EMBO reports

# The meaningless pseudo-category of "GMOs"

*The trouble with the "new techniques" for genetically modifying crops demonstrates the illogical process-based definition of GMOs in EU regulation*

Giovanni Tagliabue

In the early 1970s, when recombinant DNA technology became available, scientists exercised a healthy amount of caution. Within just a few years, as effective laboratory safety rules were established, it became clear that DNA recombinant organisms posed no greater risk than any other biotechnology, including particularly agricultural biotechnology. This evident lack of special risk is what has led biologists and geneticists to make explicit and reiterated requests to political decision-makers that regulations governing genetically modified organisms should rationally assess the characteristics of the individual *product* of such genetic manipulation, rather than be based on unfounded fears related to the *process* of creating recombinant organisms.

> *"... we have tools and standards to assess the safety of such plant products—whether food or non-food—and unsatisfactory or dangerous outcomes simply end up in the waste bin..."*

Are the various techniques for splicing DNA sequences in the genome of existing plant cultivars inherently dangerous, whether the intention is to introduce desirable traits or delete undesirable ones? The answer from almost all individual biologists and scientific societies has been "no": there is nothing inherently dangerous in these techniques. Of course, the use of any *process* to improve *products* can lead to bad results, but bad results are no more likely to result from gene splicing than from any other biotechnology. Moreover, we have tools and standards to assess the safety of such plant products—whether food or non-food—and unsatisfactory or dangerous outcomes simply end up in the waste bin, and scientists learn from their failures. During the past twenty years, numerous genetically modified cultivars have been discarded before reaching the market owing to unsatisfactory results; the same happened throughout the history of the breeding and domestication of plants and animals. On the other hand, various "events"—so-called genetically enhanced crops—have been deemed "safe" after careful testing and have been cultivated and consumed by humans and livestock, with no credible adverse effects reported so far. Wheat, for example, has multiple copies of many genes and multiple mutated genes compared to ancestral species, probably as a result of thousands of years of selective breeding, but no one is worried about whether or not bread is safe. However, if scientists were now to use recombinant DNA technology to add a gene that enabled wheat to better survive drought, there would be a public outcry that such "unnatural" wheat is too dangerous.

Scientists have never called for a general deregulation of biotechnologies; rather, they have been recommending that each new cultivar, created via any method, should be tested and assessed based on its traits and its unique profile of risks and benefits. The same approach is outlined in the *Codex Alimentarius*, which outlines international food safety standards.

> *"... EU legislators have translated indefinable prejudices against a new technology into contorted laws that hinder scientific research and agricultural progress..."*

This rational appeal has gone unheeded, however, and the fake "GMO" concept has been born. It has created a bizarre flaw that amounts to a rickety fence tentatively erected on a fuzzy border to separate the bogus category "GMOs" from more traditional breeding methods—including physical and chemical mutagenesis—even when the traits thus obtained are the same. In contrast to the substantially more rational approach adopted by Canada, EU legislators have translated indefinable prejudices against a new technology into contorted laws that hinder scientific research and agricultural progress, denying producers and consumers many of the potential benefits of applying biotechnological methods in agriculture. A sound precautionary approach was overstretched and deformed, asymmetrically and obsessively applied only to "GMOs" in a muddle of oppressive regulations, redundant analysis, pointless bureaucracy and inflated costs.

The EU's legislation on agricultural biotechnologies is hopelessly messed up. The fault lies at the origin of the

Carugo, Italy. E-mail: giovanni.tagliabue@uniedi.com
**DOI** 10.15252/embr.201541385 | Published online 11 November 2015

 

problem, namely in the basic definitions of *processes* and *products* that underlie the law. According to Directive 2001/18/EC, which regulates "the deliberate release into the environment of genetically modified organisms," 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" [1]. As far as agriculture is concerned, it would seem that targeted cross-breeding of animal and plant species, so-called artificial selection, is considered "normal," while any product that is the outcome of "unnatural" methods, such as DNA recombinant technology or chemical or physical mutagenesis, is a GMO. It is not that simple though. If we turn to an Annex to the Directive, we find a definition of acceptable approaches to "natural" gene manipulation: "Techniques [. . .] which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules [. . .]: (i) *in vitro* fertilization, (ii) natural processes such as: conjugation, transduction, transformation, and (iii) polyploidy induction." [1]. But what happened to physical and chemical mutagenesis, which apparently do not result in a GMO? Here, we must turn to yet another Annex, which says that: "Techniques/methods of genetic modification yielding organisms to be excluded from the Directive [. . .] are: (i) mutagenesis, (ii) cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding methods" [1].

