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Once, a certain number of papers in a specific thematic, is reached, the Academy might edit a special paper issue in parallel to the electronic version.

FOREWORD

The Frontiers in Science and Engineering International Journal is devoting the present issue to life sciences, and especially to genetically modified organisms (mainly crop species and a few mammal species).

The articles included in this issue have the merit of deciphering the history of the development of genetically modified organisms (GMOs), and of describing the growth rate and expansion of these organisms in agriculture, food industry and animal breeding.

These reviewed articles correspond to presentations made by the authors during a seminar, which was organized in 2016 by the College of Life Sciences of The Hassan II Academy of Science and Technology and the Mohammed V University of Rabat.

Driss OUAZAR
Executive Director and Associate Editor-in-Chief

Genetically modified crops (GM crops) and derived foods: Brief review of their impact on health and environment, and of their social acceptance *

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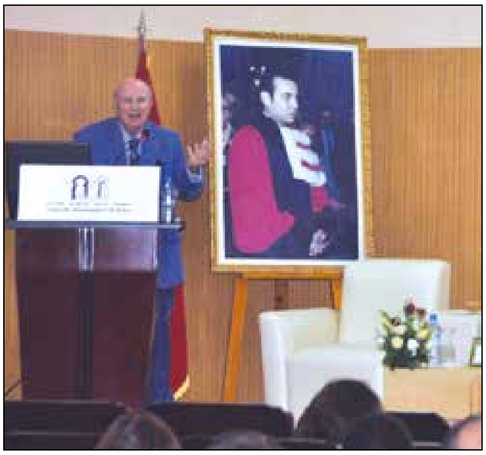
(*) Rabat, Morocco, revised December 2017.

(**) Until February 2017.

Introduction



The first genetically modified living being was a bacterium transformed in 1973, followed the same year by a transgenic mouse; it was in 1996 that the first transgenic or genetically modified plant was created: a tomato with delayed maturation, and later on a transgenic tobacco. In the laboratories transgenic animals were produced such as mice, chickens, flies, worms, zebra fish, small pigs, and the famous sheep breed Dolly…, as well as genetically modified plants with a view to producing some interesting molecules (e.g. pharmaceuticals), studying disease and trying to better understand their underlying basis and find a cure.

Since 1996 several crops have been transformed, mainly soybeans, maize and cotton (but also canola, alfalfa, sugar beet), with a view to making them more resistant to plagues and pests and/or more tolerant to herbicides that could kill weeds without harming the transformed crops. In 2016 these genetically modified crops were grown on 185.1 million hectares in about 30 countries. The period 2006-2015 is the second decade of commercialization of GM crops and it seems that during this decade more growth would be recorded in Asia and Africa compared with the first decade which was the decade of the Americas. Brazil with the adoption of soybeans, maize, beans, sugar cane, cotton and forest-tree species was emerging as the driving engine of growth in GM crops in Latin America. Argentina is also playing an important role (almost all its soybeans are genetically transformed). See Sasson (2013).

In 2016 more than 80% of the soybeans grown across the world was genetically modified, as were roughly more than half of the cotton and over a quarter of maize. An important feature of this second decade of GM crops commercialization is that several developing countries (e.g. China, Argentina and Brazil) are now producing their own GM crops with their own R&D means and not just using the seeds from developed countries (e.g. a drought-tolerant GM soybean in Argentina or a virus-resistant bean in Brazil). See Sasson (2013).

New genome editing techniques, such as the CRISPR-Cas9, could genetically modify animals and crops in a faster and less expensive way: silencing some genes, overexpressing others, correcting them, without transferring genes from microbes or plants as this is the case of the current transgenic organisms. This new form of transforming the living beings, considered extremely powerful, could escape the regulations set up for controlling the dissemination of first-generation GMOs. This is what the industrialists hope. The first application of CRISPR-Cas9 to a crop was performed in China. It aimed to develop a mildew-resistant wheat at Beijing's Institute for Genetics and Development Biology, by the team of Caixia Gao. The latter stated: "China continues to consider the products obtained using CRISPR-Cas9 as GMOs, but this is not the case everywhere. We are in the process of submitting our new wheat to the United States Department of Agriculture" (Leplâtre, Herzberg and Morin, 2016).

In the United States Pioneer, a seed company subsidiary to DuPont, announced in April 2016 the commercialization within five years of a higher-yielding new sweet hybrid maize variety (waxy) of which the seeds have a high content of amylopectin (which interests the industry). The US Department of Agriculture let understand Pioneer that it would not object to the commercialization of this new maize variety. A few days earlier it had done the same for a button mushroom who was resistant to browning and was developed at the University of Pennsylvania. It seems that this regulatory approach was adopted by the US Department of Agriculture for the plants genetically transformed using the new genome-editing techniques. But this approach may not be shared by the health department or the Environmental Protection Agency (EPA) [Leplâtre, Herzberg and Morin, 2016].

A new report from the American National Academies of Sciences, Engineering and Medicine

In May 2016 in an approximately 400-page report, the not-for- profit academic group evaluated 20 years of research into the environmental effects of plants modified with genes that enable them to repel pests and withstand herbicides, and what happens when those crops are made into food for people or processed into feed for poultry or livestock. This report reviewed 900 scientific studies published on the subject and it was supervised by a panel of independent experts led by Fred Gould, an entomology professor at North Carolina State University. The overall verdict was: GM crops are safe for people and do not seem to directly harm the environment. The report also played down any unique risk of cancer, autism or other diseases alleged to have been associated with genetically engineered (or transgenic) crops (Bunge, 2016).

The committee did not find "any evidence" that GM crops are harmful to human health. Furthermore the studies with livestock animals and of chemical composition did not reveal any difference for human health between the consumption of food derived from GM crops and foodstuff which comes from a normal crop. By contrast, there seems to be evidence that GM crops resistant to pests could have a positive impact on human health because of the reduction of intoxications by pesticides. There are GM crops which may have, because of their composition, a beneficial effect on human health, as this is the case of golden rice, a variety genetically modified to contain beta-carotene; this has not yet been approved for cultivation after years of discussions, while millions of deaths of infants could be avoided through the provision of provitamin A against blindness and malnutrition (see below).

"After carefully examining the benefits and potential risks of GM crops and food in the commercial marketplace for the past two decades, we are pleased that the study reiterate what the world's scientific authorities have repeatedly concluded over the years: that agricultural biotechnology has many demonstrated benefits to farmers, consumers and the environment," stated Brian Baenig, head of food and agriculture for the Biotechnology Innovation Organization, a trade group representing seed firms. However the report is unlikely to put to rest debates about potentially unknown effects from growing GM crops – or eliminate some consumers' deep distaste for the technology. The report released on Tuesday 17 May 2016 was nevertheless welcome news for food industry groups such as the Grocery Manufacturers Association, which estimated that 70% to 80% of packaged food in the United States contain GMOs, as well as seed developers like Monsanto Co. and DuPont Co. (Bunge, 2016).

Despite the fact that in the United States the food and agriculture industry has been battling state-level efforts to require labels for food products made from GM crops – a step consumer groups have stated would provide desired transparency, but that companies fear would unnecessarily scare off consumers – the report "confirms the importance of transparency and the need for mandatory GMO labeling on the package," stated Gary Hirshberg, chairman of organic yoghurt maker Stonyfield Farm and chairman of Just Label It, a group that promotes labeling of GMO-derived foods. "And it acknowledges that as long as companies hide basic facts from consumers, the latter will be unable to make food choices that reflect our values," he added (Bunge, 2016).

Regarding the impact of GM crops on the environment, the report states that these are not reducing the diversity of plants or insects in the areas where they are planted. The report acknowledges that the genes of GM crops have been invading agricultural areas, but this has not provoked any detrimental effect on the environment. The report acknowledged "the difficulty of determining long-term effects, which makes difficult to reach definitive conclusions." This is the only aspect where the report of the various Academies identifies impacts which question some of the benefits of GM crops. The report confirmed that there are insects which develop resistance towards the type of pesticides used on GM-crop areas. But this resistance seems to be detected in areas where the guidelines recommended to avoid the development of such resistance are *not* followed. The report also noted that there are weeds which developed resistance against glyphosate, the active ingredient of Monsanto's Roundup which is mostly used in the cropland where GM crops are grown. In addition glyphosate "probably" causes cancer in people, according to the International Agency for Research on Cancer, which informed the World Health Organization. But this is a controversial issue (see below).

As for the argument that GM crops can help to feed the world and lift small-scale farmers from poverty, the Academies' researchers had a mixed view. No genetically engineered crop species so far has proven to increase potential fields – rather they protect crops from losing yield due to pests and weeds, according to the report. GM crops can help poor farmers boost their income, but the higher cost of the modified seeds and access to credit can limit their availability in impoverished parts of the world, the report found. Poor farmers need the support of technical agencies as well as that of the state for helping them to have access to cheap fertilizers, to have storage facilities and to be part of the local, regional and national markets. Monsanto does not share this opinion and maintains that the production of soybeans, maize and cotton, since they have been introduced, had a positive impact on yields.

Finally the report recommended that the regulations of new types of crops should be based on the characteristics of the product developed from the crop (e.g. higher content of vitamins) and not on the process involved in the development of these crops (via genetic modification or conventional selection). According to the report the difference between a transgenic crop and a conventional one is being blurred by the use of new genome-editing techniques such as the CRISPR-Cas9. A crop variety developed through this technique would not be considered as really transgenic in many countries. Furthermore the same features that could be developed through this method could be obtained through the irradiation of seeds, followed by the selection of the most appropriate ones, a process that is considered as "conventional" in a large number of countries.

This raises the issue of what is exactly a transgenic food derived from a GM crop. Brandon R. McFadden and Jayson L. Lusk, belonging to the University of Florida (Gainesville) Department of Food and Resource Economics, as well as the Oklahoma State University (Stillwater) Department of Agricultural Economics, published in the *FASEB* (Federation of American Societies for Experimental Biology) *Journal*, on 19 May 2016, their analyses of data from consumer polls on genetically modified (GM) food and biotechnology (McFadden and Lusk, 2016). They showed that these polls are often presented as evidence for precaution and labeling. But how much do consumers know about these issues? New data collected from a nation-wide (United States) survey revealed low levels of knowledge and numerous misperceptions about GM food. Nearly equal numbers of consumers (80%) preferred mandatory labeling of foods containing DNA (which meant a labeling of practically all foods existing in a supermarket), as did those preferring mandatory labeling of GM foods (84%). When given the option, the majority of consumers preferred that decisions about GM food be taken off their hands and be made by experts. After answering a list of questions testing objective knowledge of GM food, subjective, self-reported knowledge declined somewhat and beliefs about GM food safety increased slightly. Results suggested that consumers thought they knew more than they actually did about GM food, and queries about GM facts caused respondents to reassess how much they knew. These findings questioned the usefulness of results from opinion polls as a motivation for creating public policy surrounding GM food (McFadden and Lusk, 2016).

