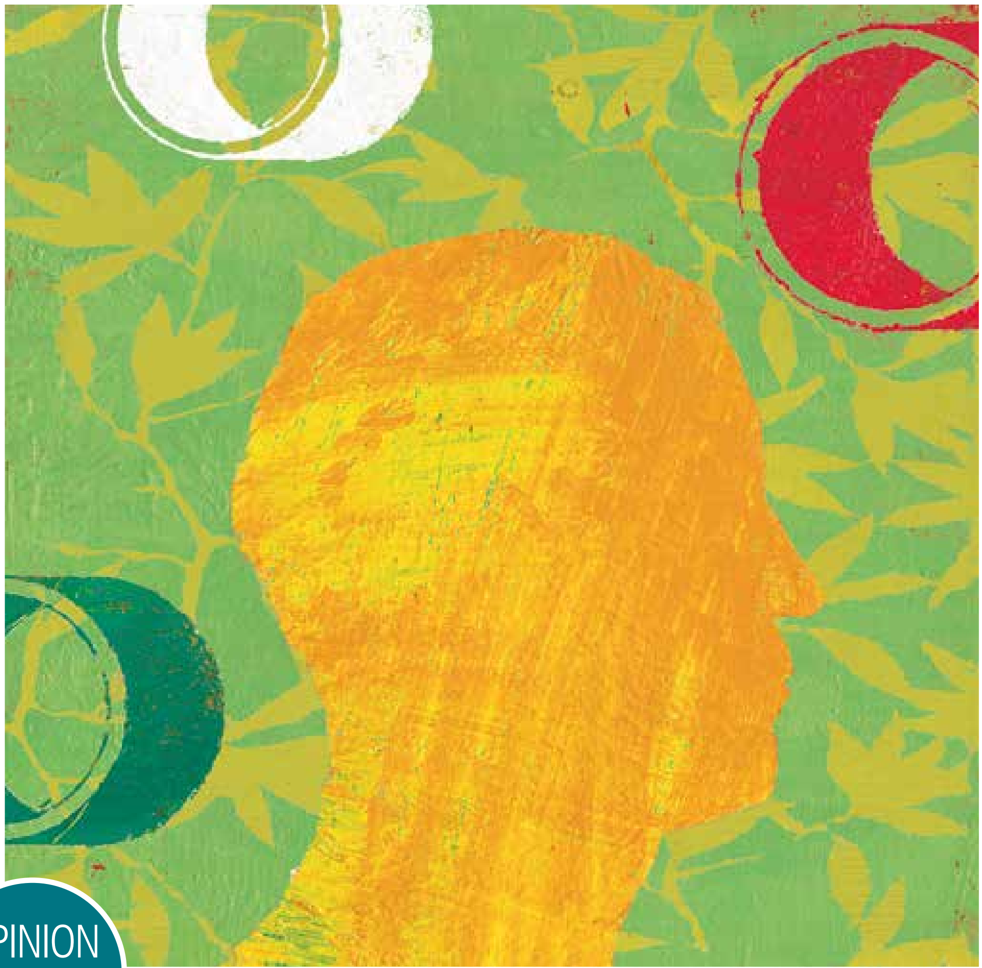
Joint INRA–CIRAD–IFREMER
Ethics Advisory Committee



OPINION 11

ON new plant breeding techniques

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Ethics Advisory Committee

OPINION 11 ON new plant breeding techniques

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President of INRA
President of CIRAD
President of IFREMER

For the attention of:

The President of the Joint INRA–CIRAD–IFREMER Ethics Advisory Committee

Paris, November 4, 2016

Subject: *Referral to the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee regarding issues raised by new biotechnologies (such as CRISPR-Cas9 genome editing) when used to perform research and develop innovations focused on plant and animal production*

Dear Committee President,

The scientific community is undergoing a technological revolution driven by novel methodologies that allow researchers to make easy, inexpensive, precise, reliable, and rapid modifications to genomes. Although these techniques are first and foremost powerful research tools that reflect a breakthrough in our ability to engineer and control living organisms, there also exist potentially valuable industrial applications for these new technologies, notably in plant and animal breeding. However, at the same time, society remains focused on the debate surrounding genetically modified organisms (GMOs), polyploid organisms, and mutants.

Among such tools, the best known is the CRISPR-Cas91 genome-editing system. Other technologies have recently become available, including knockdown agents that can sterilise farmed fish by inhibiting gene expression or polyinosinic:polycytidylic acid (poly I:C), a synthetic double-stranded RNA analogue that can be injected into farmed fish or oysters to stimulate an antiviral response. Furthermore, the crop sciences have witnessed the emergence of new plant-breeding techniques (NPBTs).

There are diverse environmental, economic, and ethical considerations associated with these new technologies. Their use in plants and animals, and notably in farm animals, raises concerns about the following issues:

- the transmissibility and effects of the genes involved, as well as the possibility of irreversible impacts on biodiversity
- the risk of environmental damage, especially since certain experiments can only be performed under natural conditions
- the lens through which stakeholders—such as industry representatives (e.g. in aquaculture), consumers, and everyday citizens—view these technologies as a result of their use in research contexts
- intellectual property rights, particularly when such technologies are used in innovative applications

Past experiences have shown us that differences in opinion exist among scientists, industrial stakeholders, and advocacy groups (e.g. NGOs) alike. It is thus crucial to encourage broadscale cultural adaptation to the life sciences and to promote debate of the ethical questions being raised, so that these new technologies and any resulting innovations are perceived as societal advances.

To date, two initiatives have begun to address ethical concerns related to new genome-editing technologies: (1) INSERM has elaborated an ethical approach to research utilising the CRISPR-Cas9 system, where the focus has been placed on the tool's therapeutic potential for humans and its ecological impacts on species that negatively affect humans (e.g. "pests" and pathogens) and (2) the French High Council for Biotechnology is examining the effects of the crop biotechnologies (i.e., NPBTs) used to improve plants and, in particular, seeds.

We propose that the Joint INRA-CIRAD-IFRE ni ary approach when considering the diverse ethical issues that arise in research, notably those that involve sectors creating animal-based products for human consumption.

Moreover, given that the Joint INRA-CIRAD Ethics Advisory Committee for Agricultural Research issued an opinion on synthetic biology in 2013, it would be desirable to structure the opinion(s) requested here (on genome-editing technologies such as CRISPR-Cas9) in such a way as to complement the opinion on synthetic biology. It is worth noting that the Committee for Ethics and Precautionary Principles in Agricultural Research (COMEPRA), jointly run by INRA and IFREMER from 2003 to 2007, issued two relevant opinions in October 2004: one on the use of biotechnologies in oyster farming and the other on genetically modified plants.

We leave it to the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee to decide whether plants, animals, and micro-organisms should be dealt with separately (i.e., in separate opinions), if this subdivision could facilitate the committee's work. Indeed, while some concerns may be shared, new genome-editing technologies could raise distinct questions depending on the field of application, whether that be crops, farm animals, "pests", or disease vectors. Thus, a first opinion could look at plants (a group for which work in this domain is already well underway). Algae, and perhaps fungi, could come next, laying the foundation for a discussion of genome-editing in animals.

Consequently, we propose that the committee first examine NPBTs, including those based on the CRISPR-Cas9 system. Any ethical issues not already addressed by prior studies could be tackled. Discussion could centre around the technologies themselves; the ways in which they are perceived and promoted by research stakeholders; and the ways in which they can be exploited. It is thus important to examine not only the place of such technologies within the genome-editing toolbox for plants, but also the role of plant improvement itself within the suite of potential strategic pathways for confronting the challenges of the twenty-first century, namely those related to climate change, the bioeconomy, and biodiversity.

Following its exploration of the above issues, the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee should be able to make concrete recommendations and direct the attention of the three research institutes towards specific points of concern that merit continued monitoring.

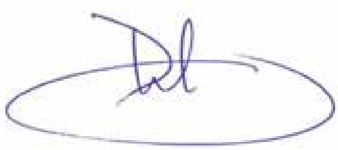
Building on this foundation, a more global analysis can be performed that draws upon the synthetic biology and COMEPRA opinions with a view to answering the following questions: To what degree are the previous recommendations still applicable? Which elements should be adjusted and/or further developed? Is there a need for the approaches to be brought up to date? Finally, what type of follow-up to these opinions does the committee recommend?

It would be ideal if the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee could produce an opinion focused on genome-editing in plants within a period of approximately 12–15 months (between now and summer 2017), so that the committee could then immediately begin its work on animal biotechnologies and, more specifically, on the precision editing of animal genomes, given the high stakes in this domain.

We are available should you require any additional information, and we greatly appreciate your attention to this matter.

Sincerely yours,

INRA President and CEO



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Agriculture, biotechnology and society

The Neolithic revolution introduced the management of plants and animals for human use and consumption, transforming hunter-gatherers into farmers. Over subsequent millennia, the selection of crop varieties and animal breeds from the range of naturally available resources has made it possible to radically change the food humans consume and, with it, society. In the late-nineteenth century, scientific research on "hybridisation" by figures such as the monk, Gregor Mendel, opened the door to the inclusion of crosses between different varieties in the selection process. The twentieth century brought discoveries in molecular genetics and developments in cell biology that enabled breeders to increase the genetic diversity of the populations for selection, not least, the development of methods to induce mutagenesis through chemical modification and radiation, the fusion of protoplasts and forced hybridisation. Laboratory work on plant propagation and cell cultivation in the nineteen fifties laid the groundwork for the developments in genetic engineering that, in the nineteen eighties, would lead to DNA recombination. The first transgenic plant was obtained in 1983. This marked a significant paradigm shift; specific agronomical traits were no longer produced by selection, they were instead introduced using molecular processes.