> *"...as biotechnologies progresses, new methods that are not listed in Directive 2001/18 [...] make it increasingly awkward to distinguish GMOs from non-GMOs"*

This convoluted and disorganized text is the basis for contorted and contradictory regulation. The general definition—in a very loose sense—insists on the "unnaturalness" of GMOs. On the other hand, although we can each form our own opinion as to the naturalness of *in vitro* fertilization or polyploidy induction—the latter can be induced by various physical or chemical methods—they are acceptable approaches according to the Directive, as long as they do "not involve the use of recombinant nucleic acid molecules." Why, if the effect is exactly the same, are certain techniques allowed and others not? The answer, according to European lawmakers, is that if you *directly* interfere with any part of the DNA, no matter how minor, the cultivar becomes "a GMO." In addition, it is claimed *by law* that numerous genetic modification techniques "are not considered to result in genetic modification," which shows a complete disregard for reality and for the principle of non-contradiction.

The reason for these wanton and arbitrary contortions is clear: while lawmakers struggle to keep GMOs at bay to appease the "anti-GMO" brigade, they must save a myriad of existing agricultural products. If the numerous ridiculous exceptions to the definition of GMOs were not in place, several thousand cultivars and their derivatives—from pasta to beer—would end up being classified as GMOs. These policy contortions therefore are aimed at establishing a pseudo-category of products to be regulated separately, in a sectoral and sectarian way.

Yet, most important scientific bodies in Europe strongly recommended the principle of regulating the *product* regardless of the *process*, right from the start of recombinant DNA research. By way of example, the European Molecular Biology Organization (EMBO) noted in 1988 that "EMBO strongly believes that there is no scientific justification for additional, special legislation regulating recombinant DNA research *per se*. Any rules or legislation should only apply to the safety of products according to their properties, rather than according to the methods used to generate them" [2]. But neither EMBO's recommendation, nor two letters [2] in 1989 and 1990 to the European Community by sixteen European Nobel laureates in medicine and chemistry, convinced European politicians to abandon the special regulation of GMOs. These regulations were formulated in two Directives in 1990, 90/220 of which regards agricultural products (eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31990L0220), and reiterated a decade later in Directive 2001/18. A partial change was introduced by Directive 2015/412 (eur-lex.europa.eu/legal-content/EN/TXT/?qid=1426590211658&uri=OJ:JOL_2015_068_R_0001), but its significance is outside the scope of this article.

A harmful and foreseeable effect of this illogical regulation of processes rather than products has become evident in recent years: as biotechnologies progresses, new methods that are not listed in Directive 2001/18—such as cisgenic gene transfer or TALEN and CRISPR gene editing—make it increasingly awkward to distinguish GMOs from non-GMOs. As a result, regulators are at a loss about how to include these methods into the legal framework because of the arbitrary distinction between "allowed" and "prohibited" technologies, which means that they must pigeonhole any new method. What do politicians usually do in such cases? They ask a group of scientists to advise them: but this apparently reasonable initiative is a dead end in the case of GMOs, because it means they must inevitably persist in the initial error, which was to ignore scientific advice and basic logic.

> *"The EU's legislation on agricultural biotechnologies is hopelessly messed up"*

Nevertheless, the Dutch government tried this approach. When agribiotech firms asked the government whether six new agricultural technologies should be subject to GMO regulation, it engaged an *ad hoc* committee of experts to specify "whether they can be considered genetic modification and whether their products must be characterized as GMOs" [3]. The six techniques considered were as follows: reverse breeding, agroinoculation, grafting on genetically modified rootstock, gene silencing by DNA methylation, the use of oligonucleotides and specific mutagenesis with homologous recombination. The scientists generated a long and detailed report that examined the six techniques one by one and asserted that yes, they did result in GMOs, then that they did not, and then that they might; in the end, they deferred to further studies, knowing full well that no definitive response could be given to a badly formulated question.

For diplomatic reasons, these experts did not say what should have been said: not only that "the dividing line between what is a GMO and what is not is becoming increasingly more difficult to determine" [3], but also that the very question makes no

sense, because the answers are multifaceted. "GMO-ness," for example, can be provisional (when the final product has passed through a mere transient stage of gene recombination) or partial (when a non-transgenic plant is grafted on to a rootstock whose DNA has been enhanced). At the end of all the analysis, the experts referred the Dutch government to the European Commission, since any decision taken at a national level—should it be challenged or not recognized by other states—would produce serious commercial problems.

*"As the vast majority of scientists recommend, the nonsensical "anti-GMO" fence should be taken down and the same rules and analysis should be applied impartially to each and every product"*

In 2007, the European Commission, at the urging of the Netherlands, set up an international working group to assess the progress of agricultural biotechnology: "In order to take account of the scientific and technical developments in biotechnology, upon a request of National Competent Authorities, the Commission set up in 2007 a New Techniques working group to assess whether a number of new breeding techniques could fall or not within the scope of the GMO legislation" (http://ec.europa.eu/food/plant/gmo/legislation/plant_breeding/index_en.htm). Let us not be fooled into thinking that Europe wanted to know whether the products generated by these methods, which initially are not specified, would be more or less risky for human and/or animal health, and/or for the environment—which in any case could not be known *a priori*. What the scientists were asked to ascertain was whether and which of the new techniques—which the scientists themselves are invited to list—can be located in the labyrinth of the current law and which fall outside of it in some sense. In short: whether the new techniques generate GMOs or not.