An open letter addressed by more than 100 scientists to Greenpeace

A total of 109 scientists including a majority of Nobel Laureates (out of 296 who are still alive) have addressed an open letter to Greenpeace with a view to requesting that international non-governmental organization (NGO) to put an end to its opposition against genetically modified organisms (GMOs). In that letter the scientists lay emphasis on the case of golden rice, developed many years ago via genetic engineering in order to contain high amounts of beta-carotene (provitamin A); and which could be a good means to control the juvenile blindness (due to xerophthalmia) that affect 250,000 to 500,000 children each year worldwide. Half of the children die during the first 12 months after having lost their vision according to the World Health Organization. A study made by German researchers in 2014 estimated that the relentless opposition of Greenpeace to the release of golden rice for large-scale cultivation has resulted in the loss of 1.4 million years of life just in India.

The initiative was presented on Thursday 30 June 2016 at the National Press Club in Washington, D.C., in the framework of a wider campaign on "Support GMOs and Golden Rice". This was organized by Richard Roberts, scientific director of New England Biolabs, and Phillip Sharp, Nobel Laureate in Medicine or Physiology in 1993, for the discovery of genetic sequences called introns. In their open letter the scientists emphasized that genetically modified crops (GM crops) are as safe for human or animal consumption as those produced by other methods of selection. They indicated that 20 years since their cultivation on a large scale, there was not a single case of disease due to their consumption, and that their environmental impact was not more detrimental than that of their conventional counterparts. In an interview with the *Washington Post* R. Roberts stated: "We are scientists. We are aware of the logics of science. It is easy to see that the action of Greenpeace causes a grave prejudice and is antiscientific…"Greenpeace at the beginning, and thereafter some of its allies, deliberately scare the people. This is a way to recover money for their cause." "We request Greenpeace and those who follow the same approach to examine the experience of farmers and consumers worldwide with respect to GM crops and foods derived from them through biotechnology, to recognize the conclusions of competent scientific institutions and of regulation bodies, and to abandon their campaign against GMOs and more specifically against golden rice." According to the United Nations Fund for Children (UNICEF) there are between one and two millions of deaths that could be avoided each year among children suffering from vitamin A deficiency, if golden rice was produced and consumed by these children.

In their letter the 109 scientists mentioned the recent report by the American National Academies of Sciences, Engineering and Medicine whose main conclusion was that GM crops and foods derived from them were as safe as their conventional counterparts. One must emphasize that the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) have recognized their safety for human and animal consumption, as well as their role in achieving a more sustainable agriculture that contributes to the struggle against starvation and to the adaptation to climate change. There has never been question that agricultural biotechnology would be the panacea to eliminate starvation in the world; this needs many more decisions and tools, including the technical one afforded by agrofood biotechnology. But there is no doubt that this could bring a valuable contribution to feeding the increasing number of people and to the changing of food diets.

Among the signatories of the open letter to Greenpeace one could mention the Nobel Laureates David Baltimore, Paul Berg, Elizabeth Blackburn, Steven Chiu, Daniel Kahneman and Harold Varmus. They "requested the governments to reject the opposition of Greenpeace against GMOs and more specifically against golden rice; and while opposing Greenpeace's action, to facilitate the access of farmers to all the tools of modern biology, e.g. the seeds improved through biotechnology. The opposition based on emotion as well as a dogmatic view about the experimental results must be abandoned"…"How many people across the world should die before admitting that this is a crime against humankind?"

Stéphane Foucart, a scientific journalist at the French daily newspaper *Le Monde* and who has followed all the controversy about GMOs and GM crops, tried on 5 July 2016 to put the things in their context. The signatories of the open letter to Greenpeace suggest that this international NGO has blocked the commercialization of golden rice and, therefore, is responsible for the deaths of hundreds of thousands "poor people". Henceforth, a crime against humankind. For Stéphane Foucart the scientists amalgamate agrifood biotechnology and humanitarian action, thus letting people to understand that the primary function of GMOs is to save lives. But this is not true (Foucart, 2016).

It is true that Greenpeace has for many years strongly criticized the endeavours of the International Rice Research Institute (IRRI, Los Baños, Philippines) to develop and commercialize golden rice. The international NGO believes that golden rice is not a proper way to control poverty and avoids the real issue which is a diversified diet; that this GM crop would fail, his innocuity has not been proved and it will open the door to other commercial GM crops. S. Foucart does not deny the dogmatic approach of Greenpeace and agrees that we should try and see if golden rice could improve the health of so many people. But this variety of rice should be available in sufficient quantities; and "by contrast to what the Nobel Laureates think, golden rice has never been blocked by public opposition or by Greenpeace," explained Glen Stone, an anthropologist and professor at the Washington University in Saint Louis, Missouri, who has led for four years a research programme on rice cultivation the Philippines. "Golden rice is not yet ready," he stated. It seems that IRRI as well as the Philippines Rice Research Institute have made a trial on several plots in 2012 and 2013, but golden rice "had yields lower than a crop variety without the transgenes," said G. Stone. Consequently both research institutes have not yet submitted golden rice to the regulation authorities for commercialization. While the position of Greenpeace against GM crops is contrary to the scientific consensus, the NGO is not responsible for the non-approval of golden rice for large-scale cultivation (Foucart, 2016).

According to Glen Stone, "such story seems to be a manipulation of public opinion through giving the floor to scientists who are not fully informed about the subject…" "Among the Nobel Laureates there were one for peace, eight for economy, 24 for physics, 33 for chemistry and 41 for medicine or physiology…" "Science is based on evidence, not on authority," he added on Twitter. "What do they know about agriculture? Have they led relevant research programmes on the subject?" (Foucart, 2016). In my view, quoting one scientist – an anthropologist – as a means to show the irrelevance of the Nobel Laureates' open letter or even a manipulation of public opinion, is going too far. S. Foucart is known for his articles that are not pro-GMOs, to say the least. He is certainly well informed as should be an investigation journalist, but he is tweaking the relevance of the protest made by respected scientists – whatever their discipline – against Greenpeace.

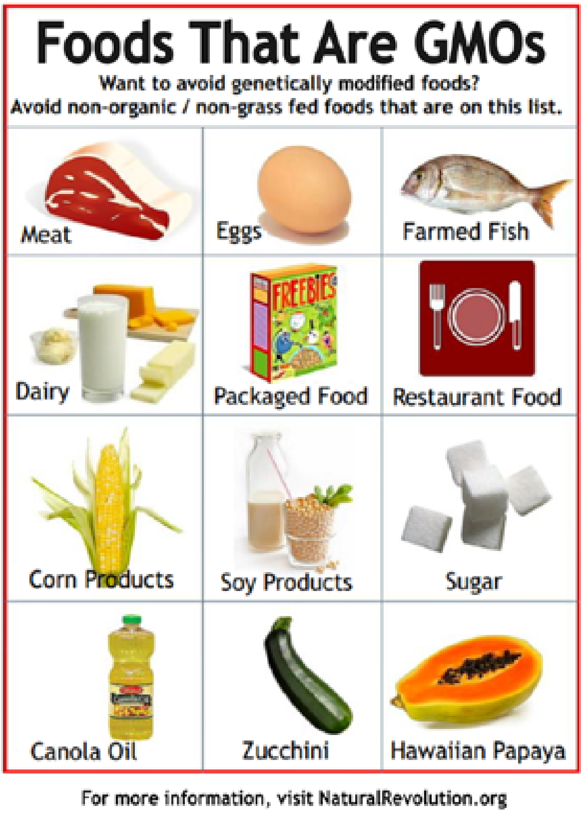
Both the report by the American National Academies of Sciences, Engineering and Medicine, and the open letter to Greenpeace by Nobel Laureates happened in a moment where the agrofood industry and agrobiotechnology are grappling with the mandatory labeling of GM food; with the "war" against glyphosate – the herbicide mostly used with GM crops – because it may cause cancer; and with how to name the future generation of genetically crops (would they be transgenic and, if not, they should not be submitted to the current regulation). Not to speak about the lobbying impact of seed companies, and Monsanto Co. in particular, on the decisions made about regulation by scientists who may have conflicts of interest. And S. Foucart has made some investigations in this respect (see below).

Labeling of GM food in the United States

Despite myriad of assurances from scientists that foods containing genetically modified ingredients are safe to eat, American consumers are likely to see more and more products labeled "GMO-free" in the not-too-distant future. As happened with the explosion of gluten-free products, food companies are quick to cash in on what the consumers believe regardless of whether it is scientifically justified. In May 2015 the U.S. Department of Agriculture (USDA) announced a voluntary certification programme that food companies would pay for to have their products labeled GMO-free. By the end of June 2015, Abbott, the maker of Similac Advance, began selling a GMO-free version of the leading commercial baby formula in the United States (it already had such a product, Similac Organic) to give consumers "peace of mind". In April 2015 Chipotle announced that it would start preparing foods with no GMOs, although its restaurants will not be free of such ingredients (Brody, 2015).

But the fight over GMO labeling has been long, contentious and expensive. Food and biotechnology companies spent roughly US$100 million to oppose this labeling in 2015 alone, according to the Environmental Working Group, on advocacy group that favours labeling. The money helped defeat State labeling proposals in California, Colorado, Oregon and elsewhere. But many food executives fretted that these were Pyrrhic victories, since their own research were showing that most consumers wanted to know which foods contained genetically engineered ingredients (Strom, 2016).

In 2014 the State of Vermont passed a law requiring the labeling of foods that contains GMOs (Connecticut and Maine have labeling laws that will go in effect when surrounding States pass them). The law in Vermont went into effect on July 2016. The Grocery Manufacturers Association and the biotechnology industry challenged the law in court, but by the time a judge ruled in favour of Vermont in 2015, many companies have already begun the process of figuring out how to comply with the tiny State's law. Some companies have already started to label their product to meet Vermont's requirements. Campbell soup was the first to break ranks, announcing in January 2016 that it would put GMO labels on all its products nationally. Whole Foods Markets, with 410 stores in 42 States, Canada and Britain announced that it would require all food they sell with GMOs to be so labeled by 2018. General Mills, ConAgra and others quickly followed suit, and now many food packages contain tiny print affirming the presence of genetically engineered ingredients. "We believe that this is the clearest and most transparent way to communicate with consumers on this issue that so many of them have said it is important to them," said Mark R. Alexander, president of Campbell's simple meals and beverages business in the Americas (Strom, 2016).



