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The genome editing revolution

Report on the economic, environmental, health and ethical challenges of biotechnologies in light of the new research avenues

Report compiled, on behalf of OPECST, by Mr Jean-Yves Le Déaut, deputy, president, and Mrs Catherine Procaccia, senator, vice-president, April 2017.

ABSTRACT: Biotechnologies have experienced a revolution everywhere worldwide since the invention of genome editing techniques, especially with the CRISPR-Cas9 breakthrough innovation in 2012. These technologies are giving rise to considerable hope of curing diseases hitherto incurable, but pose the ethical question of heritable changes to the human genome. Gene drive holds promise in combating insect-transmitted diseases. New plant breeding techniques (NPBT) help improve the plant and animal species used in agriculture. The rapport presents twenty or so recommendations on the need to continue research, on evolution of the rules in force and how a fresh public debate could be brought about.

REPORT SUMMARY

A request concerning the economic and environmental challenges of biotechnologies was submitted to OPECST by the National Assembly's Sustainable Development Committee asking it to take stock of the state of research in that respect. OPECST wanted to broaden the subject to health and ethical issues and combined it with two related requests on resistant vines and triploid oysters.

Biotechnologies have recently made considerable progress, especially with genome editing technologies. Among these technologies, the discovery of the 'CRISPR-Cas9' system by Emmanuelle Charpentier and Jennifer Doubna, in 2012, forms a breakthrough innovation as it is simpler and faster to implement, less costly and functions in all living organisms.

The possible applications are very promising in human medicine and in agriculture (plants and animals). A 'post-GMO' era is coming. Such applications permit industrial processes respectful of the environment. The fears are as big as the potential advances: ethical issues naturally arise as regards modification of the human species, but an environmental and health assessment of new plant breeding techniques should also be made. These new techniques raise the questions of intellectual property, biosecurity, and whether the prevailing rules in France, Europe and internationally are adequate.

BREAKTHROUGHS IN RESEARCH ON BIOTECHNOLOGIES SINCE THE BEGINNING OF THE 2000S

With CRISPR-Cas9 in particular, the number of scientific publications has

increased exponentially. Laboratories worldwide have latched onto it. CRISPR-Cas9 has resulted from basic research on the defence mechanism of bacteria against phages and associates a molecular scissor with an RNA guide which allows precise genetic targeting to the level of individual genes. New biotechnologies are not limited to genome editing – the European Commission has listed seven other techniques.

France has a long tradition of excellence in biotechnology research but the rejection of plant GMOs since two decades ago has demobilised research teams and laboratories. French research is now sixth-placed for the number of major-impact publications and so the country appears to be letting itself get left behind the lead pack.

BIOTECHNOLOGIES APPLIED TO HUMAN MEDICINE HOLD PROMISE

Many diseases have genetic causes. 'Repairing' the genome offers hope and forms a promising therapeutic avenue. Three million people in France and 30 million across Europe are concerned by genetic diseases.

The fall in the cost of research with CRISPR has allowed a multiplication of projects worldwide. The first clinical trials on patients are expected in the United States in 2017 (cancer and Leber congenital amaurosis). A little girl affected by incurable acute leukaemia received treatment on compassionate grounds and was cured in the United Kingdom in 2016 thanks to the TALEN technique developed by the French company Cellectis. Unfortunately, WHO has not sufficiently gauged the importance of these technologies and has not reactivated its human genome project.

All the scientists questioned replied that the off-target effects had already fallen in number and were now less numerous than the natural mutations observed in all living organisms.

However these technologies raise ethical questions and must lead States to raise questions about the rules. A distinction must be made between somatic cell interventions, which concern just the patient being treated, and germ cell interventions where the changes are transmissible to the progeny and which remain banned by the signatory States parties to the Oviedo Convention. In 2015, the United Kingdom authorised mitochondrial transfer, a genetic repair of a human cell organelle.

The rapporteurs consider it necessary to continue research and that a moratorium is neither advisable nor possible. However, they feel that is unacceptable to modify the human germline to improve it or 'enhance' it, in accordance with transhumanist ideas. Many researchers believe that, when these technologies are very safe tomorrow, it will be difficult to ban hereditary modifications of the human genome, on a case-by-case basis, to treat a serious or incurable disease. This decision will have to be taken after a necessary broader consultation with civil society. WHO and UNESCO should, to our mind, enlist a standing experts committee based on IPCC, which would be tasked with assessing the degree of maturity of the new therapies, assessing the challenges and proposing guidelines. Re-examination of the French Bioethics Act, scheduled in 2018, should provide the opportunity to raise the issue of mitochondrial genome modification.

BIOTECHNOLOGIES APPLIED TO BIOLOGICAL CONTROL AND SUSTAINABLE DEVELOPMENT

Insect transmitted diseases are responsible for hundreds of thousands of diseases a year. **Gene drive**, a biotechnology made possible with CRISPR-Cas9, should become rapidly operational. It allows either the insect's gene to be modified to make it resistant to the virus it transmits, or to

extinguish the species. The latter possibility raises an ethical and environmental problem.