This change of paradigm is emblematic of the wider changes occurring across society at the end of the twentieth and beginning of the twenty-first centuries, dominated by concepts such as speed, interventionism, rationalisation, optimisation, concentration, specialisation and globalisation. The consequences for farming are well known: productivity certainly increased, making it possible to feed a rapidly expanding population, but these changes also led to a decline in numbers of agricultural communities, intensive mechanisation, the massive use of inputs with profitability as the only goal and a very real lack of attention the ecological consequences of such practices. The end of the three charmed decades, France's "thirty glorious years", that followed the second world war, saw the emergence of a number of social crises accompanied by a growing awareness of threats to the environment. This last provoked a variety of challenges to the thinking that underlay the system. Some of these challenges have been radical, embedded in a philosophical vision and value system that fundamentally questions the status quo. This has been particularly the case for farming practices.

This, then, is the background against which the INRA, CIRAD and IFREMER leadership teams made their request to this Committee. Their question concerns the consequences for agriculture and fisheries of the introduction of new biotechnologies that exploit the fact that it is now possible to re-write parts of the genome in the process known as "precision editing". The opinion here delivered, at the beginning of 2018, concerns plant genomes. The

Committee will next consider the application of these technologies to animal genomes. The present opinion first situates precision editing in the wider context of plant biotechnologies, before going on to summarise this technique's nature and applications, identify opportunities and constraints, and indicate the possible associated risks. It then describes the ideological differences that have divided public opinion and the agricultural world over the acceptability and desirability of the practices involved. In particular, two strongly contrasted positions have emerged on the new technologies discussed here, one of which is founded on more analytical, molecular and reductionist approaches, while the other adopts a holistic approach. And, indeed, these opposing views are worthy of consideration. Some of the concepts involved embrace a complex and varied reality, a case in point being agroecology, which some groups have declared to be an important goal. This opinion addresses the issue of the compatibility between precision genome editing in plants and agroecology in the different acceptations of the latter term. While the existing intellectual property framework for plant varieties constitutes a valid ethical choice, the discussion demonstrates that this framework could be brought into question by the new biotechnologies under consideration. Overall, the Committee draws our attention to the importance of the decisions taken on this matter for the sort of society we aspire to live in.

Axel Kahn, President
Michel Badré, Vice-President

Opinion on New Plant Breeding Techniques

Introduction

This opinion concerns novel genetic improvement techniques for plants (known as new plant breeding techniques or NPBTs). Its particular interest is in genome-editing techniques, that is, the targeted modifications to the genome (site-directed mutagenesis) that are used to improve plant varieties. The CRISPR-Cas9 system is the chosen focus of the opinion, in that it offers a practical example of the deployment of these new techniques.

Scientific context

Our knowledge of the genome structures and gene functions of numerous plants has advanced considerably in recent years. Databases such as Pytozome (https://phytozome.jgi.doe.gov/pz/portal.html) or Plaza (http://bioinformatics.psb.ugent.be/plaza/) record the genomes of the hundred or so plant species that are of greatest scientific and agronomic interest. These data are used to study the dynamics of plant genomes and to identify genes of interest (for example, those involved in plant development, metabolism and reactions to its environment, in particular its reactions to pathogens). The availability of this information is increasingly important for genetic crop-improvement programmes.

In the field of plant genomics, genome-editing techniques are used to bring about targeted mutations in previously-identified genes selected for their proven or anticipated agronomic interest.

The general procedure followed in genome editing is the introduction of nucleases into the genome (nucleases are enzymes whose action can cause a break in double-stranded DNA). To enable the modification of specified sites on the genome, new types of targeted nucleases (site-directed nucleases) have been developed: meganucleases that recognise a long sequence of DNA; nucleases coupled to proteins (zinc-finger nucleases); TALEN nucleases which rely on the recognition of DNA sequences by fungal factors and, more recently, nucleases of Cas9-type bacterial origin for which CRISPR-Cas9 has provided the archetype.

A number of recent expert reports provide an up-to-date overview of the opportunities and constraints resulting from these new tools[1]. Genome editing technologies have also inspired discussion on the legal, economic, ethical and political aspects of their current and future use in agriculture[2].

Social context

Clearly, site-directed mutagenesis techniques have not emerged in a cultural vacuum. They have been developed in an historical, economic and social context that affects their growth, the interest they attract and the significance attributed to them. Since their first appearance, therefore, plant genome editing techniques have been the focus of a public debate that is influenced by existing opposition to genetically modified organisms (GMOs), especially in France.

Of the available technologies for genome editing, the CRISPR-Cas9 system is of greatest interest to researchers. Its usefulness as a laboratory tool to enhance our understanding of living beings is recognised. In the same way that the development of chemical synthesis considerably increased what could be learned through analysis, genome editing provides an invaluable tool to validate or exclude results from sequencing to identify genes and alleles of interest for agriculture.

[1] See for example, European Academies Science Advisory Council (2017) *Genome Editing: Scientific Opportunities*, Public Interests and Policy Options in the European Union, EASAC Policy Report 31, Halle, German National Academy of Sciences; European Commission (2016) *New Techniques in Agricultural Biotechnology*, Brussels, European Commission; National Academies of Sciences, Engineering and Medicine (2016) *Genetically Engineered Crops: Experiences and Prospects*, Washington DC, National Academies Press.

[2] See for example, Haut Conseil des Biotechnologies, Comité scientifique (2017) *Avis sur les nouvelles techniques d'obtention de plantes* (New Plant Breeding Techniques - NPBT), Paris, Haut Conseil des Biotechnologies; Nuffield Council on Bioethics (2016) *Genome Editing: An Ethical Review*, London, Nuffield Council on Bioethics; Office Parlementaire d'Évaluation des Choix Scientifiques et Technologiques (2016) *Les enjeux économiques, environnementaux, sanitaires et éthiques des biotechnologies à la lumière de nouvelles pistes de recherche*, Paris, OPECST.

However, with the growth of technoscientific research, which has brought an increased use of technology for biological research[3], the tools and methods developed by researchers run the risk of being put to purposes other than the pursuit of knowledge. Whole areas of biological research long ranked as pure scientific activities have now found themselves caught up in economic and industrial interests. As a result, they can no longer be shielded from ethical and political questioning by the distinction between pure and applied research.

Nor should it be forgotten that a proportion of the financial support for research on site-directed mutagenesis derives from choices of investment in the bioeconomy. It has been suggested that this new bioeconomic paradigm could, over the course of the twenty-first century, come to replace the current economic system based on petrochemicals, and the scientific policy world takes as great an interest in it as the general public. This interest in the bioeconomy nevertheless spans two contrasting views. One view is that the bioeconomy should involve the deployment of biotechnologies, particularly new plant breeding techniques, to increase economic competitiveness, while ensuring that development is more sustainable. The other view of the bioeconomy, by contrast, rejects the emphasis on productivity, viability, standardisation and growth, displaying a commensurate shift towards ecological drivers, especially towards the principles of agroecology[4]. The tension between these two different visions of the role of biology and its techniques in twenty-first century economics is central to the decisions taken by INRA, CIRAD and IFREMER on research priorities.

Drawing on the particular example of the CRISPR-Cas9 system, this opinion will elucidate the ethical and political questions raised by genome editing. Contrary to what might be supposed, the ethical and political issues raised by this system and its use in the genetic improvement of plants have not as yet been greatly discussed, so the present opinion should be viewed as a preliminary exercise. In particular, the opinion offers a fresh reading of the debate based on an analysis of the value systems and symbolic representations that underlie the various issues it identifies. The choice of the ethical and political questions addressed by the opinion has been based not only on a review of expert reports and of the literature relating to genome editing, but also on the prominent position occupied by these issues in the debate surrounding GMOs, which would appear to be playing out here once again.

After a brief description of the differences between the processes involved in the CRISPR-Cas9 system and transgenesis (1), this opinion will examine the following ethical and political questions (2): the risks associated with site-directed mutagenesis; the legal status of organisms and products resulting from use of the CRISPR-Cas9 system; intellectual property practices and implications for the plant sector; and the CRISPR-Cas9 system's compatibility with agroecology. It then discusses the issue of social responsibility in research as it arises in areas of technoscientific controversy (3). The opinion ends with recommendations from the Committee to the institutions' leadership teams (3).

3 Publicised by the proponents of synthetic biology, see in particular, Robert Carlson (2010) Biology Is Technology: *The Promise, Peril, and New Business of Engineering Life*, Cambridge MA, Harvard University Press.

4 Les Levidow, Kean Birch and Theo Papaioannou (2012) "EU agri-innovation policy: two contending visions of the bio-economy", *Critical Policy Studies* 6 (1): 40-65.

1 ■ The role of CRISPR-Cas9 in plant breeding

Improvements that are intended to confer new properties on plants rely on the availability of varied plant populations. The work of the plant breeder is to carry out crosses between populations until varieties are obtained that include the traits desired. In recent years, it has become possible to introduce new characteristics using molecular techniques. This often involves the modification by scientists of existing varieties to obtain new varieties with the particular traits requested by the various interested parties.