It is true that a review of the pros and cons of GMO labeling strongly suggests that the issue reflects a poor public understanding of the science behind the GMOs, along with a rebellion against the dominance of food and agricultural conglomerates. What is needed is a dispassionate look at what GMOs means and their actual and potential good, not just a fear of harmful possibilities. Nothing in this life is risk-free, but this is not enough reason to reject valuable scientific advances. That is why a fair bill must be approved to regulate GMO labeling (Brody, 2015). On 4 November 2014 voters in Colorado rejected a ballot initiative that would have required special labels for food with genetically engineered ingredients. Voters in Oregon seemed likely to say no to a similar proposal. Regardless of the outcome, however, these referendums indicate the strength of feeling generated by GM crops: the Oregon was the costliest ballot in the State history. By chance, the day before the poll saw the publication in *PLOS ONE* of the largest review conducted of the crops' effect on farming. It concluded that these have been overwhelmingly positive (*The Economist*, 2014).

The review in question is a meta-analysis, i.e. a statistically rigorous study of studies, rather than a mere summary of literature. Its authors, Matin Qaim and Wilhelm Klümper, both of Göttingen University, Germany, went through all examinations of the agronomic and economic impacts of GM crops published in English between 1995 and March 2014. This provides a near-complete survey. Most studies of the subject have been published in English, and the widespread adoption of such crops began only in the mid-1990s. The study found herbicide-tolerant crops have lower production costs – though this was not true for insect-resistant crops, where the need of less pesticide was offset by higher seed prices, and overall production costs were thus about the same as for unmodified crops. With both forms of modification, however, the yield rise was so great (9% above non-GM crops for herbicide tolerance and 25% above for insect resistance) that farmers who adopted GM crops made 69% higher profits than those who did not (*The Economist*, 2014). This increase in yield and of revenues of farmers having adopted GM crops were not found in the report by the American National Academies of Sciences, Engineering and Medicine (17 May 2016).

M. Qaïm and W. Klümper found that GM crops do even better in poor countries than in rich ones. Farmers who use this technology in developing nations achieve yields 14 percentage points above those of GM farmers in the rich world. Pests and weeds are a bigger problem in poor countries, so GM crops confer bigger benefits. In debates about GM crops the methodology of studies have often generated as much controversy as the crop themselves. M. Qaïm and W. Klümper have done something to moderate these controversies, too. Though some studies they included were not peer-reviewed, and a few of the early ones did not report sample sizes, limiting their value, the data they used for the meta-analysis – which include conference papers, working papers and book chapters as well as work published in academic journals – may correct for perceived publication bias, the tendency of journals to publish only the most dramatic findings. Both authors conclude by expressing a hope that their work "may help to gradually increase public trust in this promising technology" (*The Economist*, 2014). It remains that the present preoccupation of the consumers is a fair labeling of food that contain GMOs.

The bill being discussed at the United States Senate would require food manufacturers to use one of three types of labels to inform consumers when genetically engineered, or GMO, ingredients are in their products. The label requirements would also apply to growers of fruits and vegetables that are genetically engineered like the Arctic Apple and some zucchini. The bill moved forward on Wednesday 6 July 2016 in a 65-32 procedural vote and was expected to receive final approval in the Senate as early as the beginning of the second week of July 2016. This approval is a big victory for food companies, farm groups and the biotechnology industry, which began pushing for a national standard in 2015 to head off a Vermont labeling law that went into effect on 1 July 2016. "From my perspective, it is not the best possible bill, but it is the best bill possible under the difficult circumstances we find ourselves in today," stated Senator Pat Roberts, a Republican from Kansas who helped write the legislation. P. Roberts had tried and failed to pass a voluntary labeling bill earlier on in 2016. Proponents of labeling and Vermont's law were quick to express their disappointment. The bill imposes no penalties or fines for non-compliance, and it may leave many genetically engineered ingredients exempt from labeling requirements (Strom, 2016).

Both Republicans and Democrats expect the bill to get final approval in the Senate. How it fares in the House of Representatives, which in 2015 voted in favour of a voluntary labeling system, remained to be seen. The Vermont law requires a plain language statement on the package of food itself. The Senate bill allows companies to choose from three options for telling the consumers about the presence of GMOs in their products: a statement on the package, direction to a website or phone number, or a QR code, also known as a quick response code. People can scan the code with their smartphone to obtain a variety of information about a product. Proponents of labeling insisted that nothing short of text on packages would do (Strom, 2016).

The bill states that foodstuffs requiring labeling must "contain genetic material that has been modified through *in vitro* recombinant DNA techniques" and be modified in a way that could not be replicated through conventional breeding. The Food and Drug Administration (US FDA) which oversees most food labeling in the United States, said such language would exempt foodstuffs containing oils and sweeteners that, after being processed, no longer contain any genetic trace of the genetically modified crop they came from. On the Senate floor on Wednesday 6 July 2016 Senator Debbie Stabenow, a Democrat from Michigan who helped write the bill, dismissed the FDA interpretation, noting that the Agency has long opposed GMO labeling on the ground that genetically engineered foods are safe for human and animal health (Strom, 2016).

Finally President Barack Obama signed what was considered the weakest labeling law imaginable, according to Mark Bittman, a fellow at the Union of Concerned Scientists and a former columnist for the New York Times. And to most of the food movement, this felt like a loss (Bittman, 2016). The compromise on GMO labeling was forced by Vermont's passage of its own stricter labeling law (now rendered null by the federal law), which would have spread to other States. The new law mandates that the US Department of Agriculture define what constitutes a genetically modified food ingredient and then requires food manufacturers to label products that contain them. Disappointment among labeling proponents stems from the latitude the law gives food companies in how labeling is done (Bittman, 2016).

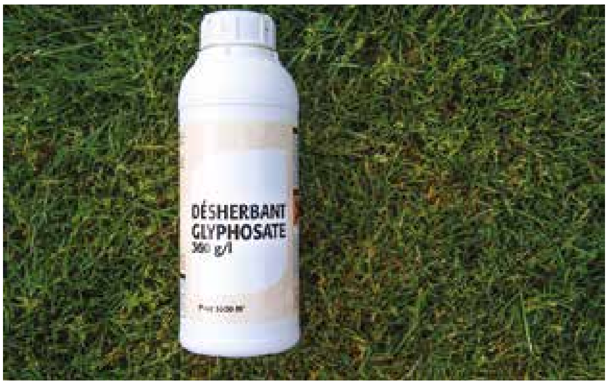
M. Bittman said: "We were long overdue for a transparency revolution… Of course, there is much more we could know about our food than whether it was genetically engineered. Now that we are "allowed" to know about GMOs, there are some other questions about the food that we buy that we might like answered. For example: Where are the ingredients from? Were antibiotics routinely administered to animals? What pesticides and other chemicals were used, and do traces of these chemicals remain? Was animal welfare considered, and how? What farming practices were used? How much water was required? And so on… But now that the new labeling law has opened in the disclosure door a crack, why not open it wide and see what is inside?" (Bittman, 2016). He thinks that even though an estimated one-third of adults in the United States do not have a smartphone to obtain information on product bar codes, the potential for educating the public about the food they eat is almost unlimited; and companies that are doing things well should seize the chance to put whatever they can on the package, and a bar code to provide even more data (Bittman, 2016).

We can therefore conclude that the bill passed and signed by the president will still have detractors that could challenge it. At the State level the Vermont's example could be followed, but there may be States that would oppose labeling on the same basis as the FDA. And what about the new generation of genetically improved crops that do not need a transfer of a gene (transgenesis) for their genetic transformation (through genome-editing techniques like CRISPR-Cas9)? Should we call them transgenic while the genetic transformation takes place inside their genome, e.g. for silencing a gene or overexpressing another one? Ornamental-plant growers already use this kind of technique with a view to obtaining different kinds of colours or a longer shelf-life.

The controversy about glyphosate

Invented in 1970 by Monsanto Co. and whose patent has expired in 1991, it is the most widely used herbicide in the world, sprayed on farms, in forests, on roadsides and in gardens. Having become generic, glyphosate is considered a "behemoth" of the phytosanitary industry. It is not only part of Monsanto's Roundup, but it is an ingredient of *ca.* 750 products, commercialized by more than 90 manufacturers in about 20 countries. Glyphosate which is the active ingredient of Monsanto's Roundup herbicide is associated with other chemicals and commercialized as what the agrochemists call ''formulated products.'' These associated substances or compounds facilitate the penetration of glyphosate into plant tissues and their destruction. Without these "surfactants" glyphosate will have no action.

The use of glyphosate soared in the last two decades because of Monsanto's genetically engineered crops, called Roundup Ready, which now account for the vast majority of maize and soybeans in the United States, but also in Argentina and Brazil. These crops, according to data provided by the industry, have been genetically modified to withstand glyphosate, allowing farmers to spray their fields to kill weeds without harming the crops. It was estimated that 80% of herbicide-tolerant crop species or varieties could withstand glyphosate. Consequently global production of the herbicide soared from 600,000 tons in 2008 to 650,000 tons in 2011 and 720,000 tons in 2012, according to the International Centre for Research on Cancer (CIRC, French acronym). In the United States the quantities sprayed have been multiplied by 20 in two decades, from 4,000 tons per year in 1987 to 80,000 tons per year in 2007. In France *ca*. 8,000 tons were sprayed per year (Pollack, 2015; Foucart, 2015b).



In 2011 a study published by *Environmental Toxicology and Chemistry* the US Geological Survey announced it had detected glyphosate in three-quarters of samples of rainwater and air collected in a region of large-scale agriculture. It is also the mostly detected herbicide (along with its degradation product, AMPA) in the rivers of France (Foucart, 2015b). In 1985 in the United States an Environmental Protection Agency committee determined that the popular weedkiller Roundup might cause cancer. Six years later, in 1991, the agency reversed itself after reevaluating the mouse study that had become the basis for the original conclusion. In 2015 the issue was back, in an even bigger way. In a four-page article published on the 20 March 2015 issue of *Lancet Oncology*, signed by the working group in charge of monographs at the International Centre for Research on Cancer (CIRC), it was announced that the World Health Organization (WHO) declared that glyphosate "probably" caused cancer in people. One piece of evidence cited was the same mouse study. The 17 scientists of 11 nationalities that were convened by the CIRC to make that evaluation provoked an angry response from Monsanto which qualified the WHO conclusion as "junk science" and accused the international agency of having "an agenda" and "cherry-picking" the data to support its case. Monsanto requested the director-general of WHO, Margaret Chan, to "rectify" the classification of glyphosate as a "probable" cause of cancer (Pollack, 2015; Foucart, 2015b).