The rapporteurs favour a continuation of the work but call for a reversibility mechanism in the event of an undesired effect and they oppose any extinction of a living species.

The study has shown that the new plant breeding techniques do not have a negative impact on **biodiversity**. On the contrary, these techniques increase the number of desirable traits for agriculture and limit the use of pesticides, some of which are likely to destroy all insects without distinction.

White biotechnologies allow the replacement of polluting chemical compounds derived from traditional chemistry by more sustainable products.

BIOTECHNOLOGIES APPLIED TO AGRICULTURE: THE POST-GMO ERA

Genome editing techniques could have revolutionary applications in agriculture allowing the speed of breeding to be accelerated. They represent a fundamental breakthrough with respect to 'old' GMOs insofar as such genome editing is precise and almost undetectable. The sought traits no longer concern just resistance to herbicides or the improvement of productivity as is the case with the today's GMOs. Such traits can improve nutritional quality, grant greater resistance or extend storage life. Genetically modified plants should help decrease the use of toxic phytosanitary products.

New plant breeding techniques complement agroecology methods. They even have huge potential for organic farmers.

GMOs are defined legally at European level in Directive 2001/18. Along with chemical or radiation mutagenesis, new plant breeding techniques, which are more precise, should be excluded from the scope of that directive and subject to biomonitoring rules.

Green biotechnologies form an important economic sector worldwide. Their falling cost provides an opportunity for Europe to take them up again.

A meta-analysis by the American Academy of Sciences in 2016 shows that there has never been a single confirmed case of a negative result on human or animal life due to the consumption of GMOs. Nor moreover of a negative consequence on the environment or biodiversity. In contrast, the appearances of resistances to phytosanitary products or to pests are proven. That however represents the constant battle as old as life itself and ill-adapted agricultural practices are probably the cause.

INRA (French National Institute for Agricultural Research) has developed in the past thirty years, by conventional plant selection, varieties of **vines resistant** to downy and powdery mildew fungi while keeping their oenological qualities. These varieties help to greatly reduce the use of fungicides, especially copper sulphate which has a real impact on soil and proven toxicity.

The rapporteurs favour a rapid classification of the new varieties so that they can be marketed. They feel that the use of genome editing techniques should allow the resistance traits to be rapidly passed on to other varieties, such as those used in champagne or cognac.

IFREMER (French Research Institute for Exploitation of the Sea) has developed the cultivation of **triploid oysters** resulting from genetic mutation by conventional selection. The criticisms as regards increased mortality in these oysters or concerning their invasive nature have never been scientifically demonstrated.

The rapporteurs feel that the coexistence of several different ways of cultivating oysters – hatchery-nursery and

traditional oyster farming – is not threatened by triploid oysters.

LEGAL AND SECURITY ISSUES

The **intellectual property** of biotechnologies is a major economic issue. Two parties are vying for the initial intellectual property of CRISPR-Cas9. Since 2012, a large increase has been seen in the filing of patent applications for the intellectual property rights of biotechnology applications, mainly in the United States and China, Europe and the other countries remaining far behind.

The development and ease of accessing CRISPR-cas9 technology should allow small structures to develop seeds which hitherto, owing to their cost, remained the monopoly of large agrochemical firms, with often excessive royalties.

Biosecurity has two aspects: security in laboratories and bioterrorism. The simplicity and low cost of the techniques contribute to the apprehension that bio-hacking will develop. Potentially malicious uses of biotechnologies, like the creation of a virus or the modification of mosquitoes, are now possible. In response to these threats, the French government created in 2015 the National Advisory Board for Biosecurity (CNCB).

The rapporteurs recommend strengthened coordination in civil and military research work, with increased funding under parliamentary supervision.

ASSESSMENT OF HAZARDS AND PUBLIC DEBATE

In France, the Higher Council on Biotechnology (HCB) **assesses** the health and environmental hazards related to the cultivation of GMOs. The hazards related to foods containing GMOs are assessed by the French Agency for Food, Environmental and Occupational Health Safety (ANSES). The HCB is however crossing a series of crises with the resignation of several of its members.

The rapporteurs recommend that all the duties entrusted today to HCB's scientific committee be transferred to ANSES which has recognised expertise and enjoys technical support. HCB would be formed by a single college grouping all the competences of its present Economic, Ethical and Social Committee (CEES).

The arrival of new biotechnologies requires a broad **public debate**. Note must be made of the difficulties of public debate in France on this topic as on other technological fields.

The rapporteurs consider that this debate must be started right now, even if these biotechnologies are still at an experimental stage, otherwise it could confiscated by its systematic opponents. They suggest that the *terminales S* (scientific sixth form classes) of all French grammar schools debate on the 'genetics and evolution' topic.

The *report* can be consulted on OPECST's website (tomes I and II).