The variability on which the research depends can of course be natural. Here, the characteristics of interest are to be found among existing populations of either the chosen species involved or neighbouring species. However, variability can also be produced through mutagenesis. It has in fact been known since the mid-twentieth century that certain chemical substances and ionising radiation have the capacity to cause breaks in DNA, bringing about mutations. Such mutations, however, appear randomly in the genome, making it necessary for crosses between mutated and non-mutated varieties to be carried out in order to retain only those mutations that are of interest, to eliminate any other mutations, and to study the phenotypic effects obtained.

In some cases, the trait of interest is not already to be found among existing populations of a plant species and it is not possible to obtain such characteristics through the simple mutagenesis of an existing sequence. Since 1983, a new method to overcome this difficulty has been available, namely, the transgenic production of what is termed a genetically modified plant (GMP). GMPs are produced by introducing fragments of DNA into a plant. These fragments carry a sequence matching the gene that codes the desired characteristic. The source of the gene can be a plant, animal or microorganism. It can even, in some cases, be of synthetic origin. The complete gene must usually be constructed in a laboratory using genetic engineering techniques. The construct is then usually introduced into plant cells using the bacterium Agrobacterium tumefaciens or by using biolistic techniques that deposit fragments of DNA on the surface of metallic particles which are fired at great speed into plant-cell cultures. Because these techniques insert the gene randomly in the target genome, selection of the expected characteristics must subsequently be carried out to retain only those without undesirable effects.

Considered to be the most precise, rapid, easiest to implement and least onerous of all the technologies for the genetic improvement of plants[5] the CRISPR-Cas9 system is now used widely in laboratories across the world, including those at INRA and CIRAD. Unlike earlier techniques, it allows users to target the part of the genome where they wish to introduce a modification. It also allows a number of genes to be targeted in a single operation, making it possible to envisage the modification of multigenic traits. This work is usually carried out for one of two purposes: to increase knowledge of genes or to introduce new traits.

The interviews we conducted at INRA and CIRAD enabled us to identify two main uses for genome-editing techniques: the study of the function of genes* and the addition of traits of interest for agriculture**.
This research is mostly carried out within the GENIUS project, coordinated by INRA and funded by a PIA grant (from the French Investments for the Future programme)

* *Arabidopsis, Physcomitrella, Brachypodium* and *Medicago* figure among the model species, along with cultivated crop species including wheat, corn, rice, tomato, potato, pea, rapeseed, strawberry, melon, rose, poplar and apple.

** Traits involving resistance to disease and to stress, effective use of nutrients, biofortification and biomass production.

We should remember that the CRISPR-Cas9 system makes it possible to break the DNA at a preselected point and, potentially, to direct the spontaneous repair of the break or to introduce a new fragment of DNA.

The simplest approach is to produce mutations that deactivate a gene (SDN1). Traditionally, these mutations were looked for in existing populations or were produced using mutagenesis, or even transgenesis, to inhibit the gene's expression. These various approaches have been used in the INRA and CIRAD laboratories and continue to be extremely useful in validating the functions of genes.

5 European Commission (2017) *New Techniques in Agricultural Biotechnology*, Brussels, European Commission.

A second possibility offered by genome editing is to modify part of a gene (SDN2). To do this, a fragment of DNA must be provided to serve as a model for the repair of the break introduced by the CRISPR-Cas9 system. The mechanism makes use of homologous recombination, a process based on the exchange of nucleotides between identical DNA molecules, an exchange that rarely occurs spontaneously in plants. One fragment of the sequence is replaced by another, but without the introduction of new DNA.

The third application of the CRISPR-Cas9 is defined by the insertion of a new gene, previously constructed in the laboratory, into a particular site in the sequence (SDN3). Here, a GMP has clearly been produced. However, given that the insertion site has been specified in advance, it has been suggested that the scientific analysis of the consequences for humans, animals and the environment of the organisms and products derived from the CRISPR-Cas9 system should be less extensive than is the case for "classic" GMPs where the insertion is random.

2 ■ What are the main ethical and political issues at stake?

The advent of genome editing techniques, particularly those of the CRISPR-Cas9 system, has been hailed as a high-value innovation that makes it possible to rewrite the genome of living beings. In counterpoint to this enthusiasm for scientific progress encountered in media coverage of technoscientific advances, an alternative narrative is gradually being constructed. More nuanced in character, this second narrative emphasises the scientific and technical limits of the new genetic improvement techniques for plants. It also points to the ethical and political questions set out in the introduction to this opinion, that is, the risks associated with site-directed mutagenesis (2.1), the legal status of organisms and products derived from the CRISPR-Cas9 system (2.2), the question of intellectual property rights to knowledge in the plant sector (2.3), and the CRISP-Cas9 system's compatibility with agroecology (2.4).

As there can be no place here for a detailed discussion of the debates surrounding each of these questions, we will summarise those key features necessary to tease out the tensions that underlie them. These tensions relate, respectively, to the scope of the risks to be considered in formulating a judgement on the acceptability of genome editing and its applications, the vision of human-plant relationships that subtends the choice of regulatory system governing the marketisation of organisms and products derived from genome editing, the prioritisation of values entailed by the choice of an intellectual property system, and the not infrequently divergent views that exist on the nature of agroecology and the values it should promote.

As we shall see, the ethical and political questions raised by genome editing concern the CRISPR-Cas9 system itself just as much as the purposes to which it is put or the ways it is viewed and promoted by researchers and civil society. In this respect, therefore, the opinion includes discussion of the particular place of CRISPR-Cas9, as compared to other tools for the genetic improvement of plants, in the development of future pathways to cope with the challenges facing us in the twenty-first century.

2•1 Risks associated with new techniques in genome editing

The new techniques in the genetic improvement of plants have been criticised by environmentalist groups and countryside organisations in particular, as well as from a small number of researchers. These opponents of the system focus their arguments on a certain number of risks that are involved. Research has been carried out in response to these concerns. Others have argued that the techniques could potentially contribute to the mitigation of external risks such as climate change. There nevertheless remains a significant level of uncertainty and controversy over a number of issues. The analysis we offer is based on these debates, which we here seek to describe and not to resolve.

Two observations can be made by way of introduction:

- The risks considered here are wide-ranging in nature; they are environmental, sanitary, agricultural, economic, social and political. They are nevertheless strongly interrelated, even if their complex relationships are hard to analyse due to the continued uncertainty over the legal framework and forms of regulation to be applied to plants produced using these techniques.

• Of these risks, only a small number are directly associated with the new techniques for the targeted modification of the genome – one such being the possibility that they might make it easier to access some form of bioterrorism. But, in the case of plants, the threat remains abstract – the genetic modification of invasive species to destroy crops is evoked, rather than the genetic modification of the crops themselves.

Environmental and health risks

As they are described in this debate, the environmental risks associated with the dissemination of varieties that have been produced using genome-editing techniques are similar to those already cited for GMPs. They thus include a reduction in biodiversity, the emergence of plants resistant to mechanisms designed to contain them, and the development of allergenic and carcinogenic properties linked to possible mutations other than those targeted [6].

Given that these concerns are not new, what lessons have been learned over the few years in which GMPs have been in use?

In fact, the consensus among most analysts is that that the jury is still out. First, they emphasise the fact that the use of GMPs can have perceptible effects on the environment. Thus, although the specifics will vary according to species and environment, the transfer of transgenes between varieties and species has been demonstrated. This fact has led to the rules governing distances to be respected between modified and unmodified crops. Effects on the insect and arachnid populations have also been observed. These effects can be positive in some cases (such as increased biodiversity levels compared with those recorded where pesticides are in use) and negative in others (such as the appearance of resistance in the species targeted by genetic modification).

Second, analysts are agreed that it is not possible to demonstrate cause and effect between the use of GMPs and the appearance of environmental or health problems. Third, they refuse nevertheless to conclude that such relationships do not exist; they emphasise the complexity of the processes involved and the uncertainties that arise as a result. They call for publicly financed research and detailed impact studies to be carried out so that expert analysis can be obtained independently of vested interests in the development of GMPs[7].

Risks to agriculture

The risks to agriculture that are described as being linked to site-directed mutagenesis are chiefly associated with the reduction of biodiversity in agriculture. This involves the loss of plant varieties as well as reductions in the genetic variability within individual species. Diversity loss, of whatever kind, is associated with the increase of standardised monocultures. This last is problematic in that it weakens agricultural systems which become, for example, more vulnerable to disease. This risk is not, however, the direct result of genome editing but is a consequence more generally of the use of intensive farming methods.

The reduction of the biodiversity of crops is also out of step with the cropping methods that prevail in some Southern countries. As researchers from CIRAD have had the opportunity to observe, farmers in these countries favour biodiversity as a means to manage multiple risks. By mixing crop varieties, some of which are more resistant to drought and others more resistant to certain diseases or to particular pests, they build resilience to potential catastrophes and ensure there will always be something to harvest. The agro-biodiversity in these countries is very rich and is associated with a wealth of local knowledge that nevertheless continues to be undervalued in the technoscientific world. Hence, the ill-thought-out introduction of modified crop varieties may introduce an impoverishment that is at once agricultural and cultural. It nevertheless remains the case that choices can be difficult when the difference in yields is large.