The new controversy and the reversal by the US Environmental Protection Agency more than thirty years ago demonstrate how the same data can be interpreted differently – and how complicated and politically fraught such a decision can be. But the discrepancy between Monsanto and the CIRC/WHO can be partly explained by the specific way the agency analyzed the data. The CIRC stated they had no agenda other than to inform the World Health Organization. It said the conclusions were based on studies of people, laboratory animals and cells (Pollack, 2015). This announcement could shatter the whole agrobiotechnology because the exponential development of glyphosate was based on the idea that this herbicide was almost completely innocuous for humans. Monsanto executives stated at the end of March 2015 that they did not expect the announcement by CIRC/WHO to affect sales. But that could depend on whether regulators around the world impose restrictions on glyphosate use, following the international agency's pronouncement. A spokesman for the California Office of Environmental Health Hazard Assessment stated that the office was evaluating whether products containing glyphosate might have to be labeled as having a cancer hazard under the State's Proposition 65 (Pollack, 2015).

At the European level the European Commission was expected to authorize or not the glyphosate for the next ten years, by the end of 2015 (see below). The German Federal Institute for Risk Evaluation (Bundesinstitut für Risikobewertung or BfR) delivered in 2014 a report to the European Food Safety Authority (EFSA) that discarded any carcinogenic potential of the herbicide and even proposed to heighten by 60% the present threshold level of safety! The EFSA was expected to review the preliminary version of the BfR report and thereafter send a positive advice to the European Commission. The pronouncement of the CIRC/WHO has shattered all this procedure. In France the ministry of ecology has requested on 8 April 2015 the National Agency for the Sanitary Safety of Food, Environment and Work (ANSES, French acronym), to evaluate that pronouncement. An urgent decision was made to request four French experts to proceed immediately with an assessment of the divergent conclusions of the CIRC/WHO and of the German BfR. The latter has updated its reevaluation taking into account the conclusion of the CIRC and was expected to deliver it to the EFSA before the end of 2015. Regarding EFSA which has been often criticized for its positions showing some kind of conflicts of interest, it has tried to be fair by announcing it would consult with all the European safety agencies (authorities) before making a pronouncement (Foucart, 2015b).

Field spraying of glyphosate

Efforts have been made to try to find a compromise between the opinions of experts. At the EFSA it was stated that "One should understand that the pronouncement made by CIRC was not an evaluation of the risk. The CIRC said that glyphosate could be causing cancer probably, and not that it represents a risk of cancer for the whole population!" However the CIRC and BfR do not agree on the properties of the compound. In a preliminary report the BfR made a judgment that "an appropriate sample of studies *in vitro* and *in vivo* did not give significant results about the genotoxicity of the herbicide," while the CIRC estimated that the available data were "sufficient" to draw the conclusion that glyphosate could cause cancer. This conclusion was in particular based on a study carried out on village communities living in the high plateaux (*altiplano*) of Colombia: it was found that after spraying the glyphosate the percentage of abnormal lymphocytes increased markedly in the blood of those examined (Foucart, 2015b).

How to explain such divergences? "A first reason lies in the nature of studies carried out and examined by both groups of experts," explained Gérard Lasfargues, deputy director-general of the French ANSES. "The BfR had examined studies carried out by enterprises, which are not generally published because of industrial secret; this was not done by the CIRC." In fact the CIRC/WHO bases its pronouncement on the published findings or data, and on studies published in peer-reviewed journals. Several NGOs, including Greenpeace and the Corporate Europe Observatory (CEO), have strongly criticized the non-transparent evaluation of the BfR. Furthermore it seems that four experts out of the dozen who are members of the BfR Pesticides Committee were employed by agrochemical companies or by private laboratories having research contracts with these companies. By contrast the experts of the CIRC are selected because of their competence and expertise, and also because of the strict absence of conflicts of interest among them (Foucard, 2015a). This may explain the suspicions about the discrete influence of agrochemical or seed companies in tweaking the results of evaluation studies (see below).

Another reason of the divergence between the evaluations made by the CIRC and the BfR is more surprising according to S. Foucart (2015b). "The CIRC has involved in its evaluation epidemiological studies that were discarded by BfR," explained G. Lasfargues. "And the CIRC did so in order to take account of certain criteria, called "Klinisch criteria," which evaluate the value of these studies. But what is questionable is that these criteria apply to toxicological studies and not to epidemiological studies, and we do not know how these criteria have been eventually adapted." The fact is that several of these epidemiological studies, examined by the CIRC, suggest an increased risk of non-Hodgkin's lymphoma (NHL) – a blood cancer – among agricultural workers exposed to glyphosate. It should be born in mind that, according to a French epidemiologist, "the results of the large prospective study on the health of agricultural workers (called Agricultural Health Study, carried out in Iowa and North Carolina, in the United States) did not indicate an association between exposure to glyphosate and this blood cancer (NHL)"[Foucart, 2015b].

Still in Europe a scientific working group appointed by the French National Institute for Health and Medical Research (INSERM, French acronym) had concluded from a study carried out in 2013 on the effects of pesticides on health, that glyphosate was genotoxic, and it suspected its association with NHL, as did the CIRC. On the other hand, in its press release on 23 March 2015, Monsanto highlighted that the FAO/ WHO Joint Meeting on Pesticides Residues (JMPR) had in its last pronouncement discarded any carcinogenic potential of glyphosate. It was confusion galore because two groups belonging to WHO (CIRC and JMPR) arrived at two opposite conclusions. A third group of experts was convened by WHO on an urgent basis and in September 2015 it released its audit where it criticizes the JMPR, who did not take into account several studies published in the scientific literature and useful data, as did the CIRC. The JMPR has been requesting "to proceed to a complete reevaluation of the effect of glyphosate." Opponents of GM crops (including Friends of the Earth, National Resources Defense Council) have seized these findings to highlight the conflicts of interest among four of the JMPR's eight experts who work with the agrochemical industry (Foucart, 2015b).

It should be mentioned that both the regulations in Europe and the United States do not require agrochemical companies who sell ''formulated products'' containing glyphosate (including Monsanto's Roundup) to evaluate the long-term effects on health of the chemical compounds associated with glyphosate. Many toxicologists suspect that these effects, if evaluated properly, might be linked to the ''probable'' genotoxicity of glyphosate-containing herbicides (Foucart and Morel, 2017d).

Dispute about the link of glyphosate to cancer in the United States

On 27 March 2015 some consumers and environmental groups urged the Environmental Protection Agency (EPA) to revisit its recent approval of a pesticide from Dow Chemical that combines glyphosate and another herbicide, 2,4-D. Regarding the pronouncement of the CIRC/WHO it was highlighted that this international agency looks at a very narrow question – whether a substance or behaviour might cause cancer under some circumstances, even if those circumstances might be unlikely to occur. It does not weigh the benefit versus the risks of a chemical, leaving that up to national regulators. Kathryn Z. Guyton, a senior toxicologist at the CIRC, said the reviews made by her agency considered only studies published in journals or government documents that are publicly available. That typically excludes many studies done by chemical companies to get their compound approved by regulators. In the paper published in *The Lancet Oncology* on 20 March 2015 the reviewers cited studies from the United States, Canada and Sweden, suggesting that farm workers exposed to glyphosate had a high incidence of non-Hodgkin's lymphoma (NHL), even after correcting for exposure to other chemicals (Pollack, 2015). But, as mentioned above, the Agricultural Health Study did not find any problems. Philip Miller, Monsanto's vice-president for global regulatory affairs, accused the CIRC of "disregarding" this study, which is clearly mentioned in *The Lancet Oncology* article. K. Z. Guyton said because of that study, the reviewers had concluded that there was only "limited" evidence from human studies that glyphosate could cause cancer (Pollack, 2015).

There are several ways to measure a possible effect. Are there more cancers in animals exposed to the chemical than in a control group? Do higher doses mean more cancers? Are the rates higher than expected based on historical data? In many studies not all three measures are positive. Take the mouse study at issue in the EPA review more than 30 years ago and also cited by the CIRC. There were three cases of a rare type of kidney cancer in 50 male mice fed the highest dose of the chemical. While the CIRC/WHO reviewers focused on the rise in cancer with dose, the EPA reviewers in 1991 said the findings were not meaningful, in part because there was no significant statistical difference overall between the exposed mice and the control group (Pollak, 2015). Another finding cited by the CIRC was an increased rate of hemangiosarcoma, a cancer of the blood vessels, in male mice, as discussed in a document issued by the WHO and the FAO in 2004. But the authors of that document dismissed the significance of the finding and stated the study had "produced no signs of carcinogenic potential at any dose." Another sign of whether something can cause cancer is whether it causes mutations or chromosomal damage. Bacterial tests did not show that glyphosate caused mutations. However the CIRC reviewers said there is evidence of chromosomal damage in studies involving animal and human cells (Pollack, 2015).

The regulatory toxicological tests generally evaluate the effect of the active principle or ingredient of a pesticide (glyphosate). But that pesticide is commercialized as a mixture with surfactants, which enables it to enter the cells and thereby to increase its effect. It is not therefore easy to differentiate between the two kinds of studies, and this may explain why glyphosate by itself is not carcinogenic. Regarding its neurotoxicity, Philippe Grandjean, professor at Harvard University, claimed that this has been demonstrated in studies carried out on animals and also on humans in case of acute intoxication. Ph. Grandjean, who has been a pioneer in the study of the effect of environmental pollutants on the central nervous system, reckons that it is difficult to know the rate of exposure to glyphosate when these deleterious effects appear. There has been, according to him, no study carried out using the regulatory standards with a view to evaluating the effects of glyphosate on neurodevelopment, while it is the currently-mostly used pesticide in the world (Foucart, 2015b).

On 27 November 2017 the *Journal of the National Cancer Institute (JNCI)* published the data of a large epidemiological research aimed at showing the impacts of pesticides on farmers and agricultural labourers. The main result of this Agricultural Health Study (AHS) was the absence of association between the use of glyphosate with "solid" cancers, nor with non-Hodgkinian lymphomas (blood cancers), by contrast with the results of previous studies on the effects of glyphosate. Such study may add confusion to the controversial debate on glyphosate. Nonetheless the AHS shows that there may be a link between the use of the herbicide and acute myeloid leukemia – this possible relationship was not detected up to now. Among the most exposed users of glyphosate, the risk to develop such a leukemia was more than twice the risk of non-exposed persons. But the relationship was statistically significant only for those using the herbicide for at least 20 years (Foucart, 2017b).