Time passes. The European Food Safety Authority (EFSA) also gets involved in the extremely laborious assessment to produce an opinion on the status of cisgenesis and intragenesis [4], as does the Joint Research Centre's Institute for Prospective Technological Studies, whose specialists publish various analyses [5,6]. The "official" working group increased the list of the techniques on which an opinion must be expressed to eight: oligonucleotide-directed mutagenesis (ODM); zinc finger nuclease technology (ZFN) comprising ZFN-1, ZFN-2 and ZFN-3; cisgenesis comprising intragenesis; grafting; agroinfiltration; RNA-dependent DNA methylation (RdDM); reverse breeding; and synthetic genomics. A final report was produced in April 2012 after more than three years work. It has still not been officially published but—in a classic example of "grey literature"—has leaked out online and then has been placed in a remote area of the EU Website (webservices.edcc.eu/attachments/index/0890994/draftreportversion_9_final.pdf). The authors were hamstrung from the start, as they had to broadly discuss terms and expressions that are anything but clear in the underlying convoluted definition of GMOs provided by Directive 2001/18 and in the related Annexes. Just by way of example, the experts are divided on a particularly tricky problem, which is the transitory state in which a genetic modification is only provisional: it is a GMO; no it is not; maybe it is, only for a while. Similar, irresolvable problems have been pointed out by commentators, whom individual governments have asked for an opinion on the not-yet-officially-published report (www.gov.uk/government/publications/genetically-modified-organisms-new-plant-growing-methods; www.bvl.bund.de/SharedDocs/Downloads/06_Gentechnik/ZKBS/02_Allgemeine_Stellungnahmen_englisch/05_plants/zkbs_plants_new_plant_breeding_techniques.pdf?__blob=publicationFile&v=2).

I have some sympathy for the appointed experts who doubtless had to spend many hours discussing useless, nit-picking questions and wasted time and energy to establish whether this or that technique falls into the hodgepodge and inconsistent definition of GMOs and its related strange exceptions and incoherent digressions. Much effort has been expended in attempting to formulate answers that no scientist can provide, because the question itself is wrong! The results of biotechnological manipulation—the qualities or phenotypical characteristics of potato or sorghum or apricot, which are determined by tests—cannot be inferred *a priori* from the characteristics of the processes applied to achieve them and consequently cannot provide the basis for a more or less stringent law regarding the expected healthiness or otherwise of what is being produced. There is even less sense in the inane attempt to fit certain processes—the "new techniques"—into the deformed pre-existing European law, which is akin to grafting new branches on the warped wood of a law that should be completely erased and rewritten from top to bottom.

In an ideal world, the experts who were called upon would have refused the appointment, explaining to the EU Commission that the question raised, in many cases, cannot be answered. Instead, the biologists wrote an accurate and detailed report that explains precisely and in detail what zinc finger enzymes are, as well as oligonucleotides, the methylation of DNA, and so on. But it is a pointless effort, because the potential use of any of the listed methods—or a combination of them—cannot by definition provide preliminary information on the healthiness of the products that might be obtained. In any case, the question of whether the "new techniques" produce GMOs or not—and therefore how they relate to the existing law—is Sisyphean, even if it could be answered, because progress is not going to stop. Biotechnological research will continue, and in the coming years, four new techniques might emerge, or 13, or 56, and "[t]here is no way that legislation based on processes is ever going to keep up with the introduction of new ways of doing things" (www.independent.co.uk/news/science/scientists-renew-call-for-lighttouch-legislation-on-secondgeneration-gm-crops-9619769.html).

*"If the numerous ridiculous exceptions to the definition of GMOs were not in place, several thousand cultivars and their derivatives—from pasta to beer—would end up being classified as GMOs"*

Will political bodies therefore simply allocate more and more public money to raising questions about the risks, benefits and regulation of every new technique? Will our politicians continue to commission endless studies and risk assessments on biotechnological *processes*, even though

 

nobody can know whether or when the application of one or another or a combination of these methods might generate unsatisfactory *products*? Can we imagine a more pointless waste of taxpayers' money? The results cannot be known *a priori*, owing to the "blurred box" in which the transition from genotype to phenotype takes place. Instead—as should be hammered into the minds of politicians—the results can only be ascertained *a posteriori*, by empirical analyses and by checking the phenotypical traits. There is therefore no point in assessing each and every *process*, but rather each and every *product* on its own merits, deficiencies and risks. In other words, it is necessary to cut "the Gordian knot binding European plant science through continuing policy failure and political timidity" [7].

