Lacks and possible improvements in European Union law concerning GMOs

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Abstract: Because of the complexity of many environmental problems, we need their holistic assessment. That is why, in such a matter, a multidisciplinary approach is necessary. It has also been the guiding line for this present study on the European regulation of the GMOs, crossing the different points of view of a lawyer and a biologist. According to the European legislation, molecular biology and dissemination of genetically modified organisms are mainly regulated by two major directives of the European Parliament and of the Council: Directive 2009/41/EC on the contained use of genetically modified microorganisms, and Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms. Two different approaches are possible to analyse those directives and suggest possible improvements.

Keywords: genetically modified organism; GMO; European law; risk; sustainable development.

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"We can contribute to reach a more sustainable environment by a holistic assessment of the European Union law regulating biotechnologies."

1 Introduction

Because of the complexity of many environmental problems (such as the impact of biotechnologies, or other new technologies on environment or health), we need their holistic assessment. That is why, in such a matter, a multidisciplinary, or even 'transdisciplinary' approach is not only useful, but also necessary.

Such organisations as the multidisciplinary Risk Pole of the House for Research on Human Sciences at the University of Caen Basse-Normandie, the Committee for Research and Independent Information on Genetic Engineering (CRIIGEN, http://www.criigen.org/), and the European Network of Scientists for Social and Environmental Responsibility (ENSSER, http://www.ensser.org/), for instance, have well understood that reality. In a recent paper, Robinson et al. (2013) have highlighted the conflicts of interest at the European Food Safety Authority (EFSA, http://www.efsa.europa.eu) which erode public confidence.

It has also been the guiding line for this present transdisciplinary study of the European regulation of the genetically modified organisms (GMOs), crossing the different points of view of a lawyer and a biologist. Well, as we could experiment, this way of working really helps to reach a better assessment of such regulations, with regard to the aim of sustainable environment.

Very interestingly, the interactions between biology (including genetic) and international legislation have already been pointed out by Chaturvedi et al. (2012)

through a problem of policy harmonisation. Indeed, according to those authors, 'access and benefit sharing' (ABS) policies concern plant genetic resources (PGRs) and microbial genetic resources (MGRs) but exclude human genetic resources (HGRs) without scientific reasons really explaining such an exclusion. In accord with this approach, we have tried in the present article to explain that some GMOs have been excluded from specific European directives for reasons far from sciences.

Several reasons explain the special importance of the European law on GMOs.

Firstly, we can observe that Europe, for a long time now, actually cares for environment and health.

Secondly, the European rules will come into force, directly or indirectly, not only in France, England, Italy, etc., but also in all the member states of the European Union.

Thirdly (finally yet importantly), we have the great chance that this regulation has to be reviewed by the European Parliament, and that the reviewers will be directed by Corinne Lepage, who is especially well aware of the necessity of a holistic assessment of such technologies. Lawyer, Former French Ecology Minister, C. Lepage was elected to the European Parliament in June 2009. Former First Vice President of the Committee on the Environment, Public Health and Food Safety (ENVI), she is also a substitute member of the Committee on Industry, Research and Energy (ITRE).

More precisely, according to the European legislation, two main directives of the European Parliament and of the Council regulate biomolecular construction and dissemination of GMOs: Directive 2009/41/EC on the contained use of genetically modified microorganisms, and Directive 2001/18/EC on the deliberate release into the environment of GMOs.

We will analyse those directives and suggest possible improvements from two quite different approaches:

On the one hand, a comparative analysis of the evolution of some major definitions enforced by the aforementioned directives (Part I), and, on the other hand, a specific analysis through the study of a typical example based on Directive 2009/41/EC, Annex II, Part A, Section 4 (Part II).

2 Comparative analysis through major definitions (since 1990)

Why have the main definitions basing the regulation of GMOs changed since 1990?

2.1 What is a GMO?

According to the Article 2 of the Directive 90/220/EEC, which previously regulated the deliberate release into the environment of GMOs, a GMO is:

> "an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."

However, according to the Article 2 of the Directive 2001/18/EC repealing Directive 90/220/EEC, a GMO is:

> "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."

If the definition proposed initially in the Directive 90/220/EEC (discarding vertical and horizontal gene transfers) is clear, the definition proposed in the Directive 2001/18/EC adding the restriction "with the exception of human beings" is scientifically unacceptable: a man who would be altered at a genetic level would be definitely a GMO.

Consequently, the legislative definition is not in accord with the scientific semantic.