The researchers of the National Cancer Institute, led by Gabriella Andreotti and Laura Beane, have analyzed the latest data derived from the monitoring of a group of more than 50,000 agricultural workers, that had been recruited in Iowa and North Carolina at the beginning of the 1990s. The AHS was therefore based on one of the largest cohorts of agricultural workers followed through the world (Foucart, 2017c).

The CIRC/WHO considered that the results of the AHS were not sufficient to contradict other epidemiological studies carried out in several countries that show the relationship between the use of glyphosate and cancer. In addition to the AHS another large epidemiological study – the North American Pooled Project (NAPP) – was being finalized. This project that was carried out by some of the scientists involved in the AHS, consisted of collecting and analyzing all the data of studies called "test cases" and conducted in North America on the relationship between the use of glyphosate and cancer. The preliminary results of the NAPP, announced during conferences, contradicted those of the AHS : they indicate the doubling of the risk of non-Hodgkinian cancer among those persons who had been in contact with glyphosate more than two days a year (Foucart, 2017b).

Why this contradiction? In a report prepared at the request by the plaintiffs of a class action launched in the United States against Monsanto, Beate Ritz, vice-president of the University of California, Los Angeles (UCLA) department of epidemiology, highlighted that "there has been a very large increase in the use of glyphosate and in the exposure to that substance since the mid-1990s." In fact the cultivation, as of 1996, of genetically modified crops, tolerant to glyphosate and called Roundup Ready, had resulted in the increase of spraying glyphosate from 5,700 tons in 1990 to about 45,000 tons in 2000 and to more than 125,000 tons in 2017. Such a massive use had led to an overall exposure of the American population to the herbicide, and obviously of the cohort of agricultural workers. Under these conditions how to make sure that the most exposed workers had been discriminated from the lesser exposed ones? (Foucart, 2017b)

Another potential bias of the AHS concerns the fact that the use of protecting equipments (e.g. gloves and protecting dress) was taken account of and it was concluded that these equipments reduced by 60% the exposure to glyphosate. However, according to a French scientist, Alain Garrigou – one of the rare specialists of the subject – "these equipments do not necessarily protect against the use of pesticides, and it may be the reverse ... This will depend on the material making up the equipment and on the pesticide being used" (Foucart, 2017b).

As we can see the debate is not over both in the United States and in the rest of the world – particularly Europe – and more independent research is certainly needed, as well as an accurate analysis of the results obtained.

What is at stake?

Sylvie Bonny, a researcher at the French National Agricultural Research Institute (INRA, French acronym), drew the following conclusion at the end of an important study published in *Environmental Management*: "During the first years of the introduction of GM crops (since 1996) tolerant to a herbicide, mainly Roundup or glyphosate, the use of herbicides was decreased.

However the extension of these herbicide-tolerant GM crops and the systematic sprays of glyphosate have contributed over the last ten years to the appearance of weeds resistant to the herbicide. Henceforth an increase in the use of glyphosate and of other herbicides." By early 2015, 14 herbicide-resistant weeds have been recorded in 38 States of the United States. It was not surprising to see that the quantity of weedkillers did increase with the spreading of new herbicide-resistant weeds. For instance in the case of soybeans the average quantity of herbicide sprayed rose from 1.35 kg per hectare in 1996 to slightly over 2 kg per hectare in 2012 (the areas of glyphosate-tolerant soybeans have amounted to 90% of the total surface of this crop since 2007). "It seems that the effect was less obvious with maize, because the adoption of herbicide-tolerant maize crops has been slower," according to S. Bonny (Foucart, 2015b).

But the environmental and sanitary impact of herbicides is not just due to the quantities sprayed. The French Association of Plant Biotechnology has estimated that the Roundup keeps "a better toxicological and eco-toxicological profile than most of the herbicides he replaces," that it is cheap and that it "facilitates the use of no-tillage-techniques." In the United States the control of new herbicide-resistant weeds by the agrochemical companies is to "pile-up" genes that made the crops more tolerant to other herbicides. Yves Dessaux, a researcher at the French National Scientific Research Center (CNRS, French acronym) Institute of Cell Integrative Biology, who co-lead in 2012 the evaluation by the CNRS and INRA of the benefit and risks of herbicide-tolerant crops, stated that "if these new crop varieties and herbicides associated with them were utilized like those tolerant to glyphosate, without rotation, without a better care regarding the dosage and without an agronomic vision, new herbicide-resistant weeds would be created and that would become a very serious situation" (Foucart, 2015b).

The response of the European Food Safety Authority (EFSA)

If glyphosate could cause cancer, this would undermine the sales of glyphosate-tolerant crops and would be a serious threat to the whole agrobiotechnology. And as mentioned above opponents of genetically modified crops had immediately argued for more restrictions on glyphosate. Therefore the pronouncement by the European Food Safety Authority (EFSA) was expected by the bioindustry and by consumer and environmental associations.

On Thursday 12 November 2015 the EFSA issued its pronouncement which was to continue to use glyphosate. This would help the European Commission to authorize for another ten years (or less) the cultivation of the crops genetically modified to tolerate this herbicide (Roundup). The EFSA has estimated that it was "improbable" that "glyphosate could be genotoxic (i.e. toxic for DNA) or that it could threaten human health." That pronouncement was angrily welcomed by many NGOs. Greenpeace in particular declared: "The European law predicts that a "likely" link with cancer means that a herbicide cannot be used, except when the exposure of humans to that pesticide is demonstrated to be "negligible". In the case of glyphosate which is so widely used, human exposure is unavoidable. The compound is often detected in the air, in water, in public gardens, on agricultural land and in food." Despite the strong reaction of NGOs the pure and simple withdrawal of the glyphosate does not seem possible, according to S. Foucart (2015c).

S. Foucart in his article published by *Le Monde* on 14 November 2015 quoted the opinion of Christopher Portier, former director of the National Centre for Environmental Health of the CDCs (Centers for Disease Control and Prevention, Atlanta, Georgia) who contradicted the EFSA's pronouncement and criticized the "cherry-picking" approach of the European Agency in eliminating several studies that showed the genotoxicity and carcinogenic effect of glyphosate or products containing it. For C. Portier, the EFSA's pronouncement should be revised, but one must recognize that this battle between toxicological experts, despite the virulence of the arguments on both sides, is not well perceived by non-experts. And although S. Foucart (2015c) seems to agree with the opponents of the EFSA's pronouncement, it is not so easy to make one's opinion. Certainly more research is needed as well as rigorous standards should be applied. And a similar careful approach is recommended when one deals with the role of agrochemical and seed companies in making decisions about the authorization of these products. Nobody could deny the lobbying made by these companies, but this should not be overestimated.

How close are the relations between scientists and experts with agrochemical companies?

On 5 September 2015 the *New York Times* published the correspondence between university people – agronomists, biologists and other scientists – and some executives of agrochemical companies or with Ketchum, the public-relations company that represents the interests of Monsanto, Bayer, Dow Chemical, DuPont, etc. The published e-mails show how the agrochemical firms use the expertise, credibility and authority of scientists from the academic world in the war with their competitors. The major part of the correspondence published was obtained by the association US Right To Know (USRTK), thanks to a disposal of the American bill on the access to administrative documents (Freedom of Information Act, FOIA). The USRTK requested 43 public universities to transmit any internal documentation – including the e-mails of scientific staff – that contain the terms "Monsanto", "genetically modified crops" or "Ketchum", etc. When the article was published in the *New York Times*, only nine universities had transmitted the data requested by USRTK (Foucart, 2015a).

Kevin Folta, a molecular biologist and professor at the University of Florida, is among the scientists incriminated in this kind of lobbying; his correspondence with executives of Monsanto and Ketchum shows that "he has rapidly become a member of a consultant group (lobbyists) who work on a strategy designed to impede certain American States to apply mandatory labeling of GMOs, and more recently to help the United States Congress to block any kind of legislation in this respect," according to the *New York Times*. S. Foucart (2015a) added that K. Folta travelled to Pennsylvania and to Hawaii in order to respond to audits on this subject requested by the local authorities. He regularly informed the industry about his activities and his expenses were taken care of. He was requested to respond to questions raised by Internet users and to publish his answers on GMOAnswers.com, an Internet site administered by Ketchum. In August 2014, Monsanto decided to transfer to him US$25,000 in order to pursue its lobbying work. "I promise you a solid return on investment," he wrote to Monsanto's executives (Foucart, 2015a). But K. Folta responded on his blog that he never said or wrote anything that was not founded on evidence. He even stated that his opinion in favour of plant biotechnologies was anterior to his contacts with the industry.

S. Foucart (2015a) also tells about the story of David Shaw, vice-president for research and economic development of the University of Mississippi, whose e-mails have been recovered by USRTK. During the last decade his research work was financed by Monsanto up to US$880,000 (or €785,000). Furthermore his correspondence showed that the firm of Creve Coeur (Missouri) requested him, in June 2013, to testify before the American agriculture ministry in favour of the authorization for large-scale cultivation of new GM crops of cotton and soybeans tolerant to herbicides. Dow Chemical made a similar request for another GM crop. Both Monsanto and Dow Chemical have seen their products approved by the regulation authorities. What was the exact role of D. Shaw? S. Foucart does not give a clearcut answer because D. Shaw did not respond to the request of an interview with *Le Monde*.

The story does not end there. Bruce Chassy, a professor of human nutrition at the University of Illinois, had also received from Monsanto a subsidy to promote plant biotechnology. He may have been involved, according to the correspondence he had with Monsanto's executives, in lobbying the Environmental Protection Agency (US EPA) not to pursue a project aimed at restricting the use of pesticides. Bruce Chassy reacted to *Le Monde*'s journalist by saying: "It is a witch hunt…" "They explore our relations with the industry because they cannot contest the truth of our arguments." "It was the support given by the industry to my university which enabled me to express my academic freedom" (Foucart, 2015a). He may be right: in the United States and elsewhere the funding by the industry of biological (or other kind of) research is common, and once again the truth is often not on one side.

The New York Times requested several public universities to deliver their eventual relationships with the industry regarding organic agriculture. This was done on purpose because USRTK focused on plant biotechnology and not so much on organic agriculture (because it is mainly financed by the latter). The American newspaper summarized that these relationships exist, even though the expenses made on lobbying and public relations by organic agriculture are just a small percentage of those devoted to biotechnology companies. "For instance, Charles Benbrook, an agronomist, who was working at the Washington State University, has been in close contact with Stonyfield Farm, Whole Foods, Organic Valley and United Natural Foods. His correspondence with these companies highlighted their interest in having a scientist from the academic world to underline the benefits of organic agriculture, but also the risks associated with GM crops. C. Benbrook did therefore make a strong plea in favour of mandatory GMO labeling in foodstuffs as well as against the authorization of new crop varieties tolerant to herbicides. He did so in the scientific press but also before regulation authorities. In an editorial published in August 2015 in the New England Journal of Medicine he omitted to mention its links with organic agriculture companies, but later on he corrected his declaration of interests (Foucart, 2015a).