Similar comments on the unpredictability of results have been made by the EFSA in reply to a query from the European Commission on the comparative risks of traditional genetic enhancement, cisgenesis and transgenesis [7]. Rather half-heartedly, the idea has also been put forward that it would be better to assess the potential risks of individual products rather than biotechnological–agricultural processes, which are always evolving: "Given the fast development of new breeding/production technologies applied to organisms, which may need a revision of current regulatory definitions of genetic modification, EFSA is prepared to investigate risk assessment strategies for modified organisms, based on the characteristics of obtained products rather than based on the applied breeding/production technology" [8].

Regulators in various non-European countries, including Argentina, Australia, Japan and South Africa, have also addressed the same insuperable problems of matching new techniques with various peculiar national laws. The exceptions—where an approach at least partially based on analysis of the products, rather than on the biotechnological processes, eases the aforementioned problems—are the USA and, above all, Canada [6].

Quite predictably, the European seed industry is afraid that any extension of the current stringent and costly regulation on GMOs to new techniques might create a serious competitive disadvantage for the EU's agricultural developers (https://www.euroseeds.eu/system/files/publications/files/esa_12.0446.2.pdf). Unfortunately, we envisage that some of these fears will become reality; that European bureaucrats, having thrown taxpayers' money into producing a pointless report—which is certainly not the fault of the committee that wrote it—will now adopt a restrictive approach in regard to products deriving from the new biotechnologies. In doing so, they will stay on the side of the anti-GMO movement, whose members are numerous in the EU Parliament and in Brussels, and will thus perpetuate the mad European law.

As the vast majority of scientists recommend, the nonsensical "anti-GMO" fence should be taken down and the same rules and analysis should be applied impartially to each and every product, whether it is "GMO" or otherwise. This should be done *a posteriori*: "A future regulatory framework should be product rather than process based so that it is consistent and applies to the novelty of the characteristics of new plant varieties" (http://www.easac.eu/home/reports-and-statements/detail-view/article/planting-the.html).

A rational, science-based technical legal framework is already available: the Stanford University Project on Regulation of Agricultural Introductions [9, 10]. It provides guidelines for an attentive, well-calibrated risk assessment approach to new cultivars to ascertain the pros and cons of each new plant. The different biotech methods are considered irrelevant: the "GMO" blunder has evaporated. Instead, rational questions are provided for field tests to assess the ecological impact and human health issues. The authors of the Stanford model emphasize that their guidelines are not a mere theoretical exercise, but draw inspiration from similar experiences which are already well tested in the real world: "One great advantage is that it is analogous to existing regulatory regimes, such as those for quarantine regulations for plant or animal pests, and also to the U.S. government's approach to handling dangerous pathogens or other microorganisms in the laboratory. In other words, the approach is not fundamentally new and has worked well in practice for decades" [10]. The question is whether such a reasonable mindset will win out sooner or later.

## References


1. European Union (2001) Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities L106: 1–39, europa.eu/legislation_summaries/agriculture/food/l28130_en.htm
2. Cantley M (1995) The regulation of modern biotechnology: a historical and European perspective. A case study in how societies cope with new knowledge in the last quarter of the twentieth century. In *Biotechnology*, Rehm HJ, Reed G (eds), pp 508 – 681. Weinheim: Wiley-VCH
3. COGEM - Commission on Genetic Modification (2006) New techniques in plant biotechnology. The Hague, Netherlands: COGEM report CGM/061024-02
4. EFSA - European Food Security Agency, Panel on Genetically Modified Organisms (GMO) (2012) Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis. *EFSA J* 10: 2561 – 2593
5. Lusser M, Parisi C, Plan D, Rodríguez-Cerezo E (2012) Deployment of new biotechnologies in plant breeding. *Nat Biotechnol* 30: 231 – 239
6. Lusser M, Davies H (2013) Comparative regulatory approaches for groups of new plant breeding techniques. *New Biotechnol* 30: 437 – 446
7. Giddings VL, Potrykus I, Ammann K, Fedoroff NV (2012) Confronting the Gordian knot. *Nat Biotechnol* 30: 208 – 209
8. Waigmann E, Paoletti C, Davies H, Perry J, Kärenlampi S, Kuiper H (2012) Risk assessment of Genetically Modified Organisms (GMOs). *EFSA J* 10: s1008 – s1014
9. Barton J, Crandon J, Kennedy D, Miller H (1997) A model protocol to assess the risks of agricultural introductions. *Nat Biotechnol* 15: 845 – 848
10. Miller H (2010) The regulation of agricultural biotechnology: science shows a better way. *New Biotechnol* 27: 628 – 634