The contrasting argument emphasises the positive contribution of genetic engineering, including the CRISP-Cas9 system, to the provision of adequate solutions to current environmental problems (for example, climate change and pollution). The possibility of producing plants resistant to drought and extreme

[6] Gene drive is a case in point and arouses much caution because it is hard to reverse. This possible application of the CRISPR-Cas9 system, in which the transmission of a particular inherited gene (e.g. a gene producing sterility) is made easier, will not be addressed in this opinion but in the following one, which deals with new techniques for the genetic improvement of animals.

[7] National Academies of Sciences, Engineering and Medicine (2016) *Genetically Engineered Crops: Experiences and Prospects*, Washington DC, National Academies Press.

temperatures, or to flooding, is emphasised. It also envisages that it will one day be possible, with the help of genome-editing tools, to improve the effectiveness of biological processes or the nutrient content of plants, to reintroduce agro-biodiversity and to develop the cultivation of new species etc. Given the possible threats to agricultural production, the potential contribution made by genetic engineering to the safeguarding of the basic right to food is worthy of consideration.

Of course, the inclusion of genetic modification in a positive scenario doesn't necessarily mean that the latter will come to pass. It is highly probably that the cultivation of drought-resistant plants in zones where habitats for wild fauna and flora have been preserved would have environmental consequences. The benefits of such an introduction could well be disputed and it could result in changes that were even more destabilising. As a consequence, such projects demand caution.

The above considerations lead us to conclude that the way that a technology is integrated into agricultural models and practices is crucial, that it must be considered at an early stage in project development by research organisations and scientists working on new varieties, and that this consideration must be carried out in collaboration with the intended producers and local communities. It is the responsibility of research organisations and of researchers to reflect on this integration in such a way as to ensure that the innovative products and processes they develop serve sustainable goals in both environmental and social terms.

Economic, social and political risks

Beyond their environmental, health and agricultural risks, genome-editing techniques give rise to concerns over a number of economic, social and political risks.

The seed sector has experienced two major developments in the past decades which have heightened perceptions of these risks:

- With the entry of agrochemical businesses into the seed market, which have favoured the emergence of genetic engineering, a rapid sectorial consolidation has taken place through a series of buyouts of biotechnological start-ups and seed businesses. The purpose of these moves was to protect extended copyrights and substantial market shares, mechanisms that, notably, provide a way for companies to amortise the costs of regulatory requirements and intellectual property protection. Not all conventional seed merchants have been taken over, though, and some of them – Limagrain being a typical example – have in turn moved defensively to consolidate their respective positions through takeovers of smaller businesses. Some commentators are critical of the consequences of this consolidation, which include high seed prices, the obligation to use only specified agrochemical products with some seeds, a reduction in the rights of farmers and the increased dependence of farmers on the industry[8]. There is also the fear that, in facilitating the creation of varieties that may be protected by patents, the new genome-editing techniques are strengthening the hold of large consortiums over the sector: how far might these novel techniques increase the imbalance between industrial companies and farmers?

- To a certain extent, public research bodies have withdrawn from the production of new varieties as the commercial sector, which is able to rely on a protective intellectual property system, has developed[9]. This development raises questions. In particular, through it, might public organisations have relinquished their role in shaping political options that are in tune with public expectations[10] ?

Last, there is the fear that agro-biodiversity will come under the control of private organisations and individuals via the patenting of genetic sequences responsible for traits – regardless of such traits occur naturally and in varieties obtained by conventional selection techniques.
In short, these different questions all indicate the same underlying concern: what can we do to ensure that genome-editing techniques, when they come into contact with intellectual-property systems, do not deprive citizens of their freedom to act with regard to objects of common interest?

Rethinking the relationships between technologies and the agricultural system

Currently, the use of genetic engineering, which includes genome editing, is closely associated with an agricultural system designed to enable the production of particular varieties at the expense of others. This

8 Philip H Howard (2015) "Intellectual property and consolidation in the seed industry", *Crop Science* 55:1-7.

9 According to Fugeray-Scarbel and Lemarié: "Public research today thus concentrates on particular areas of upstream research, for example, on selection methodologies or understanding of the function and development of the genome; on less mainstream strategic crops (peas and fava beans); on particular characteristics or crops of environmental interest (e.g. varieties adapted to reduced input levels, resistance to drought); on the safeguarding of genetic resources (collection management); and on public expertise (for example the CTPS expertise on the impact of GMOs…)". Aline Fugeray-Scarbel and Stéphane Lemarié (2013) "*Évolution de l'organisation de la recherche et du secteur des semences*", *Le sélectionneur français* 64: 23-34.

10 For example, according to Guy Kastler, a member of the Confédération Paysanne, the "lock applied by three transnational companies on the first link in the food chain is such that no government can resist them" and "beyond the rights of farmers and the right to food autonomy, it is the sovereignty of States that is threatened". Guy Kastler (2017) "Nouvelles biotechnologies: questionnements éthiques et conséquences économiques et sociales sur l'agriculture et la biodiversité", *Annales des Mines - Réalités industrielles* 1: 99-102.

strategy is in line with the use of genetic engineering as a means to increase productivity, protected by the system of intellectual property rights which works to its advantage.

Should we lay the blame at the door of the technique alone, or are the abusive agricultural models and practices we have noted also at fault? Expressed differently, is it possible to disentangle genetic engineering techniques in agriculture from the economic and social networks within which they are used and to deploy them in innovative agricultural models? This question will be discussed below when we address the compatibility of the CRISPR-Cas9 system with agroecology.

2•2 The legal status of organisms and products derived from the CRISPR-Cas9 system

The question of the legal status of the organisms and products derived from the CRISPR-Cas9 system lies at the heart of the concerns raised by genome editing. Indeed, the challenge confronting public decision-makers is whether or not to extend the field of application of the existing regulatory systems for GMOs to include organisms and products deriving from genome editing when these do not easily fit the definitions currently in force for genetic modification[11]. The main difficulty thus concerns whether organisms and products derived from the new genome-editing techniques should be designated as GMOs or non-GMOs.

GMOs or non-GMOs?

In Europe, opinion is divided over the appropriate interpretation of Directive 2001/18/CE concerning the deliberate release into the environment of genetically modified organisms[12].

A first view hinges on the adverb "naturally", which is to be found in the definition of the term "Genetically modified organism (GMO)" provided by Directive 2001/18/EC:

> "genetically modified organism (GMO)" means 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; (Article 2 (2))

This first position involves the proposition that the basis on which newly-produced DNA sequences should be designated is whether or not they can occur "naturally." In this view, which is shared by a fair number of those working in the industry and researchers, it would be possible for plants that do not incorporate DNA alien to their species and which cannot be distinguished from varieties that could be the result of spontaneous or induced mutations or sexed cross-breeding to be exempted from the field of application of regulations SDN1 and SDN2 on a case-by-case basis.

The second view, held by those opposed to GMOs, calls for the strict application of the precautionary principle, deeming all organisms and products derived from new genome-editing techniques to be GMOs. This option thus excludes all possibility of a proportional approach in which assessment requirements are adjusted to match the risk level (measured according to e.g. technique used, selected trait, type of modification carried out), a recommendation which is nevertheless frequently seen in expert opinions[13].

A new regulatory system?

Because of the legal uncertainty produced by the lack of any clarificatory decision by the European Commission on the status of organisms and products derived from the CRISPR-Cas9 system, the adequacy of the European regulatory system, which is process-based, is brought into question.

Indeed, some observers have suggested that the European model should be replaced by a product-based (in other words, phenotype-based) system in order to improve its capacity to respond to future developments in genetic engineering technology. Thus, the regulatory trigger that activates the control system in force would no longer involve the process by which the organisms or products had been obtained but would instead concern the physical or biochemical traits or characteristics of each organism or product[14].

While such proposals may differ among themselves, the opinions expressed are broadly in favour of the adoption of a new European product-based or phenotype-based regulatory system[15].

11 D. Jones. 2015. "Future of Breeding by Genome Editing Is in the Hands of Regulators." *GM Crops & Food* 6(4): 223-232, 224.

12 Agnes E. Ricroch, Klaus Ammann and Marcel Kuntz (2016) "Editing EU legislation to fit plant genome editing", *EMBO Reports* 17(10): 1365-1369, 1366. See also Thorben Sprink, Dennis Eriksson, Joachim Schiemann and Frank Hartung (2016) "Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts", *Plant Cell Reports* 35: 1493-1506.

13 See for example, European Academies Science Advisory Council (2017) *Genome Editing: Scientific Opportunities, Public Interests and Policy Options in the European Union*, EASAC Policy Report 31, Halle, German National Academy of Sciences; Haut Conseil des Biotechnologies, Comité scientifique (2017) *Avis sur les nouvelles techniques d'obtention de plantes (New Plant Breeding Techniques-NPBT)*, Paris, Haut Conseil des Biotechnologies; Nuffield Council on Bioethics (2016) *Genome Editing: An Ethical Review*, London, Nuffield Council on Bioethics; Office Parlementaire d'Évaluation des Choix Scientifiques et Technologiques (2016) *Les enjeux économiques, environnementaux, sanitaires et éthiques des biotechnologies à la lumière de nouvelles pistes de recherche*, Paris, OPECST.

14 At INRA, this approach can be found in Peter Rogowsky's proposal and the GENIUS project. See Charlotta Zetterberg and Karin Edvardsson Bjornberg (2017) "Time for a new EU regulatory framework for GM crops?", *Journal of Agricultural and Environmental Ethics* 30: 325-347, 325-6.