It is true that special texts regulate medicinal products for human use. In particular, Regulation (EC) n° 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products, including gene therapy, have duly modified the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

However, the European lawyer has not mentioned the case of human beings using gene therapy into the exemptions listed by the Directive, in spite he could have easily argued this case depends on a specific regulation. The EU lawyer has chosen to exclude this case from the definition of a GMO. It is important to consider the meaning of such a choice.

Well, this exemption appears to be scientifically wrong.

Nevertheless, according to juridical and ethical principles, could we accept the idea of calling 'transgenic' a human being? It would attempt to his dignity.

Then we must take into account the risk (we should say the danger) of creating different kinds of human beings (fundamentally different, with the risk linked of discrimination), opposing the 'transgenic' ones and the 'not transgenic' ones, nearly as for alimentary products in a supermarket, labelled either 'GMO' or not (or even 'GMO own')!

In addition, since the European law classifies all GMOs (including GMMs, Table 1) in four classes depending on the degree of their (estimated) dangerousness, genetically modified humans should also be graded from one to four (or, in other words, from the first class to the fourth class), depending on their hypothetical impact on the environment, which is ethically doubtful.

Table 1 Classification of the contained uses of GMMs (Directive 2009/41/EC)

Class 1	Activities of no or negligible risk, that is to say activities for which level 1 containment is appropriate to protect human health and the environment
Class 2	Activities of low risk, that is to say activities for which level 2 containment is appropriate to protect human health and the environment.
Class 3	Activities of moderate risk, that is to say activities for which level 3 containment is appropriate to protect human health and the environment.
Class 4	Activities of high risk, that is to say activities for which level 4 containment is appropriate to protect human health and the environment

A transdisciplinary study helps to understand the real reasons having led the European lawyer to introduce in the GMO's definition such a scientifically arguable restriction in 2009.

2.2 What is a microorganism?

According to the Article 2 of the Directive 90/219/EEC on the contained use of genetically modified microorganisms, a microorganism is:

> "any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material."

Depending on the pathogenicity degree of microorganisms, those are classified in four groups (Table 2).

Table 2 Biological agents including microorganisms (Directive 2000/54/EC)

Group 1	That is unlikely to cause human disease
Group 2	That can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available
Group 3	That can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available
Group 4	That causes severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available

However, according to the Article 2 of the Directive 2009/41/EC recasting Directive 90/219/EEC, a microorganism is:

> "any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including *viruses, viroids, animal and plant cells in culture*".

If the definition proposed initially in the Directive 90/219/EEC is in accord with a scientific approach, the definition enforced by the Directive 2009/41/EC, which is complemented by "*including viruses, viroids, animal and plant cells in culture*", is scientifically unacceptable: animal and plant cells are definitely not microorganisms.

The European legislation imposes this doubtful complement in order to control technical constraints[1] far from the scientific semantic.

Well, there is also a juridical problem:

- Directive 2001/18 deals with GMOs (rightly or wrongly) considered as safe enough to be deliberately released into the environment.
- Directive 2009/41 deals with genetically modified microorganisms presenting a risk justifying to only allow their confined use (Table 3).

However, what about GMOs, which are not precisely microorganisms, but potentially dangerous? The European Law has to take into account that possibility.

Table 3 Containment levels of microorganisms, genetically modified or not.

Group 1	Laboratory L1	Animal units A1	Glasshouse P1
Group 2	Laboratory L2	Animal units A2	Glasshouse P2
Group 3	Laboratory L3	Animal units A3	Glasshouse P3
Group 4	Laboratory L4	Animal units A4	Glasshouse P4

We must not accept the idea that such GMOs, potentially dangerous for environment or health, do not have to be confined according to the strict rules of the Directive 2009/41, for the only reason they are not microorganisms.

In order to avoid such a doubt (or temptation), it would probably be better to change the title of the two directives, such as, for instance : Directive 2009/41/EC on *the contained use of potentially dangerous GMOs*, and Directive 2001/18/EC on *the deliberate release into the environment of safe enough GMOs*.

Here we are! Communication is probably much easier about 'microorganisms' than about 'potentially dangerous' GMOs, either microscopic or not.

That is time now to complete the previously explained definitions with some major exemptions, and especially one of them, detailed in the Annex Part of the Directive 2009/41.

3 Specific analysis through an example: Directive 2009/41/EC, Annex II, Part A, Section 4

Several directives, decisions and regulations have substantially supplemented both original Directives 90/219/EEC and 90/220/EEC in order to improve the legislation. In fact, many modifications have led to restrict the original directives by excluding some biological organisms genetically modified by using specific methods or technologies considered 'as safe'. Thus, the initial scientific concern based on the risk generated by genetic engineering has been, since 1990, insidiously discarded by a 'biotech-determinist' methodology.

