



## Legal status of products derived from « new techniques of genetic modification of plants »

In 2008, the European Commission listed eight new techniques of genetic modification of plants :

- Oligodirected mutagenesis
- Cisgenesis / Intragenesis
- Site directed Nucleases (SDN) : zinc finger nucleases (have emerged since : Talen / CrisprCas9 / meganucleases)
- RNA dependant DNA methylation
- Grafting
- Reverse breeding
- Agro-infiltration
- Synthetic biology

The European Commission first asked a group of experts to say whether those techniques are producing GMOs or not. Facing scientific controversies, this group was unable to reach a unanimous conclusion for each technique. DG Health, in charge of this policy in the European Commission, decided to release a legal opinion on the first seven techniques. This opinion aims at preparing a « communication from the European Commission » to be approved by all the commissioners and to be published before the end of 2015. Regarding synthetic biology, the European Commission considers that there's a need to better define the extent of this concept. By the end of 2013, the European Commission hoped – and its communication have not changed since then – that this work could also be the reference for other techniques that might emerge in the future (see in French : <http://www.infogm.org/spip.php?article5566> ).

### I – Which legal arguments can answer the European Commission's question ?

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Those seven techniques of genetic modification aim at modifying the plants' genetic material “*in a way that does not occur naturally by mating and/or natural recombination*”. (GMO definition according to 2001/18 Directive, article 2.2<sup>1</sup>).

None of the new techniques is strictly limited to the techniques listed in part 2 of Annex 1A of 2001/18 directive and which “*are not considered to result in genetic modification*”<sup>2</sup>. Those new techniques do give rise to GMOs according to directive 2001/18.

All those new techniques are about applying “*in vitro techniques to nucleic acid*” in at least one of their steps and then, are giving rise to GMOs, or products derived from GMOs, according to the Cartagena Protocol<sup>3</sup>.

## **I – 1. Techniques of directed-mutagenesis.**

Some of the techniques listed by the European Commission are using mutagenesis (oligodirected mutagenesis and zinc finger nuclease/Talen/meganuclease/CrisprCas9, methylation). According to Annex 1B of 2001/18 directive<sup>4</sup>, mutagenesis is a technique of genetic modification giving rise to GMOs. But those GMOs are excluded from the directive's scope of application “*on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms (falling under the scope of application)*”

Those techniques of mutagenesis are using DNA or RNA which will not be found in the final product and for which the use of the term “*recombinant nucleic acid*” is subject to scientific controversy. Companies contest that an oligonucleotide is to be considered as a recombinant nucleic acid because it is, according to them, a molecule synthesised *in vitro* by adding nucleotides one by one. Companies also underline that no additional DNA is found in the final product.

The legal opinion cannot be based on this sole argument to define the status of products obtained through the use of those techniques, or to consider whether they fall under the scope of application of the directive. The directive itself is the text of reference allowing to know what were the motivations of the legislator when excluding some GMOs from the scope of application of the directive. Such reasons are given in whereas 17 : “*This Directive should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record*”.

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<sup>1</sup> “*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”

<sup>2</sup> “*Techniques referred to in Article 2(2)(b) which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms made by techniques/methods other than those excluded by Annex I B: (1) in vitro fertilisation, (2) natural processes such as: conjugation, transduction, transformation, (3) polyploidy induction*”.

<sup>3</sup> Article 3, i) “*“Modern biotechnology” means the application of:*

a. *In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or*

b. *Fusion of cells beyond the taxonomic family,*

*that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection;”*

<sup>4</sup> “*Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are:*

(1) *mutagenesis,*

(2) *cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding methods”.*

All those techniques of mutagenesis do give rise to GMOs and are new. None of them have been conventionally used for different applications and therefore they cannot be considered as having a long safety record. Consequently, organisms derived from<sup>5</sup> those techniques cannot be excluded from the scope of application of the directive.

## **I – 2. The other techniques.**

Cisgenesis / intragenesis are “*techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation*” considered to give rise to GMOs in accordance with Annex 1A part 1, point 2) of directive 2001/18 and not techniques considered to produce organisms to be excluded from the scope of application of the directive in accordance with the restrictive list of Annex 1B.

Grafting, reverse breeding and agro-infiltration do give rise to either GMOs, or organisms produced from GM plants or bacteria falling under the scope of application of the directive.

