABA tomatoes). They give hope in veterinary medicine (swine fever, bovine tuberculosis) and in animal welfare. Improvements in the plant sector are just as important, both in terms of extending a better control of pests and diseases of a greater number of crops, but also by creating new varieties that can adapt to changing environments linked to climate global warming (*e.g.,* drought, halophilia) .

GMO regulation: a key point

Given the novelty of transgenesis in the 1980s (random mutagenesis had been used since the first half of the twentieth century), regulations were introduced in various countries to provide a framework for the use of these new genetically engineered products, also named "genetically

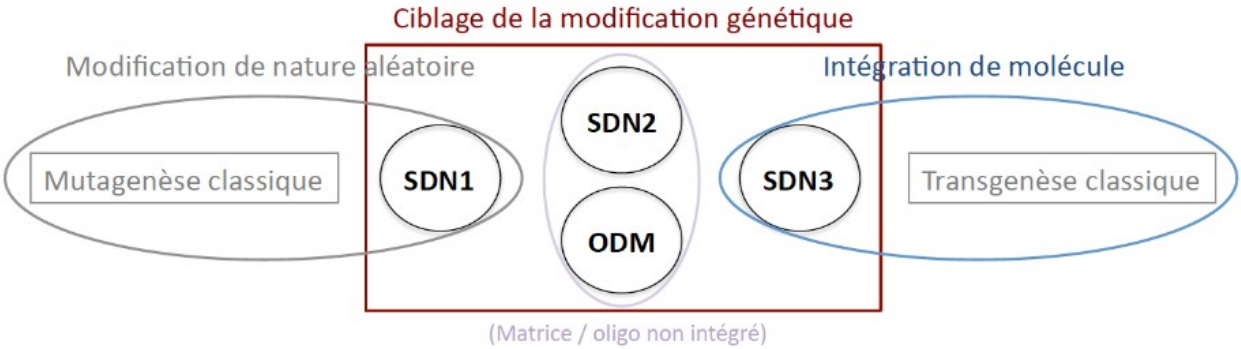

Figure 1. New plant breeding technologies (NPBT): SDN-1 differs from conventional mutagenesis in that it targets a specific site on the genome, usually, but not automatically, leading to loss of function in the gene targeted (gene knockout). Nucleases are introduced into the cell to target a mutation site, but the nature of the mutation is not predefined. With SDN-2, a DNA tempate is introduced into the cell together with the site-directed nucleases, enabling the nature of the modification to be defined. The template itself is not incorporated into the genome. The same purpose can be achieved using oligonucleotide-directed mutagenesis (ODM, RTDS). SDN-3 allows targeted integration of a sequence. It is this targeting of the transgene insertion site that distinguishes the latter technique from conventional transgenesis (Source: HCB, 2017).

modified organisms" (GMOs), and to monitor their sanitary and environmental behaviour.
The regulations that apply to them are not identical from one country to another. They apply to certain techniques and exclude others, depending on national legislation. The GMO definition and their benefit/risk assessment are not universally shared.
While the medical applications of first-generation biotechnologies have been welcomed in all countries as a source of therapeutic progress, the same cannot be said for agricultural applications. In France, the beginning of anti-GMOs campaigns began with the newspaper *Libération's* title "Alerte au soja fou" [Beware crazy soya] (Jaillette, 1996). This "crazy soya" was the first import of the new transgenic crop grown commercially for the first time in the United States in summer 1996. Militant NGOs such as Greenpeace decided to campaign against these transgenic crops (Le Buanec, 2016; Kempf, 2023).
Nearly 30 years later on, the world is now divided between countries in favour of agricultural biotechnologies – those that grow transgenic plants and export them – and countries against them - those that prohibit cultivation at home but import them from the first ones. On the one hand, the countries of North and South America, the major Asian countries (China, India, Pakistan, Japan, Philippines, Myanmar, etc.) and some African countries (mainly South Africa, followed by Nigeria and Sudan), and on the other, the Eurasian bloc, with the exception of the countries of the Iberian Peninsula, Spain and Portugal.

Deregulation for certain NGT products

It is not surprising, then, that NGTs have been greeted differently in different countries according to this gap. In view of the immense prospects that genome-editing techniques offer, the countries favourable to biotech (USA, Japan, Argentina, Brazil, Australia, etc.) have decided to treat differently genome-editing products and GMOs obtained by transgenesis (Regnault-Roger, 2021a). These countries located in North and South America and in the Asia-Pacific region have decided to deregulate a number of NGT products, *i.e.,* to exempt them from GMO regulations.