15 Haut Conseil des Biotechnologies, Comité scientifique (2017) *Avis sur les nouvelles techniques d'obtention de plantes (New Plant Breeding Techniques - NPBT)*, Paris, Haut Conseil des Biotechnologies; Nuffield Council on Bioethics (2016) *Genome Editing: An Ethical Review*, London, Nuffield Council on Bioethics; Agnes E. Ricroch, Klaus Ammann and Marcel Kuntz (2016) "Editing EU legislation to fit plant genome editing", *EMBO Reports* 17(10): 1365-1369.

Underlying visions that shape regulatory systems

Whichever regulatory model is adopted, it will be the expression of a particular vision of our relationship with plants which, not being universally shared, may give rise to criticism, or even rejection, of the system. It is therefore important to tease out the symbolic representations that are associated with the two types of proposed regulatory system, while bearing in mind that no definitive conclusion can be reached without a supporting study to provide detailed analysis of the content of the legal instruments in force and of the proposals put forward.

If plant varieties are regulated as a function of their physical or biochemical traits or characteristics the emphasis is placed on their biological structure. Such a view of the relationship between humans and plants belongs to the objectivist approach to be seen in the natural sciences, namely, that structure determines properties which, in turn, determine functions or actions. Accordingly, plants are understood to be the expression of a programme in which we can intervene. This approach is abstract in that it considers plants independently of their habitat and locality. When the focus is on plant characteristics independently of their context of expression, the degree of abstraction is even greater. Plants are then treated as objects removed from the ground and from time, as objects that have no individual histories. In this view, they are essentially objects of science. The scientific and industrial worlds generally support this regulatory model based on the product or the phenotype, endorsing the human-plant relationship that is associated with it.

The foregoing explains, in part, the resistance to be found among members of the ecologist and anti-GMO movements to this approach. As a vision, it effectively runs counter to the general direction of travel in bio- and eco-centric thought currently found in environmental ethics . In addition, it may arouse unrealistic expectations, masking as it does the complexity of the mechanisms at work in the expression of genes and the transmission of traits. That said, the field trials conducted before any new seed variety is brought to the market always take into account its interaction with the environment. This stage of the process, which is a requirement in all plant breeding procedures, should, in principle, dissipate some of the concerns of the ecologist movement.

To target the process by which genetic improvements, that is to say, genetic breeding techniques for plants, are accomplished by making such techniques the focal point of the regulatory system is to express a particular view of our relationship with plants. Effectively, the assessment of the technique rather than the product or phenotype is linked to a view of plants as the objects *of work by/on/and with nature*. In such a view, plants are considered to be mixed objects that combine nature with artifice and their improvement is seen as an action performed on a living being – which is the basic principle of agriculture. It therefore follows that it is the plant as a "whole" which must be the referent. As Canguilhem writes: "Given that living forms are wholes whose meaning resides in their tendency to occur as such […], they can be grasped in a vision, never in a division"[17]. Like all living organisms, a plant has its own normativity, expressed by the possibility for growth, adaptation and reproduction etc. This tendency, characterised as teleonomic[18], and determined objectively according to the nature of each living organism, is more or less affected by whichever technique is used for the genetic improvement of a plant variety. And it is this "vision" of the plant that confers on it an ethical status. Within the framework of biocentric environmental ethics, the teleonomy of living organisms requires that their integrity should be respected[19].

We can now understand the preference shown by the ecology and anti-GMO movements for the process-based regulatory system. However, in its current version, the European model fails to live up to the requirements of this symbolic representation of plants and this failure arises notwithstanding the possibility for Member States to restrict or forbid the growing of GM crops on their territory (Directive 2015/412). Indeed, for a regulatory system to reflect an understanding of our relationship with plants that recognises their intrinsic value, it would be necessary for such a system to include assessment and authorisation criteria that would guarantee respect for the value of plants in their own right[20].

In brief, depending on whether a regulatory system is based on the product/phenotype or on the process, it has the potential to be associated with either an instrumental view of plants or with the idea that plants have intrinsic value – while bearing in mind that, as we have emphasised, the detailed provisions of regulatory arrangements may either confirm or run counter to these general tendencies. Each of these visions of our relationship with plants is supported by groups who are publicly in political conflict and who

17 Georges Canguilhem ([1965] 2003). *La connaissance de la vie*, Paris, Vrin: 14.

18 Teleonomy is to be distinguished from purpose in that it excludes any idea of intentionality. See Jacques Monod (1970) *Le hazard et la nécessité*, Paris, Seuil.

19 Louis-Étienne Pigeon and Lyne Létourneau (2014) "The leading Canadian NGOs' discourse on fish farming: from ecocentric intuitions to biocentric solutions", *Journal of Agricultural and Environmental Ethics* 27(5): 767-785, 778.

20 Paul W Taylor, (1986) *Respect for Nature. A Theory of Environmental Ethics*, Princeton, Princeton University Press.

call for account to be taken of their point of view in the regulatory system. Finding a compromise solution is of course possible but, in order for this to be done, there must be a willingness to engage in dialogue.

2•3 Intellectual property in the plant sector

From the strict point of view of patent law, the appearance of a targeted genome-modification technology such as the CRISPR-Cas9 system is unproblematic. Although a legal battle has begun in the United States over the patent rights to all applications of the technology to eukaryotic organisms, that dispute is not about whether or not the technique can be patented. In Europe, it is acknowledged that it can be patented by virtue of Articles 2(2), 4(1)(b) and 4 (3) of Directive 98/44/EC on the legal protection of biotechnological inventions and of decision G2/07 taken in 2010 by the Enlarged Board of Appeal of the European Patent Office[21]. This is likewise the case for systems derived from CRISPR-Cas9, provided that the criteria for the granting of a patent are fulfilled, be it on the grounds of novelty, inventiveness or industrial applications (Articles 3 and 4(2) Directive 98/44/EC). The patentability of the CRISPR-Cas9 system and the variants and products derived from it is therefore not a matter for litigation.

Should Proprietary Variety Protection Certificates (PVPCs) be reviewed ? [22]

There is concern in some quarters that patents could become a preferred way to protect innovations in the plant sector and, specifically, plants edited using the CRISPR-Cas9 system. In fact, two co-existing forms of protection are used in the plant world: patents and Proprietary Variety Protection Certificates (PVPCs). The use of patents to protect intellectual property is very widespread, encouraged in all fields by public-private research partnerships and by the defensive strategies adopted by publicly funded research teams. The position of research institutions is indeed a delicate one. On the one hand, they must comply with the criteria of a research-funding system that encourages partnerships with private companies ; on the other, they must deliver measurable socio-economic outcomes if they are to continue to benefit from public funding, it being a requirement that beneficiaries should be held accountable for their performance. These two factors encourage the use of patents as the best way to protect intellectual property.

In a general way, patents establish "a right of industrial ownership, with use being under the exclusive control of the holder" [23]. It follows that a patented plant or a plant containing a patented trait cannot be used for the creation of varieties without the agreement of the patent holder and, where appropriate, remuneration of the latter. In plant research, the effects of the protection provided by PVPCs are different from the consequences of a patent. PVPCs recognise a right of authorship by conferring the exclusive right to market a new plant variety on its creator, but they allow the variety thus protected to remain available for use as a genetic resource by any party who obtains it through his or her own selection programme – this principle is embodied in the exemption available for selective breeders[24].

A major difference between the two forms of protection thus lies in how they provide for access to the genetic programme of the products concerned. Free access under the PVPC system is replaced by payment for the patented objects and traits under the patent system[25]. It is quite conceivable that, in practice, a barrier to access could be created, either because the patent holder refused to grant a licence or because the price tag was prohibitive.

In France and other European countries, the matter is not necessarily so clear cut. Indeed, access to patent-protected genetic varieties remains possible for the purposes of selective breeding by virtue of Article L 613-5-3 of the Intellectual Property Code. Nevertheless, the sale of varieties resulting from the work of the selective breeder in such a case still requires the acquisition of a licence for the traits covered by the patent[26]. There is not, therefore, an exact equivalence between the access to the gene pool allowed by the PVPC system and that permitted in France through the patent system.

A second difference between the patent system and the PVPC system that is frequently invoked concerns the rights conferred on farmers, that is, the right for individual farmers to use a product from their own harvest for purposes of reproduction or multiplication when this is done in person on their own land. Under the PVPC system, farmers are currently allowed to use these "farm-saved seeds". However, since changes

21 European Commission, (2016) *Final Report of the Expert Group on the Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering (EO2973)*, Brussels, DG GROW, European Commission: 26-30.

22 The members of the Ethics Committee extend their thanks to Mr. Jean-Christophe Gouache, who has made available to them a personal research paper seeking to clarify the nature and scope of the questions pertaining to the intellectual ownership of techniques and products derived from site-directed editing. The summary contained in that document has been most helpful and forms the basis for part of the analysis offered below.

23 INRA Scientific Advisory Group, 2014. Rapport de synthèse du groupe de travail sur la propriété intellectuelle sur les connaissances dans le secteur vegetal. (Summary report of the working group on intellectual property ownership of knowledge in the plant sector). Paris: INRA Science and Impact. p. 4. Page 4.

24 *Ibid*: 4 and 13.

25 European Commission, (2016) *Final Report of the Expert Group on the Development and Implications of Patent law in the Field of Biotechnology and Genetic Engineering (EO2973)*, Brussels, DG GROW, European Commission.