All those techniques do give rise to GMOs which have intended or unintended effects that need to be assessed prior to any environmental release and commercialisation as stated in whereas 5 of 2001/18 directive (“*The protection of human health and the environment requires that due attention be given to controlling risks from the deliberate release into the environment of genetically modified organisms (GMOs)*”) and whereas 19 (“*A case-by-case environmental risk assessment should always be carried out prior to a release. It should also take due account of potential cumulative long-term effects associated with the interaction with other GMOs and the environment*”). None of the last four techniques of genetic modification have been conventionally used for different applications and therefore they cannot be considered as having a long safety record. Consequently, organisms obtained through the use of those techniques cannot be excluded from the scope of application of the directive.

**Legal conclusion** : The answer to question of the European Commission is that all listed techniques are giving rise to GMOs or products derived from GM which fall under the scope of application of the directive.

## **II – Contribution to the debate among European civil society organisations but not for the European Commission : scientific controversies which are becoming the captive of pro-GM industries.**

Defining the so-called random mutagenesis as a “traditional” or “natural” breeding technique which would not give rise to GMOs is useless for the debate on new genetic techniques giving rise or not to GMOs. This technique is not even on the list of technique for which the European Commission has raised the question of the legal status. There is therefore no reason to try to define this technique as giving rise to GMOs or not in the answer to be provided to the European Commission.

In addition, such a definition (traditional or natural breeding technique) is wrong : mutagenesis is a technique of genetic modification but not a breeding technique. It does give rise to GMOs according to 2001/18 directive which are excluded from its scope of application but not from the definition. If some scientific experiments have occurred more than 50 years ago, its use to give rise to

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<sup>5</sup> obtained through the use of

commercial products has occurred more recently. But the intensity of the mutagenic stress applied to these plants is not natural. Release into the environment and commercialisation of seeds or plants obtained through mutagenesis conducted on isolated plant cell in labs is more recent. This technique is even less natural as it is practised *in vitro* on cells which are micro-organisms unable to multiply “naturally” when isolated from the parent plant. It is clearly a “modern biotechnology” in accordance with the Cartagena Protocol defining them as giving rise to GMOs. Defining mutagenesis as a “natural selection technique”, “essentially biological” or “conventional” can only create the illusion that it would not be necessary to change the existing European regulation on patents<sup>6</sup> in order to have mutagenesis not patentable. This regulation do indeed state that “*essentially biological process*” like “*crossing or selection*” are not patentable. But considering that mutagenesis has been patented many time in accordance with this European regulation for which “*microbiological*” process of genetic modification are patentable, this illusion is even more dangerous.

The other claim that the definition of a GMO is restricted to the “*direct introduction into an organism of DNA prepared outside the organism*” is useless to define the new techniques of directed mutagenesis as giving rise to GMOs. Directive 2001/18 Annex 1A point 1<sup>7</sup> which defines some techniques giving rise to GMOs require that inserted nucleic acid molecules in the cell must be “*capable of continued propagation*”. Point 2 of the same Annex1A require this “*material*” to be “*heritable*”<sup>8</sup>.

None of the directed mutagenesis techniques mentioned earlier involve introduced material capable of “*continued propagation*” in the host organism or “*heritable*” material as it is not found in the genetically modified plant. Such an argument is therefore weak, legally speaking, to obtain the GMO status. Even more, narrowing the definition of GMOs to the “*direct introduction into an organism of DNA prepared outside the organism*” is false: annex 1A part 1 of the directive 2001/18 is introduced as non exhaustive (“*inter alia*”)<sup>9</sup>. And it would also imply that techniques like grafting, reverse breeding or agroinfiltration do not give rise to GMOs.

Definition of what must be regulated or not as GMOs is a political choice, not a scientific one. The political debate – and its legal transcription - must be the only field of interest and we must not get lost in sterile scientific controversies which mainly create confusion among the public who, in return, feel helpless when facing “experts”. Such a confusion opens the door to industries' attempts to make people believe that it is scientifically justified to modify the definition of GMOs and politically impossible to modify the patents legislation even though farmers and civil society organisations are claiming for the exact opposite: keep the GMO definition as it is and forbid patents on life.

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<sup>6</sup> 98/44/EC directive and implementing regulation of the European Patent Office.

<sup>7</sup> “*recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation*”

<sup>8</sup> “*techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation*”

<sup>9</sup> “ANNEX I A - TECHNIQUES REFERRED TO IN ARTICLE 2(2) - PART 1 - Techniques of genetic modification referred to in Article 2(2)(a) are inter alia:”