3.1 Description

The Annex II, Part A of the Directive 2009/41/EC initially appeared in the Article 3:

> "1. Without prejudice to Article 4(1), this Directive shall not apply:
>
> (a) where genetic modification is obtained through the use of the techniques/methods listed in Annex II, Part A; or
>
> (b) for contained uses involving only types of GMMs meeting the criteria listed in Annex II, Part B which establish their safety to human health and the environment. These types of GMMs shall be listed in Annex II, Part C."

Amongst the highly doubtful restrictions developed by the European legislation concerning GMOs, the Annex II, Part A of the Directive 2009/41/EC lists the "Techniques or methods of genetic modification yielding microorganisms to be excluded from this Directive on condition that they do not involve the use of recombinant-nucleic acid molecules or GMMs other than those produced by one or more of the techniques/methods listed below":

The techniques/methods listed in the Annex II, Part A correspond to four sections:

> "1. Mutagenesis;
>
> 2. Cell fusion (including protoplast fusion) of prokaryotic species that exchange genetic material by known physiological processes;
>
> 3. Cell fusion (including protoplast fusion) of cells of any eukaryotic species, including production of hybridomas and plant cell fusions;

> 4. Self-cloning consisting in the removal of nucleic acid sequences from a cell of an organism which may or may not be followed by reinsertion of all or part of that nucleic acid (or a synthetic equivalent) with or without prior enzymatic or mechanical steps, into cells of the same species or into cells of phylogenetically closely related species which can exchange genetic material by natural physiological processes where the resulting microorganism is unlikely to cause disease to humans, animals or plants.
>
> Self-cloning may include the use of recombinant vectors with an extended history of safe use in the particular microorganisms."

We are going to comment the last example, about self-cloning.

3.2 Comments

The last section about self-cloning technology is doubtful at two independent levels, about communication and law interpretation on the one hand, and biology on the other hand.

3.2.1 About communication and law interpretation

It is almost impossible to understand the first sentence, which is composed of 81 words: this way of expression is deontologically questionable, especially concerning a law, which has to be clear enough to be well understood, so that it can also be fairly applied.

Nevertheless, there are different levels of reading: One of the shortest is: "self-cloning consisting in the removal of nucleic acid sequences from a cell […] which may […] be followed by reinsertion of […] that nucleic acid […] into cells of the same species".

Thus, it would be easy to simplify the development of biological concepts in the European legislation, in order to avoid misunderstanding.

Moreover, one of the conditions set down by the directive is that "the resulting microorganism is unlikely to cause disease to humans, animals or plants".

That clearly means the risk of diseases resulting of such microorganisms exists: it is improbable (according to the European law), but it exists. Well we have to ask ourselves the question: Is such a criterion convenient with regard to the precautionary principle?

We could ask the same question about another legal criterion based on "an extended history of safe use", especially about new technologies such as cloning.

3.2.2 Scientific criticisms

Pursuant to the Section 4, genetically modified microorganisms can be excluded from the scope of the Directive 2009/41/EC according to doubtful criteria:

- "*...(or a synthetic equivalent)...*"

  This extension is justified economically (patented DNA sequences), but not scientifically.

- "*...cells of the same species or [...] cells of phylogenetically closely related species...*"

  The concept of species is a discussed subject in microbiology, especially in bacteriology, for several reasons.

According to Mayr (1944), a species – with regard to plants and animals – is a group of organisms with a cohesive force, sexuality, which delays the genetic divergence among its members. Thus, a species can be defined as a reproductive community. However, sexuality, in its most formal definition, does not exist in bacteria. Thus, in these microorganisms, and contrary to the organisms known as 'higher' forms, the cohesion of each species is ensured by the pressure of the environment in which it lives, and not by the sexuality.

In an article ('What are bacterial species?'), Cohan (2002) has written: "bacterial systematic has not yet reached a consensus for defining the fundamental unit of biological diversity, the species". Scientists argue that two bacterial strains belong to the same species on phylogenetic criteria (DNA hybridation values and DNA homologies) which could conduct to group human beings and monkeys in the same species.

In those conditions what is the scientific value of an expression such as "phylogenetically closely related species" in the directive 2009/41/EC?

- "*…exchange genetic material by natural physiological processes…*"

Traditionally, biologists consider that genetic transfers of information within the life world are divided into two types: vertical and horizontal transfers.