The potential role of Monsanto in the retraction of Eric Séralini's study from the journal *Food and Chemical Toxicology*

This study was published by the journal *FCT* in September 2012, and thereafter withdrawn (retracted) in November 2013, on the basis of many flaws in methodological approaches. The study aimed to demonstrate the toxicity of transgenic maize variety NK603 in rats fed with this crop, as well as the toxicity of the herbicide Roundup. Both the GM crop and the associated herbicide (to which the crop is tolerant) are produced by Monsanto. The American association US Right To Know (USRTK) which is fighting for the mandatory labeling of GMOs, was able to have access to the correspondence between Monsanto and one of the editors of *FCT*, on the basis of the bill FOIA, with a view to revealing the influence of agrochemical companies on the opinion of scientists from the academic world. S. Foucart (2016) who narrates the story in the 13 July 2016 issue of the French daily newspaper *Le Monde*, starts by saying that there is no question to come back to the serious criticisms that explained the retraction of Eric Séralini's (University of Caen) publication from *FCT*. This study was the first to be withdrawn because it was "inconclusive". As a reaction, the supporters of the French biologist put in question – without evidence – the role of a newcomer to the editorial board of the journal, in charge of biotechnology: Richard Goodman, a professor at the University of Nebraska (Lincoln) and specialist of food allergens, was a former employee of Monsanto which he left in 2004. In a message written by himself, R. Goodman recognized that "50% of his salary" came from a research project funded by Monsanto, Bayer, BASF, Dow Chemical, DuPont and Syngenta, and consisting of selling up a database of food allergens.

In May 2012, after the publication of a press article where he was quoted, R. Goodman, who was not member of the editorial board of *FCT*, was bluntly recalled by Monsanto that his opinion was interpreted by the journalist interviewing him as meaning "that we did not know enough on biotechnologies and we cannot therefore state that they are without danger." R. Goodman reacted by writing a collective message to all his correspondents in the six agrobiotechnology companies that funded his own research, in order to excuse himself and to explain that his statements were misunderstood by the journalist. Stéphane Foucart (2016) goes on in his article by mentioning that in August 2012 R. Goodman warned his sponsors that he was going to be interviewed by the American public radio on the safety of GMOs. In this case, there were no ruffled feathers.

In 2012, when E. Séralini's publication appeared in *FCT*, R. Goodman was not yet a member of the editorial board of the journal. On 19 September 2012, he informed his correspondent at Monsanto of the publication of the French researcher and wondered whether Monsanto could provide him with critical elements. A few days later, R. Goodman was appointed as "associate editor" of the *FCT*, upon the decision of Wallace Hayes, a toxicologist and at that time editor in chief of the journal. But this decision was not made public before February 2013. S. Foucart (2016) claimed that the recruitment of R. Goodman in the editorial board of the journal was the direct and immediate consequence of E. Séralini's publication. In November 2012, when such a publication drew so much attention and controversy (see Sasson, 2013, pp. 329-397), W. Hayes e-mailed to Monsanto's executives that R. Goodman was from now on responsible for biotechnology in the review. And he added: "My request, in my quality of editor in chief of the journal, as well as on behalf of Professor R. Goodman, is to ask those of you who are very critical about E. Séralini's and his co-authors' article to volunteer as potential reviewers. S. Foucart (2016) cannot say whether this message was sent only to Monsanto, or to the other firms – W. Hayes did not wish to elaborate on this aspect. However the documents consulted by the USRTK and by *Le Monde* do not lead to believe that R. Goodman had played a role in the withdrawal of E. Séralini's paper. That was a decision made by W. Hayes. In January 2015 R. Goodman announced that he decided to leave FCT because of lack of time (Foucart, 2016).

What all this means? That there may be conflicts of interest which are not declared; that agrochemical and seed companies have an obvious power of lobbying, and that they use it versus scientists from the academic world as well as politicians (including the United States Congress); that there exist some non-ethical behaviours that must be denounced; but also there is no doubt that the scientists from the public academic institutions do their work correctly and behave in an ethical way in most cases. S. Foucart, as an experienced scientific journalist, has always been interested in this aspect of scientific life and he is perfectly right to denounce what should be denounced; but he sometimes, perhaps because of lack of space in his journal, does not treat all the actors involved in an equal way, and in my opinion reading carefully his articles leaves one with the feeling that he is not pro-GMO, to say the least. He published, with Stephane Horel, in the French daily newspaper *Le Monde*, a series of articles on "Monsanto Papers" in order to demonstrate how the agrochemical company had been trying through all means to destroy the credibility of the International Center for Research on Cancer (CIRC) which stated that glyphosate may be carcinogenic (Foucart and Horel, 2017a,b,c). The so-called "Monsanto papers" are internal documents of Monsanto (several thousand pages) that were made public since the early summer of 2017, because of a class action against the company in the United States (almost 3,500 plaintiffs). See also Foucart and Horel (2017c,d).

Europe divided about the cultivation of present GM crops and of new ones

In the **United Kingdom**, on 9 August 2015, the Scottish administration in charge of agriculture and environment announced it wanted to prohibit the cultivation of GM crops in Scotland. Such a prohibition would not apply to laboratories or to closed greenhouses in order to allow scientific studies. By doing so Scotland confirmed the moratorium it has been following for several years regarding the non-cultivation of GM crops on its territory. Richard Lochhead, minister for rural affairs and environment, stated that "the prohibition of such crops would protect and develop our reputation of being a clean and green country." He even added: "We have not the proof that Scottish consumers are willing to adopt such products, but I am worried that authorizing the cultivation of GM crops would harm the sector of food and beverages whose value is estimated at €19 billion" (Albert, 2015).

As the regulation on GMOs is managed at the European level, Scotland must formally make a request to the European Commission regarding the prohibition of these crops. But as the European Commission does deal with the member countries themselves and not with their regions, Scotland had to go through the United Kingdom's government, which is much more positive about the adoption of GM crops. This was due to Owen Paterson, the British minister for rural affairs and environment from 2012 to 2014. He thought that the opposition of the large public to this technology – including in the United Kingdom – was "a complete non sense." When he was appointed minister, he was very upset by the European opposition to GM crops. In order to authorize the cultivation of these crops, a qualified majority was needed among the members of the European Union; but the opponents of this cultivation (19, including France) were systematically against it. The overall result is that one single variety of maize, the pest-resistant Monsanto's MON810, is cultivated mainly in Spain as feed (and not for human consumption) on *ca*. 117,000 hectares in 2015 (Albert, 2015).

In order to find a by-way meant to solve the problem, the British minister imagined that part of the responsibility in this area be transferred from the European Commission to member states. This meant that each GMO would always require the favourable opinion of the European Food Safety Authority (EFSA), but afterwards, there was no need for a qualified majority in order to approve the cultivation of the GM crop; each country would decide about what to do on his territory. However O. Paterson was willing to offer to the opponents of this cultivation the possibility of enjoying the right of formal prohibition, which was legally more solid than the various moratoria applied in various countries. O. Paterson had to leave the British government for political reasons during the summer of 2014, but his approach was approved: in April 2015 new European rules were in place; the member states were requested before the 2nd of October 2015 to state if they wanted to be on the list of antiGMOs. Scotland was among the first to request to be on that list (Albert, 2015).

Meanwhile, on the English side the United Kingdom's government wanted to prepare the ground for the adoption of GM crops. A spokesperson of the rural affairs ministry confirmed that: "We support the opportunities that these GM crops can offer to British enterprises, to consumers and to the environment." But it was announced that the first crops will have to wait a few years before being cultivated, because the eight GMOs presently studied by the European Commission were not adapted to the British climate. However Helen Wallace of GeneWatch, an NGO opposing GM crops, stated that "the first crops would be grown in England as of 2017." She was fearing that a transgenic potato variety would be soon presented to the European food safety authorities and that the British government would be willing to grow it. For Pat Thomas of the association Beyond GM this would raise a serious risk of contamination of non-transgenic crops, including in Scotland. Pat Thomas was confident that the cultivation of these crops could be prohibited in England, because the public opinion is against it: a poll made in 2014 indicated that 40% of the people interviewed were against their cultivation and 22% were in favour. She concluded by stating that "there was still a chance to block their development in England" (Albert, 2015).

In **France**, the maize variety MON810, whose cultivation has been authorized by the European Commission since 22 April 1998, the agriculture minister made another decision on March 2014 to prohibit the cultivation of this transgenic variety across the French territory. He based his decision on the European legislation enabling member states of the European Union to prohibit the cultivation of a GM crop further to environmental and safety risks. This decision was attacked by farmers and several organizations of seed producers and growers of maize, which requested the advice of the State Council. The latter cancelled the minister's decision on 15 April 2016, arguing that there was not "an important risk that threatens human health, animal health or the environment." The State Council admitted that there could be a risk of development of resistance among pests (insects) or reduction of the population size of some butterfly species, as the European Food Agency Authority (EFSA) recalled. But these risks could be mastered according to the French State Council. Finally, according to the EFSA, the maize variety MON810 was not more harmful for the environment than conventional maize (Garric and Le Hir, 2016).

The State Council has therefore cancelled the minister's decision made in 2014, as he did previously with the moratoria imposed on MON810 in 2008 and 2012. This was considered a victory by the seed growers who complained about the new moratorium. But this will not mean that MON810 will be cultivated in France. The agriculture ministry insisted on the fact that "MON810 was still prohibited in France. We are opposed to these transgenic crops, which are associated with undeniable risks and do not bring in any benefit that it is worth to take these risks." Since the law of 2 June 2014 the cultivation of transgenic maize crop varieties has been prohibited across France. The European directive of April 2015 gives the right to any member state not to cultivate even a transgenic that was validated by the EFSA, for various reasons: agricultural policy, land management and socio-economic implications. In September 2015 France requested, along with 18 other member states, that another nine GM maize varieties, already authorized or in the process of validation, be excluded from his territory. In March 2016 the European Commission agreed to France's request. Luc Esprit, director of the National Federation for the Production of Maize and Sorghum Seed Producers, stated: "There will not be GM maize in France. The cancellation by the State Council of the minister of agriculture's decision is a victory about principles, because the minister's decision has no scientific basis, but it is above all a political doctrine." Greenpeace, on its side, was already looking for another battle: "The danger nowadays comes from new GMOs derived from new advanced technologies, that the industrialists want to push through the present regulation caveats. That is the new challenge at the European level," stated Anaïs Fourest, in charge of agricultural issues at Greenpeace (Garric and Le Hir, 2016).