26 *Ibid*: 18.

were introduced in 1991 by the International Convention for the Protection of New Varieties of Plants (UPOV 1991), some conditions have applied. In particular, the farmer must pay a fee to the breeders of certain plant species[27]. Under the patent system, too, Article L 613-5-1 of the Intellectual Property Code makes provision for the rights of farmers, who must abide by the conditions set out in article 14 of EC Regulation 2100/94 of the Council (27 July 1994), instituting an EU protection regime for plant procurement. Contrary to the general view, the two forms of protection are thus very similar on this point.

Ethical reasons to prefer the PVPC system

Within the research community, both types of protection are viewed positively[28]. Although the advantages of the PVPC system are not entirely eliminated by the patent system, INRA's leadership team strongly favours the use of PVPCs across the sector[29]. Indeed, on 17 May 2013 INRA's Scientific Advisory Board pointed out the French scientific community's adherence to the view that plants produced by genetic selection should be non-patentable, particularly those plants obtained by conventional breeding methods[30].

On 9 November 2017, INRA's Scientific Advisory Board updated its earlier opinion by declaring itself to be in favour of the prohibition of patent filing for edited plants.

We should first point out that the reasons to conclude that the PVPC system is superior are entirely scientific:

> " The complexity of genetic determinism renders [...] any act of privatisation of technologies or knowledge at the molecular scale relatively arbitrary where the products of such techniques are concerned, and this continues to be the case, even if the techniques themselves may be the object of intellectual property rights [...] New knowledge in epigenetics, on regulating genes that respond to the environment etc. [...] has made the relationship between sequences and phenotypes increasingly problematic as a basis on which to determine the quantitative characteristics of interest for higher plants. The future of PVPCs would therefore appear to have been made more secure by the development of molecular markers in selection[31]. "

The Enlarged Board of Appeal of the European Patent Office confirmed in any case in 2010 (decisions G2/07 and G1/08) that marker-assisted selection is not patentable because it involves an essentially biological process excluded from the field of application for patents[32].

Ethical considerations, then, founded on the values inherent to the PVPC system, can thus explain the preference shown for this system. In research and innovation, the decisions to be made between intellectual property options must take into account the tension between the value of sharing knowledge, which acts as an essential driver for research, and the values of competitiveness and viability that inform innovative research strategies. As a consequence, as explained above, the central question is one of access to genetic resources. As INRA's Scientific Board explains, it is the values that the PVPC system is associated with in this regard that justify the preference shown for it, namely, "achieving genetic progress by increasing the shared genetic resources available to all those working on plant breeding, whether public or private, national or international"[33]. The PVPC system is related, in this sense, to the accomplishment of a vision of the common good that sets out to put the ingenuity of each individual to work for the improvement of the human condition and to allow all peoples to exercise their basic right to eat.

By contrast, the patent system is part of a value set focused on private ownership and the search for profit through a form of control that runs counter to the humanist aspiration of the PVPC system. Patents are certainly a way to make inventions public and, by this very act, to authorise their sharing and accessibility. However, their primary purpose is to reward the inventor's merit, linking patents to a concept of justice that is far from universally shared. Of course, it is possible to use a patented product freely for experimental purposes (Article L 613-5 of the Intellectual property Code), and this is an important issue for research. Free permissions can be granted to Southern countries. However, the value system in force makes this an exception not the rule. If an exception is to be made, it must depend on the good will of the patent holder and, therefore, on the vagaries of the product's marketing rationale and of any defensive market and access strategies in relation to genetic resources. Moreover, it is recognised that the patent system favours richer countries, who invest most heavily in research, and the major seed companies who are in a position to

27 INRA, Conseil Scientifique (2014) *Rapport de Synthèse du Groupe de Travail sur la Propriété Intellectuelle sur les Connaissances dans le Secteur Végétal*, Paris, INRA Science & Impact: 13-14.

28 *Ibid*: 18.

29 *Ibid*: 20.

30 *Ibid*: 53.

31 *Ibid*: 20.

32 European Commission, (2016) *Final Report of the Expert Group on the Development and Implications of Patent law in the Field of Biotechnology and Genetic Engineering (EO2973)*, Brussels, DG GROW, European Commission: 26.

33 INRA, *Conseil Scientifique (2014) Rapport de Synthèse du Groupe de Travail sur la Propriété Intellectuelle sur lesConnaissances dans le Secteur Végéta*l, Paris, INRA Science & Impact: 20.

establish a monopoly of the new techniques and products patented. As a result, patents work against a distributive concept of justice and encourage the perpetuation of inequalities. This aspect of the patent system thus provides an illustration of the social, economic and political risks referred to above (2.1).

In the realm of ethics, the PVPC system appears to be clearly superior in that it guarantees both fair intellectual recognition and the availability of genetic resources. INRA's preference for the PVPC system can in this respect be seen as a key enabler for the development of new agricultural models that are compatible with the goals of agroecology and, along with the CRISPR-Cas9 system, offer a further perspective on the opinion of 9 November 2017 delivered by INRA's Scientific Board.

Open source: an option worthy of consideration

One possibility might be to treat varieties that are the product of directed mutation techniques in the same way as free digital programmes. After all, could it not be said that the processes used in such techniques, involving the re-writing of sequences, are effectively a form of data processing, as is suggested by the current common use of 'genome editing'? This sort of free framework, which has already been established by some of those working in the field of synthetic biology[34] could provide access to genetic knowledge and resources by granting free licences. The editor of a variety – be they public or private – would invest resources in a product that all developers could use freely under licence to advance their own programmes and to increase available knowledge[35]. The latter are even permitted to make a profit from their work as developers on condition that they make their own results available to others, with the same conditions attached.

It would certainly be appropriate to adapt this free-access system drawn from the programming industry but, between the extremes of patents and free access, an extensive range of intermediate possibilities is also available for exploration. The reintroduction of shared licences for non-commercial uses, of bilateral and exchange licences, of "inclusive patents", designed to favour inclusion over exclusion by requiring the resultant to be shared, and of the right to legal recourse where actors refuse to share, can indeed be envisaged[36].

The new site-directed genome modification techniques offer an opportunity to rethink the patent system established after the advent of GMOs. A system that reconciled the need to disseminate information with a return on investment could ensure that the core elements of emerging technologies that are essential to the advancement of knowledge remain accessible. A number of standardisation rules for data deposited in open access would however be necessary to make it usable. It might also have less ethical consequences, as such a system would make it possible for a State that had chosen to conduct no exploratory research to access knowledge produced by others simply through the open source system.

In the seed production sector, the open source system would favour small seed merchants by providing free access to basic components, making it possible to prevent consortiums from acquiring monopolies by buying up licenses at exorbitant prices. A return on investment, which is essential to cover development costs, could be provided by combining open access with the granting of a PVPC for those varieties that reached the market.

For farmers, the open source system (even when combined with a PVPC on commercial seeds) would guarantee greater transparency and independence from seed companies.

This would ultimately be a social innovation in agriculture that could effectively strengthen opportunities for the propagation of technical innovations for the improvement of plants.

2•4 Compatibility of genome editing with agroecology

Agroecology is an emerging concept that is interpreted in a variety of ways, while its practices are still in the course of development. It therefore follows that agroecology is not yet a fully established theoretical and practical system.

The term "agroecology" was first used to designate the inclusion of ecological considerations in agronomy. In the view of some of those involved, it favours a systemic approach to agronomy that aims to understand and control the interactions between organisms in ecosystems.

34 In the United States, the "Biobrick" movement pioneers such as Drew Endy and Rob Carlson have been developing this model with students from the international Genetically Engineered Machine competition (iGEM). It offers free access to the standard biological parts known as BioBricks which are registered in the Registry of Standard Biological Parts at MIT (the Massachussetts Institute of Technology).

35 This is not unlike farmer exemptions under the PVPC system.

36 Gertrui van Overalle (2015) "Inventing inclusive patents: from old to new open innovation", Peter Drahos, Gustavo Ghidini and Hanns Ullrich (eds), *Kritika: Essays on Intellectual Property* Vol. 1, Cheltenham: Edward Elgar: 206-277.

More recently, though, a different concept of agroecology has emerged. This encompasses not only the study of the interactions between plants, animals, humans and environments in order to profit by them, but also the relationship between plant breeders or farmers and the plants they work with, as well as the social and political networks they develop and maintain in their professional activities. This new interpretation of agroecology extends to the promotion of technical innovations, such as the replacement of chemical fertilisers by organic fertilisers, and ascribes a social purpose to these innovations in the form of the increased emancipation of farmers from the stranglehold of vested interests in the market place[37]. In this view, agriculture is not seen as a simple production activity that seeks to achieve maximum efficiency or productivity but is incorporated in the wider context of sustainable development projects that combine ecological, economic and social actions[38]. From this perspective, agriculture draws equally on advanced scientific and technical knowledge and on the experience and knowledge of farmers. The motto proposed by Michel Griffon for agroecology is "Ecology as a technical guide, fairness as social inspiration"[39].

These two dimensions, the ecological and social, are embedded in the priority workstreams at INRA and CIRAD[40]. As understood by the INRA community, the purpose of agroecology is to produce a better compromise between agriculture and the environment. Work in this area is divided into three research themes: mobilising biodiversity; optimising the major cycles for water, nutrients, nitrogen and phosphorus and improving management of landscapes and regions. For CIRAD, a key goal is to enable "adaptation by 'small' family farms to global changes without reproducing some of the dead-ends of productivist models".