Vertical transfers are, on the one hand, through sexuality that is related to the organisms known as 'higher' forms (including animals and plants) and, on the other hand, scissiparity found in the major part of the microorganisms such as bacteria. Thus, 'verticality' symbolises the time during which the perpetuation of the species is associated with the development of an organism de novo. Environmental conditions change ceaselessly, and thus force all organisms to adapt. The genetic adaptation (in parallel with the physiological and epigenetic adaptations) of a species to the modifications of its environment results, firstly, from the mutational random and, secondly, from recombination of DNA molecules carrying heredity.

In parallel with the vertical transfers, horizontal ones correspond to the natural or artificial possibility of an organism to capture a fragment of DNA, which is in its proximal environment. Horizontal transfer (Panoff and Chuiton, 2004), also called 'lateral transfer', is a common phenomenon widely identified in bacteria across three distinct natural physiological processes: transformation, conjugation and transduction. Nevertheless, for many years, the scientific community has discussed fervently on the existence and importance of horizontal transfers besides those – above mentioned – which are related to the genetic exchange of material between bacteria of the same or closed species. It is no longer sustainable to restrict horizontal transfers to the description of some academic experiments related to prokaryotes: It is a universal phenomenon and a remarkable example of the adaptation of the biological organisms to their environment.

Even if horizontal gene transfer events in the environment have been widely deduced by comparing genetic sequences from organisms that are phylogenetically distant, very few is known about the frequency of those type of genetic transfer. It is doubtful about to control mechanisms and frequencies related to horizontal transfers of genetic material.

In these conditions, the risks related to horizontal transfer of genetic structures from genetically modified microorganisms to wild microorganisms, living in the human gut or in the soil, are clearly uncontrolled but predictable: in those environments, the microflora could be unbalanced, leading to a loss of the control of the human digest process or the plant biomass product, respectively.

- "*…the resulting microorganism is unlikely to cause disease to humans, animals or plants*"

  For undetermined anthropogenic reasons, microbial communities are not on the list of the biological organisms that could be altered by an uncontained use of genetically modified microorganisms in environments such as soil or digestive tract.

- "*self-cloning may include the use of recombinant vectors with an extended history of safe use in the particular microorganisms*"

  It does not seem scientifically acceptable to evaluate quantitatively a time scale generated by history, especially concerning innovating technologies such as self-cloning.

4 Conclusions

In the present report, we initially proposed the development of two major questions:

- Can biologists approach the European legislation related to genetic engineering, or, are the biologists able to translate the legislation related to their own science in a sufficiently accessible language to permit a critical reading?
- Who is allowed to discuss the scientific value of the European legislation related to genetic engineering? Are some anonymous experts only responsible for the European legislation?

We hope we have managed to show that everyone is concerned at one's level, and has to take an active part in the current debate about genetic engineering and its regulation.

Finally, three points could be raised:

- Several kinds of genetically modified microorganisms will be excluded from the scope of the Directive 2009/41/EC, and therefore will be allowed to be used in open (uncontained) environments, according to scientifically subjective and doubtful criteria.
- Numerous scientific ambiguities in both Directives 2009/41/EC and 2001/18/EC raise the difficult question of the adequacy between, on the one hand, competences and/or deontological behaviour of the scientists and/or technicians who advise the lawyers in the drafting of the concerned directives and, on the other hand, the importance of the project.
- A transdisciplinary approach crossing biological and juridical sciences really helps to better assess European directives related to genetic engineering, in order to contribute to avoid predictive genetic pollutions in different environments such as digestive tract or soil.

Well, to summarise our purpose, we will let the European lawyer have the last word.

According to Directive 2001/18/EC, "living organisms […] released into the environment […] may reproduce […]. The effects of such releases on the environment may be irreversible"[2]. That is why "the precautionary principle had been taken into account in the drafting of this Directive"[3] regulating the release into the environment of GMOs.

We really have to hope so, because according to Directive 2009/41/EC, "the precise nature and scale of risks associated with […] GMMs are not yet fully know"[4].

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Notes

1 Containment levels are described for activities in
   a animal units
   b glasshouses
   c laboratories.

   Since microbes and cell cultures studies use similar technologies, they are artificially associated in a grouped called 'microorganisms' to simplify their control in laboratories.

2 Directive 2001/18/EC, *Introductory Whereas 4*.

3 Directive 2001/18/EC, *Introductory Whereas 8*.

4 Directive 2009/41/EC, *Introductory Whereas 9*.