A more immediate concern for the French authorities was the renewal of glyphosate use for another ten years across the European Union and his territory as of the end of 2017. A vote of the EU member states, within the permanent committee for food chain and animal health, was expected before the end of 2017. "The European Commission would not try to authorize the use of the herbicide without the support of a qualified majority (that is the support of 55% of member states representing 65% of the European Union's population)," according to relevant sources in Brussels. While no date was agreed on for the votation, discussions were being carried out concerning the controversy on the potential of glyphosate to cause cancer in humans (Foucart, 2017).

The procedure of reauthorizing the use of glyphosate started in 2013 and it was derailed in March 2015 when the International Centre for Research on Cancer (CIRC) decided to classify glyphosate in the category of "probable carcinogenic" substances. By so doing the international United Nations agency was contradicting the evaluations made by the European competent institutions (Foucart, 2017).

Due to this divergence, the European member states did not find an agreement on the future use of glyphosate. Already in 2016 France and Malta voted against this use, which another seven member states – including Germany and Italy – abstained. During the summer of 2016 a provisional authorization was delivered for only 18 months, i.e. till the end of 2017, so as to make a final decision at that time and rule about the controversy on the "probable carcinogenic" herbicide. It is true that this controversy became a polemic issue, due to divergent views of the experts belonging to the CIRC and those of European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA). While the latter decided that the glyphosate was not carcinogenic, the former maintained their position. Several scientists across the world supported this position (CIRC), while denouncing the excessive trust of European agencies versus the data provided by the platform of agrochemists that commercialize glyphosate-based products (Foucart, 2017).

In July, 2017 the non-governmental organization (NGO) Global 2000 published a report by the German toxicologist Peter Clausing, who accused the European agencies for not having their own working rules in the evaluation of experts' data. It should be recalled that in February 2017 several NGOs had launched a " European Citizen Initiative (ECI)" against the renewal of glyphosate use. Such an action, that is foreseen in the European regulation, should collect at least 1 million signatures – checked by the EU institutions – in order to be taken into consideration. But in six months the coalition of NGOs collected already 1.3 million signatures (Foucart, 2017).

In France the ministry of ecological and solidary transition (*Ministère de la transition écologique et solidaire*) announced by early September that the government was opposed to the reauthorization of glyphosate use, "due to the uncertainties relating to its toxicity." Such a position was greeted by environmental protection associations, while it was strongly opposed by the National Federation of Farmers' Trade Unions (FNSEA, French acronym for the Fédération nationale des syndicats d'exploitants agricoles). In a press release dated 30 August 2017 it stated "the reasonable use of glyphosate was necessary for the development of "good agricultural practices including agroecology, agroforestry and conservation agriculture." According to the FNSEA, "in the absence of alternative solutions, the prohibition of glyphosate use would destroy the efforts carried out by French farmers for years, their research-and-development tools, as well as a whole chain of progress which plays a key role in the ecological transition that the French society is longing for." The FNSEA did organize protests on Paris' most prestigious avenue, the Champs Elysées (Foucart, 2017).

For the chemical industry the prohibition of glyphosate use would have deleterious consequences, because it would in the end question the economic model of Monsanto, based on the sale of glyphosate associated with that of genetically-modified (transgenic) seeds of crop varieties tolerant to the herbicide. It might even threaten the alliance between Monsanto and Bayer who devoted *ca*. €59 million to acquire the Saint-Louis, Missouri-based agrochemical company (Foucart, 2017, see pp.19-23).

Finally, after two years of polemics and controversies – during which the International Centre for Research on Cancer (CIRC) associated with the World Health Organization (WHO) which reached the conclusion that glyphosate may cause cancer, on the one hand, and on the other the European expertise agencies which reached an opposite conclusion and of which their independence have been questioned several times – the European Commission, on Monday 27 November 2017, decided to authorize the use of glyphosate for another five years as of the beginning of 2018. The decision was made at the appeals committee when the qualified majority was reached, i.e. 18 member states making up 65.71% of the European population voted in favour of the reauthorization. The minimum required was at least 65% of the European population. Such result was unexpected with regard to the previous positions of a number of member states. Poland and above all Germany (16.06 of the European population) voted in favour of the reauthorization for five years, while they abstained to do so during the previous meeting (Foucart and Horel, 2017e).

In Berlin the approval of the use of glyphosate for another five years created a rift within the German government between the agriculture ministry, Christian Schmidt (CSU, conservative from Bavaria), and the environment ministry, the social-democrat Barbara Hendricks (SPD). France maintained its former rejection to the European Commission's proposal. President Emmanuel Macron stated in this regard: "I have requested the government to make all the necessary measures so that the use of glyphosate will be prohibited in France as soon as substitutes of this herbicide are found, and at least in three years." It should be recalled that the use of glyphosate had been prohibited since 1 January 2017 in public spaces, and this prohibition will become compulsory for all private users as of 1 January 2019. With regard to farmers, the French government can through its National Agency for the Security and Safety of Food, Environment and Work (ANSES, French acronym) forbid the use of all commercial formulations of glyphosate across the country. For instance, it had already prohibited almost all the formulations based on chlorpyriphos, an insecticide whose use is authorized throughout Europe (Foucart and Horel, 2017e).

Once again the director-general of the NGO Health and Environment Alliance (HEAL), Genon Jensen, speaking on behalf of some 60 civil-society associations, trade-unions of health assistants or mutual organizations, stated: "The European expertise process has ignored the concerns firmly based about the impacts of glyphosate on health and will consequently cause damage on the image of the European Union, while defiance is already quite high." Also on the same wane, but by contrast to the environmental NGOs, the farmers were quite happy to see the issue resolved. According to the French FNSEA, "we take note of the five-year compromise which resulted from the pragmatic approach by a large proportion of the European member states and we deplore that France did not follow the same approach and decided to play its own game." This statement which immediately followed the vote by the European Commission, was ushered just before the declaration by the French president about getting out of glyphosate use in farming before three years (Foucart and Horel, 2017e).

New battles and polemics about new categories of GMOs

On Monday 22 February 2016 the French High Council for Biotechnology (HCB, French acronym) was in crisis: all the environmental protection associations – e.g. Friends of the Earth, Greenpeace, France Nature Environment, Confédération paysanne – which are members of the Council's economic, ethical and social committee (CEES, French acronym), decided to suspend their participation in the work of the council – an independent body created in 2009 and in charge of giving advice on any public decision regarding genetic engineering and GMOs. This resulted in depriving that committee of about one-fourth of its membership. The reason for this secession was an advice by the council's scientific committee (CS, French acronym), that was issued by early February 2016 about the new plant breeding techniques (NPBT) (Foucart, 2016).

According to the prevailing regulation only are considered transgenic plants or crops, those to which one or several genes are introduced; they are therefore submitted to a series of evaluations of the risks they can pose, as well as to traceability and labeling (according to the European Commission's directive 2001-18). But, thanks to the NPBT, it is possible to obtain genetically improved varieties of crop species with the same features (resistance to pests, tolerance to herbicides, heat tolerance, etc.), and which do escape the legal status of the usual GMOs. These

NPBT include, for instance, artificial mutations, the use of genome-editing techniques like CRISPR-Cas9, epigenetic methods which can overexpress or silence a gene, as well as cisgenesis which consists of integrating into a plant a gene belonging to a congeneric plant that can mate with it naturally. The seceding associations of the French High Council for Biotechnology's economic, ethical and social committee (CEES) stated that "the advice issued by the scientific committee omitted to mention the divergent opinion of one member of this committee." Having been made public on 16 December 2015, after discussion of the CS advice, the opinion of the opponent member was rejected. This was that of Yves Bertheau, director of research at the French National Agricultural Research Institute (INRA, French acronym), working at the French National Museum of Natural History (Foucart, 2016).

In 2013 a working group was formed by the HCB with a view to examining the role of the NPBT. According to Y. Bertheau, "the members of the council's scientific committee received a report on Friday 11 December 2015 by late afternoon, without annexes, to be discussed during the following five days, i.e. in a very short lapse of time. Furthermore the agenda of the meeting indicated that a "synthetic note was expected," and not a formal advice by the council to be transmitted to the government …" Y. Bertheau could not express his profound disagreement and had to resign from the committee. The seceding associations were of the opinion that the advice issued by the HCB was favourable to the agrochemical and seed companies, because the new genetically improved plants or crops may escape the present regulations regarding the approval of transgenic crops (which required the companies to fill up heavy files for authorization of the crops). The president of the HCB, Christine Noiville, estimated that the advice published was incomplete and a second part was expected before it could be quoted. The NGOs reacted by saying that it might be too late because the European Commission was expected soon to make a pronouncement about the NPBT and their implications before the end of 2017 (Foucart, 2016). So the HCB was in complete disarray according to some analysts, due to these internal divisions. One of the vice presidents of the council's economic, ethical and social committee, Patrick de Kochko, also coordinator of the network Semences paysannes (Rural Seeds), resigned from his post, adding more confusion to the debate (Bolis and Foucart, 2016).

In the 14-April-2016 issue of *Nature* this French dispute within the HCB was mentioned. What is at stake is an increasing blurring of the frontier between what we call now transgenic and the future genetically improved crops. That raises a real issue for those opponents of GMOs as they must adapt to this new reality, particularly in the absence of a new legal framework (the law is slow compared with the speed of technology). Already new varieties of herbicide-tolerant canola and sunflower have been introduced in France and the antiGMOs were preaching against them in the desert: obtained via mutagenesis, they were considered as conventional and not transgenic. The French seed producers consider that these new crop varieties should be qualified as GMOs if they can be theoretically developed through successive crossings of non-GM varieties or through directed mutation. "The old techniques of mutagenesis are excluded from the European Union's directive 2001-18, and it is therefore logical that more recent techniques of mutagenesis be also excluded," argues Olivier Lucas, a specialist of that issue in the Committee for regulation and innovation of the French Union of Seed Producers (UFS, French acronym). Also fruits obtained from a non-GM scion grafted on GM plant should not be classified as transgenic, because there fruits do not contain the genetic modification of the stock (e.g. disease or pest resistance) [Foucart and Herzberg, 2017].