In light of the above, it can be assumed that the nature of the agroecological reference system will dictate whether the genetic improvement of plants using the CRISPR-Cas9 system is either accepted or rejected.

Two compatible paradigms?

Regardless of the techniques used, the genetic improvement of plants is not confined to the creation of new varieties. As has been stated, in-field assessment is an essential stage in the process that must be carried before a new variety is marketed to ensure that each variety's interactions with its environment are analysed. Strictly speaking, there is no such thing as an ideal variety, only optimal varieties that have been adapted for specific environments, be they natural, technical, economic or cultural.

Genome-editing techniques are no exception to this general rule and the varieties created through this route are likewise subjected to testing for environmental integration. A primary goal of the CRISPR-Cas9 system is to control the modification of the genome in a way that will enable the modified organism to cope more efficiently with competition from other living beings (microbes or insects, for example). This goal therefore calls for a systemic approach to in-field testing that conforms with the first definition of agroecology provided above. Indeed, the experimental approach adopted in functional genomics is complemented by the study of the interactions between plants, animals, humans and the environment in order to benefit from them. This stage of research, like fieldwork, is compatible with the first view of agroecology. It can be therefore considered that the genetic and systemic approaches can be considered to be not only compatible but complementary: to address the challenges it faces, it is important for agriculture to exploit all possible levers rather than excluding, or imposing choices between, one possible approach or another.

The issue of compatibility is more problematic for those espousing the second definition of agroecology given above. Let us consider the two paradigms within which genome-editing techniques and agroecology are currently developing. Genome editing has emerged within an industrial paradigm whose dominant values are control, precision, speed and performance. The merits of the CRISPR-Cas9 system are invariably described in these terms. Here, there is no hesitation in the use of warlike metaphors to describe the operations performed on plant genomes (e.g. target, kill, destroy, repress, knock down). It is hard to reconcile this aggressive vocabulary with the second definition of agroecology, with its concern for the protection of, and even respect for, nature. In this definition, the pursuit of agroecology is not a matter of

37 P.M. Stassart, P. Baret, J.-C. Grégoire, T. Hance, M. Mormont, D. Reheul, D. Stilmant, G. Vanloquerent, and M. Visser (2012) "L'agro-écologie : trajectoire et potentiel. Pour une transition vers des systèmes alimentaires durables", Denise Van Dam, Jean Nizet and Michel Streith (eds), *Agro-écologie. Entre pratiques et sciences sociales*, Dijon, Educagri Éditions.

38 This can be linked to the utilitarian, intrinsic and heritage values discussed by the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee in a recent opinion. See Joint INRA-CIRAD-IFREMER Ethics Advisory Committee Opinion 10 (2018) on the ethical aspects of major international agreements (Sustainable Development Goals, Paris Agreement on climate change).

39 Michel Griffon (2006) Nourrir la Planète, Paris, Odile Jacob: 455.

40 See CIRAD (2016) "Le Cirad et l'Inra se mobilisent pour l'agro-écologie", *Les faits marquants 2016*, Rapport d'activité. INRA 2016 Annual report "L'agro-écologie au service de la multiperformance".

imposing our will on passive plants but rather of observing what occurs and of guiding features that are already present. The priority is not to increase forcibly the performance of a plant variety by re-working its genetic programme, but rather to focus on the capacity of plants to cooperate with other living organisms (symbiotic or sentry organisms, for example). In this agroecological paradigm, the improvement of plants is seen in terms of the guidance of dynamic processes and is not connected with product manufacture as it is in the industrial paradigm[41]. From the second agroecological viewpoint, the researcher, like the deviser of new varieties, learns to "work with" natural processes, to negotiate with cellular or intracellular mechanisms in such a way that control over the results can never be firmly guaranteed. Additionally, the emphasis on "working with" nature found in this agroecological paradigm, is accompanied by a belief in the necessity of drawing on the knowledge and lived experience of rural communities to complement scientific knowledge and to enable differing social and environmental contexts to be taken into account.

In these contrasting profiles, defined one by product manufacture linked to the industrial paradigm and the other by the management of dynamic processes envisaged by the second understanding of agroecology, we encounter two separate ethical models which can be associated with the product-based and process-based approaches described above in the discussion of regulatory systems (part 2.2). The industrial paradigm appeals to an ethos that prizes product quality and control. The responsibility of those working on plant improvement is here to take proper account of cost-benefit assessments in accordance with an ethical rationale where the main focus is on consequences for human, animal and environmental health. By contrast, the ethical model underpinning the second version of agroecology considers a much wider range of consequences, incorporating other decision-making parameters. It pays particular attention to the economic, social and political relationships with nature that are produced by the system, nature being understood here as the totality of biotic communities along with their associated abiotic supporting factors.

What are the conditions governing compatibility?

If we consider only the products and not the processes at work to obtain them, genome-editing techniques are fully compatible with the first definition agroecology. Indeed, the products of these techniques can enable us to attain the main goals of agroecology, such as increasing biodiversity, reducing input volumes and eliminating resistance to herbicides by means of controlled mutations where the purpose is to restore plants to their uncultivated state (known as rewilding)[42].

However, establishing the compatibility of agroecology with a technology-focused approach, whether the techniques involved are those of the CRISPR-Cas9 system or not, calls for more than a shared goal once we turn to the second definition of agroecology. If it is assumed that technologies are not simply a means to an end because they commit us to a particular way of being with and acting on nature, then it would seem that three conditions must be met for genome-editing techniques to be compatible with agroecology in its second sense:

- ***Taking the time required for improvement.*** *Without doubt, there has been an enthusiastic response to the speed of the "molecular scissors" offered by the CRISPR-Cas9 system, which allows several sequences to be modified simultaneously in just a few days. But the sequences thus speedily obtained can only provide the hoped-for solutions to agricultural problems if they are then left sufficient time to engage with the competition they will encounter in natural environments. The genome of an organism should be thought of "not so much as the basis for a programme, but as a toolbox from which the cell tries out various tools as far as possible and in an exploratory way until, if its environment allows it the time to do so, it finds a 'solution'"*[43]. In setting out to replace a plant's archived memories with genomes manufactured to order, it is important not to be blinded by the short-term benefits and to take the time to evaluate long-term risks. We should remember that this sort of work requires patience and time: ten, twenty, or even thirty years of research and testing. Given that the latter timescales are hardly compatible with a project-based research system in which continued funding is dependent on publications every two years, it would appear vital to build

41 On the distinction between manufacture and management see Catherine Larrère and Raphaël Larrère (2015) *Penser et agir avec la nature. Une enquête philosophique*, Paris, La Découverte.

42 Martin Marchman Andersen et al. (2015) "Feasibility of new breeding techniques for organic farming", *Trends in Plant Science* 20(7): 426-434.

43 Thomas Heams (2011) "Expression stochastique des gènes et différenciation cellulaire", Jean-Jacques Kupiec, Olivier Gandrillon, Michel Morange and Marc Silberstein (eds), *Le hasard au cœur de la cellule. Probabilités, déterminisme, génétique*, Paris, Éditions Matériologiques: 28-59, 36.

greater flexibility into the financial support model in order to generate the necessary time for research.

• ***Adopting more comprehensive assessment systems for innovations.*** Genome-editing techniques are greatly valued because their potential applications to plant improvement carry risk levels that are considered to be acceptable. But a risk-benefit assessment is not the only deciding factor if the goals of agroecology in its second sense are to be achieved, for these goals include concepts such as equity, autonomy, social justice and care for the landscape, bringing value systems other than that of risks and benefits into play.

• ***Opening up research to the public.*** To reconcile the different value systems in operation, a rational discussion must take place that cannot be the sole responsibility of researchers and the designers of new varieties. It is essential to engage a shared and inclusive upstream discussion that sets out to make explicit the implicit values held by the various parties involved and to debate them. This is a precondition for the shared ranking of priorities, co-creating a research programme where the possibilities offered by techniques such as the CRISPR-Cas9 system can be integrated into the second understanding of the agroecological paradigm. In practice, not only do the consequences of the distribution of products need to be anticipated, but a shared conversation on research processes and their place in society needs to unfold.

3 ■ The central issue: a vision of socially responsible research

In its most widely accepted sense, the concept of social responsibility is associated with the obligation to cause no harm to others and to help others. In the context of genome editing, the first of these obligations requires that researchers should be neither imprudent nor negligent with regard to the risks generated by the new targeted genome modification techniques, and that they should take into account the probable consequences of the use of such techniques.

3•1 The moral obligation for researchers to involve the public

Research bodies and scientists who carry out research associated with controversial areas, or who use controversial techniques to carry out their research, at whatever stage of completion, must be ready to engage in public with the questions of value raised by their actions[44] and this is as much the case for research teams themselves as for their institutions. The following question then arises: what sort of society do public policy makers and, where relevant to their work, institutional leaders and researchers in areas relating to agriculture wish to build?

The science of genome editing, as it is usually carried out in our organisations, affects the future of agriculture and society. It does so through the choice of research objectives and techniques to be employed, the goals that underlie research programmes and policies on research funding, on partnerships with private-sector industries or with community stakeholders, on the management of intellectual property, on support for access and knowledge transfer etc. The transformational capacity of genome editing is the consequence of a series of institutional and individual decisions that arise throughout the research process, from the first idea for a project to the communication of its results through either conventional or commercial routes. At each of these stages, certain possibilities emerge while others disappear. We should not therefore be surprised to encounter intensive scrutiny of the work of institutions and their researchers in this field.