This deregulation is very logical according to the fact that there are NGT products obtained by genome editing that are indistinguishable from organisms resulting from natural mutation or classical selection. They result from a cut and repaired DNA without the addition of foreign DNA or with the insertion of a homologous allele (common genetic origin). These modifications are obtained in the laboratory by NGTs using the Site Directed Nuclease SDN1 and SDN2 protocols (HCB, 2016). On the other hand, SDN3-type genomic modifications, involving the insertion of a double exogenous DNA, are similar to transgenesis, although the SDN3 technique is more precise at the transgene insertion site and therefore involves fewer 'off-target' modifications (Figure 1). NGT SDN3 products remain subject to GMO regulations (Regnault-Roger, 2021).

In the European Union

In the judgment of 25 July 2018, the European Court of Justice (CJEU) ruled that all products derived from genome techniques after 2001 should be considered and regulated as GMOs. This year 2001 is the year of the publication of the Directive 2001/18/EC which regulates GMOs cultivation and importation in the European Union (EU). This legal position is obviously not based on sound scientific considerations, since the cornerstone of this decision is to distinguish between techniques developed before 2001 and those developed afterwards, in an assessment that can be summed up as follows: before 2001, the modifications made by genetic engineering were known and the regulations took the risks into account, but after 2001, it is the kingdom of unknown!

These European regulations are particularly costly for the developer, because they were introduced at a time when scientific knowledge of the risks associated with the genetic modification of organisms was poorly understood. Because of the heavy dossiers to be provided for approval, only the major international consortia such as Corteva, ChemChina-Syngenta, Bayer and BASF have the financial resources to cover the costs of applications including toxicology and ERA (environmental risk assessment), post-marketing monitoring of GMO plant cultivation as well as the environmental impact of an accidental seed spillage during transport.

This CJEU ruling put the EU in an isolated position facing its most important trading partners. Consequently, many voices raised against it. In November 2018, the Group of Chief Scientific Advisors to the European Commission (SAM Scientific Advice Mechanism) published a strong statement indicating that Directive 2001/18 was "no longer appropriate" and that, given the undetectability of some genetic modifications carried out by genome editing, the characteristics of the end product should be assessed rather than the method of production (European Commission, 2018). European students from eight different nationalities graduating from Wageningen University launched a petition in the form of a citizens' initiative entitled “Grow scientific progress: crops matter!”. They called for consideration to be given to “*the crop rather than the technique. In this way safety is ensured while the valuable benefits of new techniques are not lost to illogical regulatory hurdles*” (European Citizens' Initiative, 2019).

The French parliamentary office OPECST, in its report entitled *New plant breeding techniques: advantages, limits, acceptability* (2021) and signed by senator Catherine Procaccia as the main author, also proposed that the final product and not the breeding technique should be assessed. It suggested that the directive should be revised every five years to take account of advances in techniques as well as the public debate. The Union of European Agricultural Academies (UEAA) also called for Directive 2001/18 to be amended. Numerous political figures from Germany (including Green members of the Parliament) and France, stressing the importance of gene editing in the European Union's sustainable development strategy for plant production, also expressed their support for it; the French agriculture ministers, Julien Denormandie and Marc Fesneau, spoke of the role of NGTs in "*regaining*

our food sovereignty" (Regnault-Roger, 2023a).
Frans Timmermans, vice-president of the European Commission (EC), told that "*gene editing was part of the sustainable development strategy for the agri-food sector*" at the European Forum "New genomic techniques - the way forward for safe and sustainable innovation in the agri-food sector", on 29 November 2021, while Stella Kyriakides, European Commissioner for Health and Food Safety, emphasised the role of NGTs in achieving the objectives of the European Green Deal and the Farm-to-Fork strategy (Regnault-Roger, 2023b).

A European initiative in the way

Following these considerations, a European initiative has been underway since November 2019. But it is taking place in several stages and is not finished yet.
Firstly, on 8 November 2019, the Council of Europe referred the matter to the European Commission, asking it to submit proposals for changing the legislation on new genomic techniques. The Commission therefore commissioned studies by the Joint Research Center (JRC) on the state of the art and developments in R&D research (Broothaerts *et al.*, 2021; Parisi and Rodríguez-Cerezo E, 2021). Following the conclusions of these studies, the next stage took place in April 2021, when the Commission sent an official letter to the country holding the rotating presidency of the European Union (Portugal at the time). It asked to initiate the process for a European initiative entitled "Legislation for plants produced by certain new genomic techniques". The next phase, known as the road map, was completed in October 2022 with the gathering of opinions from European citizens, economic players and various societal bodies on the proposals to be made. This stage was the subject of a cyber-attack aimed at halting the initiative (Regnault-Roger, 2022b). However, this manoeuvre, supported by some Green members of the Parliament, was thwarted and the process then continued with a public consultation from 22 April to 22 July 2022. The results were indisputable: 80% of respondents were in favour of changing the regulations, and 17% against. The proponents of the *statu quo* are NGOs well known for their anti-technological progress positions (anti-GMO, anti-nuclear, etc.) (Regnault-Roger, 2023b)
Armed with these results, the EC published a proposal for regulations on 5 July 2023, which is open to public comment in order to inform the parliamentary debates that will take place in the European Parliament and the Council of Europe in autumn-winter 2023-2024. The whole process has now been going on for more than five years (CJUE judgement 2018) and the final decision of this on-going revision will be issued at the end of 2023 or 2024!