As has been demonstrated, contrasting options compete with each other for each of the ethical and political issues discussed. These options carry with them distinct social projects that reflect different value systems and symbolic representations of the world. It is essential to take these axiological and symbolic dimensions into account, to avoid shutting ourselves up in the ivory tower of science or dismissing the views of others as ill-informed or irrational.

44 David B. Resnik and Kevin C. Elliott (2016) "The ethical challenges of socially responsible science", *Accountability in Research. Policies and Quality Assurance* 23(1): 31-46.

42 Martin Marchman Andersen et al. 2015. "Feasibility of New Breeding Techniques for Organic Farming." *Trends in Plant Science* 20(7): 426-434.

That said, we should not expect the public debate to reach any form of consensus quick[45]. The respect for democracy in the governance of green biotechnologies is not a panacea; it offers no guarantee that it will be able to reconcile all differences. When it comes to the question of values in our contemporary pluralist societies, consensus is certainly possible, but it is most often the case that we must content ourselves with compromise . Notwithstanding this fact, the goal is paramount: we must decide collectively what we consider to be acceptable scientific progress on both cultural and moral grounds .

The need for public participation appears in a different form at institutional level. It certainly calls for institutions to demonstrate their willingness to listen to the concerns expressed over genome editing and to engage in dialogue. However, beyond these manifestations of good will, action is required, as set out in the following recommendations.

3•2 Recommendations addressed to the institutions' leadership teams

Each of the recommendations made here is based on the duty of public participation entailed by the concept of social responsibility in research as it applies to the ethical and political issues raised by the genetic improvement of plants using the CRISPR-Cas9 system. Some recommendations combine the recommendations of the INRA-CIRAD committee with those of COMEPRA.

RECOMMENDATION 1

• Be vigilant with regard to the forms of agriculture, economics and society that could be facilitated by genome editing and, more particularly, by the use of the CRISPR-Cas9 system.

RECOMMENDATION 2

• Maintain an openness in approaches to research and the choice of research topics, thereby ensuring that the resources offered by alternative techniques can also be explored.

RECOMMENDATION 3

• Provide to the research teams involved in the precision editing of plant genomes all available resources to support the understanding and discussion of opportunities and constraints.

RECOMMENDATION 4

• Define research priorities in terms of the problems to be resolved rather than as a function of what is technically possible.

RECOMMENDATION 5

• Increase co-creation in research activities at a strategic programme level as well as for individual projects.

RECOMMENDATION 6

• Support inclusiveness in the selection of research projects, from an interdisciplinary and even transdisciplinary viewpoint.

RECOMMENDATION 7

• Maintenir une activité de recherche publique dans le domaine de l'édition de précision des génomes végétaux afin de sauvegarder la capacité d'agir pour le bien commun.

RECOMMENDATION 8

• Continue to carry out public research activities in the field of plant genome editing in order to safeguard the capacity to act for the common good.

RECOMMENDATION 9

• Encourage research on the possible risks to human health, animal health and the environment associated with site-directed mutagenesis in plants and, if necessary, on ways to mitigate these.

45 Nuffield Council on Bioethics (2016) *Genome Editing: An Ethical Review*, London, Nuffield Council on Bioethics: 31.

RECOMMENDATION 10

• Set out clearly the conflict that researchers may experience between, on the one hand, the demands of competitiveness and, on the other, the requirement to contribute fully to agroecological transition.

People with whom the committee met

Benoît BERTRAND, CIRAD, Joint Research Unit for Plant Resistance to Pests

Claire BILLOT, CIRAD, Joint Research Unit for Genetic Improvement and Adaptation of Mediterranean and Tropical Plants (AGAP)

Carole CARANTA, INRA, Head of Plant Biology and Breeding Division (BAP)

Jean-Christophe GOUACHE, Limagrain, Head of international Affairs and Social Enterprise Responsibility [RSE], Chair, Scientific Board, member of Management Board

Emmanuel GUIDERDONI, CIRAD, AGAP

Olivier LE GALL, INRA, Chair of Strategic Board for the Green Biotechnologies strategic interest group (GIS)

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Mark TEPFER, INRA, Institut Jean-Pierre Bourgin (IJPB) – BAP Division

Gilles TROUCHE, CIRAD, AGAP

Appendix

Appendix 1

Committee members

Current Members (2018):

- **Axel KAHN**, President of the Ethics Committee. Doctor of Medicine and Doctor of Science, Research Director at INSERM.
- **Michel BADRÉ**, Vice-President of the Ethics Committee. Graduate engineer of the École Polytechnique – École Nationale du Génie Rural, des Eaux et des Forêts. Member of the Economic, Social and Environmental Council, in the group of environmental associations.
- **Madeleine AKRICH**, Research Director at MINES Paris Tech (Centre for the Sociology of Innovation – CSI). Graduate engineer of MINES Paris Tech and Doctor of Socio-economics of Innovation.
- **Bernadette BENSAUDE-VINCENT**, Professor emeritus at the University of Paris 1 Panthéon-Sorbonne, Associate Professor of Philosophy and Doctor of Arts and Humanities.
- **Jean-Louis BRESSON**, Nutritionist-Physician, University Professor, founder (currently Deputy Director) of the Centre d'investigation clinique Necker-Cochin.
- **Paul CLAVIER**, University professor, Université de Lorraine, previously teacher of philosophy at the Ecole Normale Supérieure, Paris until June 2017, graduate of the Ecole Normale Supérieure, Doctor of Philosophy.
- **Françoise GAILL**, Research director emeritus at the French National Centre for Scientific Research (CNRS), executive officer at the CNRS, former head of INEE (French Institute of Ecology and Environment). Biologist, specialist in deep-water oceanic ecosystems.
- **Sandra LAUGIER**, professor of philosophy at the University of Paris 1 Panthéon-Sorbonne, Head of the Centre de Philosophie Contemporaine at the Sorbonne.
- **Lyne LÉTOURNEAU**, Professor in the Animal Sciences Department of Laval University, Quebec. Doctor of Law, teacher on contemporary ethical issues for the agrifood industry and on research ethics.
- **Joséphine OUEDRAOGO - GUISSOU**, sociologist, associate of ARC Consultants (support-research-action-advice) in Ouagadougou, of which she is a founding member.
- **Pere PUIGDOMENECH**, Research Professor at the Spanish National Research Council (CSIC) at the Molecular Biology Institute of Barcelona, specialist in molecular plant biology, Doctor in Biological Sciences.
- **Michel SAUQUET**, graduate of the Institut d'études politiques de Paris, Doctor in Applied Economics. Teacher specialised in intercultural issues.
- **Hervé THÉRY**, geographer, Associate Professor at the University of Sao Paulo (Brazil), Director emeritus at the CNRS.
- **Catherine LARRÈRE**, Professor emeritus of philosophy at the University of Paris 1, specialist in the philosophy of the environment and applied ethics [mandate ends, mid-2017].

Ex-members having left the committee during 2016/17 (following two terms of office):

- **Patrick DU JARDIN**, , agronomist, specialist in plant biology, Professor at the University of Gembloux (Belgium).
- **Jeanne-Marie PARLY**, Honorary University Professor in economics, ex-government advisor.

Appendix 2

Joint Secretariat of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee

The secretariat of the committee is provided jointly by INRA, CIRAD and IFREMER. The administrative and financial support of the committee is provided by INRA.

INRAE: Christine CHARLOT (Secretary General): christine.charlot@inrae.fr
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and with the support of:

Blaise GEORGES, debate editor
Maxime BORDES, a student in a professional master's programme in philosophy specialising in applied ethics, social responsibility, and environmental responsibility (ETHIRES; University Paris 1 Panthéon-Sorbonne) who did an internship at INRA from September 1 to November 30, 2017

Appendix 3

Principles and values of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee

•1 The Committee holds as a central tenet that human life has intrinsic dignity. When making recommendations, the Committee seeks to concretely reinforce human dignity by upholding the rights set out in the 1948 Universal Declaration of Human Rights.

•2 More generally, the Committee also strongly adheres to the values that have been expressed over the past several decades in the declarations and agreements established by the United Nations and other specialised organisations, including UNESCO. Chief among these values are the protection and promotion of biodiversity and cultural expression. The principles affirmed in these texts are implemented via international normative agreements.

•3 We must be stewards of the environment to ensure the well-being of future generations. We must also take care to not deplete natural resources or disrupt natural equilibria, as doing so could permanently jeopardize the planet's future. This commitment to sustainable development requires the Committee to consider not just the short term, but also the long term and the ultra-long term. At the same time, subscribing to a principle of total reversibility is utopian and impractical.

•4 The world is a system. An action that affects one system component will also have an impact on other components. It is thus necessary to explore the secondary effects of actions, any subsequent dynamics, and the strategic responses that emerge. While we must prioritise solutions at the global scale, global measures must be compatible with local measures, accounting for real-life conditions.

•5 The Committee views robustness and adaptability as two positive system attributes. Thus, even in an open society, a certain degree of autonomy in production systems is desirable at the national and regional levels.

•6 Progress occurs in societies that are open to technical and social innovations. It is nonetheless crucial to analyse and anticipate the effects of such innovations on human lifestyles and development. The benefits that arise must be shared equitably.

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