The European Commission's regulatory proposals for NGTs

The European Commission is proposing a new regulation for targeted mutagenesis and cisgenesis techniques applied to plants, with reference to genomic modifications of plant carried out not only by NGTs but which could also be obtained by natural mutation or conventional selection (European Commission, 2023). The draft of this new regulation does not apply to micro-organisms or animals.
The proposed European new regulations distinguish between two cases:
- NGT-1 plants which are classified as equivalent to conventional plants. Minor genetic modifications produced in the laboratory using NGTs that could have occurred spontaneously in nature or resulted from a conventional selection process without the addition of foreign DNA to the gene pool will be exempt from GMO regulations. They are not subject to an ERA and the products derived from them are not subject to specific labelling; but the seeds are, in order to inform the farmer who plants them. Plants in this category have received a positive notification from the authorities, following submission of a dossier. The files contain very precise information on the genetic rearrangements. To be classified in this category,

the genetic modification must be minor (for example, a substitution and an insertion of a maximum of 20 nucleotides). The authorised genetic rearrangements are precisely listed in Annex 1. The decision is then recorded in a database open to all. EU member states are not authorised to prohibit the cultivation and experimental field trials of these plants that have received community approval.

- NGT-2 plants which have also been modified using NGTs but whose modifications do not meet the criteria for the NGT-1 category. These NGT-2 plants are subject to appropriate GMO-type regulation that should be proportionate to the modified character. A health and environmental safety risk assessment ought to be included. The application file for authorisation of NGT-2 plants is much heavier than that for NGT-1 plants. In particular, it must include: (1) molecular traceability tools or, if traceability is impossible, an explanation of the reasons why; (2) labelling that may include positive mentions (*e.g.*, tolerance to drought or disease, improved food quality, etc.); (3) environmental monitoring plans if necessary. The decisions notified by the authorities are recorded in the database mentioned above.

Several professional organisations, including Euroseeds at European level, the Spanish Bioindustry Association (ASEBIO) in Spain which holds the presidency of the European Union from 1 July 2023 to the end of the year, and the Union Française des Semenciers (UFS) in France, have welcomed the creation of the category of NGT-1 plants subject to declaration but exempt from GMOs regulations. However, they insist on the necessity to have balanced regulations based on scientific progress in order to promote the development of these new varieties at EU level without generating distortions of competition with the rest of the world (UFS, 2023).

A step forward... but a minimal revision

Are the proposed changes to the regulations up to face the agricultural challenges? The reports commissioned from the JRC emphasised that in the agri-food sector, over 80% of R&D projects concerned plant and fungal organisms. Does this mean that animal and microbiological applications should be excluded from the scope of the review? At a time when the importance of soil health and the millions of micro-organisms and telluric organisms is being emphasised as a means of improving agriculture? At a time when research into gene editing of farm animals is helping to improve not only animal health but also animal welfare... elsewhere in the world!

The French Veterinary Academy has underlined on several occasions that since animal research is conducted in a highly controlled environment, it is incomprehensible that it cannot be encouraged by appropriate European regulations (Académie vétérinaire de France, 2019; 2021). This position is fully shared by the Union of European Academies of Agriculture (UEAA, 2022), which is concerned that, at a time of zoonoses (*e.g.*, monkeypox or leptospirosis), European animal research is being hampered by this exclusion.

Should we also be satisfied with the fact that NGT-2 plants are treated as “GMO-like" products, with a simplified but consistent dossier for approval when the true question is: “Are the regulations applied to GMOs still relevant in the EU?”

Research over the past twenty years has shown that genomic modifications resulting from genetic engineering, previously considered to be artificial because of the result of human manipulation, occur spontaneously in nature but at a time not chosen by man. This involves not only spontaneous DNA mutations but also transgenic flows. On the other hand, laboratory genetic engineering makes it possible to choose the modification we want to make when it is useful, freeing us from the vagaries of nature.

As the scientific knowledge has progressed, the Directive 2001/18/EC on GMOs regulations needs to be updated. This directive, based on the precautionary principle, was published in 2001, at a time when there was still a great level of uncertainty regarding the transgenesis, this new laboratory technique. But now, more than 40 years later, the observations give no incident or accident during all these years in the whole

world. Consequently, is this 2001/18/EC Directive still appropriate? This EU initiative might have been an opportunity to reconsider the legislation on genomic modifications in the Union. Many countries in North and South America, and in Asia, have already taken this way. But obviously the European Commission has decided to promote a cautious attitude. Is it appropriate to face the EU challenges to ensure its biotechnological, economic, and agri-food sovereignty in a globalised world?

Déclaration d'intérêt : l'auteur déclare n'avoir aucun conflit d'intérêt avec le sujet traité

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