Maybe it is time to focus the debate not so much on the technique of producing a GMO or a non-GMO, but on the benefits and/or risks of these plants. In this sense S. Foucart was wise to suggest this new line of thought and finish with the view that genetic engineering applied to plants or crops is just evil (Foucart, 2016). Some scientists even go further and suggest to evaluate not the plant itself (resulting from the use of these techniques), but the trait for which it has been developed. Peter Rogowski who works at the French National Agricultural Research Institute (INRA, French acronym) in Lyon, stated: "For me the nature of the trait (e.g. resistance to drought or herbicide tolerance) is more important than the technology used to obtain it. After 30 years of research on GMOs, we did not find any deleterious effect of the technology itself. By contrast we discovered important impacts of the products on the environment, health, due to the nature of the trait" (Foucart and Herzberg, 2017).

But other scientists are not willing to abandon the technological approach. For instance, the French biologist Yves Bertheau stated: "We have a very idealistic vision regarding such techniques as the CRISPR-Cas9, which are supposed to act in a refined manner on the genome. But the reality is very distinct and there exist unknown effects on the plant genome outside the genomic sequence to be altered, and which are presently the focus of research." In other words the plants developed with the help of these techniques would be theoretically similar to those that may be developed with much more difficulty, through traditional techniques. They could bear small and fortuitous alterations of the genome or the epigenome of the plant. Such possibility is not discarded by the industrialists (Foucart and Herzberg, 2017).

For instance, would it be possible to focus on to what extent these new crops reduce the carbon imprint of agriculture, increase production within the overall framework of a sustainable agriculture, raise the protection of crops against climate change in addition to pests, improve the agricultural practices, e.g. no-tillage agriculture. As examples meant to reduce the carbon imprint of conventional agriculture, there are systems of high-density maize crops which increase the number of plants per hectare and consequently production on that area. There are studies being carried out, which are at their initial stage and which aim to develop new high-yielding maize and soybeans varieties to be planted with higher density; this project is being carried out by Monsanto and BASF, and field trials have shown good results. Another Monsanto's project meant to develop new-generation crop varieties that tolerate herbicide even better, e.g. soybeans Roundup Ready 2Xtend and cotton variety Bollgard II XtendFlex. These developments will be combined with no-tillage practices and would contribute to the diminution of emissions of greenhouse-effect gases.

Regarding the protection against insect pests Monsanto is developing a fourth-generation maize variety which resists to insects living on the soil, as well as another variety that resists to those living underneath. With respect to soybeans the new pest-resistant varieties belong to the third generation. Furthermore Monsanto was developing a project with Bayer which aims to protect the newly developed seeds with fungicides, in order to have at the time of planting maize good seeds and a wide range of resistance to pests. Another line of research focuses on soil microbes, e.g. an improved inoculant of maize which leads to an increase in production. This kind of research is being performed through the alliance BioAg which Monsanto established with Novozymes; it is focused on improving the growth of maize roots thanks to a good microbial environment, thus facilitating their access to nutrients, and subsequently a yield increase.

Pioneer's outstanding contribution

Pioneer has been initially an Iowa (Middle West) farmer's enterprise: the son of a farmer, an agronomist, who in the early 1920s continued his father's know-how. It was about that time that hybridization between distinct crop varieties was carried out (1918). Compared with pure lines (the first pure lines were isolated in England during the 18th country and the objective of the farmers was to make sure that desired trait was conserved during the multiplication of these pure lines), the new hybrid varieties perform much better (in terms of size, yield, etc.). Henry Wallace applied the hybridization technique to maize in his farm. He was convinced that his tool of creating new varieties will have a considerable impact in the development of agriculture. He thus created in 1926 his own enterprise, called Hi-Bred and was to become Pioneer. This success followed suit and Henry Wallace became the United States agriculture secretary (1933-1940) and thereafter vice-president of Franklin Roosevelt (1941-1945) [Herzberg, 2017a].

In 90 years Pioneer became a world giant in the agro-industry, first across the United States and thereafter worldwide. In 1929 it was acquired by the chemical behemoth Dupont for about US$10 billion. With *ca*. 12,500 employees, present in 90 countries, Pioneer is the world's second-biggest seed producer, just behind Monsanto. Its research centre in Des Moines (Iowa) includes three concrete and glass buildings, each one having a surface of 18,000, 20,000 and 28,000 square meters, respectively, where about a thousand researchers are working. In addition to numerous greenhouses that are fully automated, Pioneer owns a wide acreage to carry out field trials. This research centre is called the Johnston campus (Herzberg, 2017a).

Pioneer has been able to develop new crop varieties that are cold and drought tolerant, pest resistant and herbicide tolerant, through various techniques such as:

- random mutagenesis (the plants are put in close contact with a chemical, ethyl-methane sulfonate, or submitted to radiation with a view to provoke massive mutations); the plants which survive after these treatments are selected according to the desired agronomic trait (e.g. shape and size, tolerance to weather vagaries, salt- and pest-resistance); random mutagenesis was tested in 1928 and was used routinely in the 1950s;
- genetical modification; in 1983 the transfer and introduction into tobacco of an alien gene caused resistance to an antibiotic; thereafter genetically modified crop varieties (GM crops or transgenic crops) were developed in order to transfer resistance to pests, herbicide tolerance and adaptation to extreme weather conditions; *ca*. 85% of transgenic crop varieties are grown in the Americas, while in Europe they occupy 0.1% of the agricultural acreage (Herzberg, 2017a).

With the discovery and application of a genome-editing system (called CRISPR-Cas9) in 2012, it became possible to replace a gene or to modify its sequence in many plant species. There is no gene transfer. More precise, more simple and quicker – and less expensive – than any other available techniques, CRISPR-Cas9 has been adopted by a large number of laboratories across the world. "We immediately understood that it was a revolution," stated Neal Gutterson, Pioneer's vice-president for research-and-development. The group Dupont owns a research centre on lactic bacteria in Dangé-Saint-Romain in western France, where the role of CRISPR-Cas9 in the protection of bacteria against bacteriophages had been demonstrated. At the Johnston Campus Pioneer has a series of installations that have been designed over 25 years in order to develop GMOs (Herzberg, 2017a).

Pioneer's vice-president, who was recruited in 2014 after a career in biotechnology startups, stated that using CRISPR-Cas9 technique in crop selection "raised a double challenge: scientific, of course, and also cultural." In fact the technique is fraught with many difficulties. First, the site of intervention along the genome sequence must be determined: where to cut and paste in order to obtain an agronomic trait in the plant genome which is often very complex in crops. In the case of maize, for instance, there are more than 50,000 genes, the double compared with the human genome, distributed in 10 chromosomes, with duplications and repeated sequences in several genes, that are almost unknown in animal genomes. According to Jeffrey Sander, a researcher at the department of molecular engineering, "between two maize varieties, there is the same genetic distance as between a human and an ape." Pioneer does propose several dozens of maize varieties, that are adapted to soil composition, humidity, temperatures, and are pathogen or pest-resistant. Jeffrey Sander added: "To make these varieties evolve in order to improve them is the core of our work; for every assay we have to do again the sequencing of the genome" (Herzberg, 2017a).

While three years and US$32 million were needed to sequence the 2.5 billion of nucleotide pairs of the genome of a maize variety, between 2005 and 2008, nowadays a few days are necessary to carry out the same operation, and at a cost 10,000 times less. Thus it is therefore possible to make the CRISPR-Cas9 more precise, quicker and with a better capacity of reading and editing the plant genome. In the division of genomics analysis there were in 2017 at least nine sequencing machines which are working all the time in order to search for interesting traits, not only in maize, but also in wheat, soybean, rice, sunflower and canola (Herzberg, 2017a).

Once the sequence on which the change should be made has been identified, the researchers propel the system CRISPR with a "gene cannon", a classical technique to produce GMOs. But this is a true "scientific breakthrough," according to Peter Rogowski, a professor at the Ecole Normale Supérieure in Lyon (France) and a well-known figure in plant research. In addition to the Cas9 protein and the ARN that serves to guide the genome-editing system, Pioneer's researchers propel a gene (morphogenetic regulator) that stimulates the proliferation of genetically-modified cells. Pioneer's researchers reached that stage in the case of maize, rice, sorghum and sugar-cane; thus they found a way to solve one of the most difficult stages of the process: plant regeneration. Furthermore this morphogenetic regulator disappears in the modified organisms, and this is an event that might influence the adoption of the plants modified by the CRISPR-Cas9 technique. The usual GM plants or transgenic which have enabled the agrochemical industry to make huge profits, are nevertheless costly (more than US$100 million per product, according to Pioneer's estimate). Henceforth the concern of modified-seed producers to clearly distinguish both techniques: transgenesis and CRISPR-Cas9 (Herzberg, 2017a).

Their advocacy in favour of the new genome-editing gene can be summarized in three reasons, as listed by Neal Gutterson : "First of all, we do not insert any external (alien) gene inside the genome. Secondly, we just modify a few nucleotides (bases), that is to say a process similar to mutations occurring in natural conditions in the plants. Thirdly and lastly, we withdraw from the genome all the elements (components) of the system CRISPR-Cas9 that may have been incorporated into it." However, the opponents to GMOs are far from being convinced by these reasons and do believe that some parts of the system used to edit the plant genome do remain in the plant (Herzberg, 2017a).

But Gregory May, responsible for genomic analysis at Pioneer reacted by stating : "It is true that the challenge is to make sure that the modification takes place where and the way we wish to occur. We only keep 10% of the specimens. Then we check once again the genome in vivo using the best methods of sequencing. Thereafter half of the specimens is discarded. Finally a third filter is applied, which is part of Pioneer's innovation." The latter called Southern by Sequencing is able to scan portions of the genome with a view to detecting any alien element, and after that screening another 15% of the modified plants are discarded. G. May came to the conclusion: "There is no altered case left" (Herzberg, 2017a).

All this enables Pioneer to be as close as possible to products that correspond to consumers' choices. This is the second revolution induced by CRISPR-Cas9, this time a cultural one, according to Neal Gutterson who stated: "Since 1926 we have been working for the farmers. From now on, we should think of those who will consume our products. Take the example of tomatoes. During a long time, the aim has been to produce less vulnerable varieties and better-yielding ones, thus forgetting taste. May be one day and thanks to CRISPR-Cas9 we could have both." Still such a careful hope may be surprising. But the same scientist admitted: "We have so much promised with GMOs," which meant that there was quite a disappointment. Then he added: "Finally all will depend on the regulatory framework that will be adopted and on public acceptance. We will not therefore start with food, because this subject is very sensitive" (Herzberg, 2017a).

The first product derived from the use of CRISPR-Cas9 that has been already authorized by the US Department of Agriculture (USDA) and to be commercialized in 2020 is a waxy maize. This is a variety which contains almost no amylose in its starch and is to be used by industrialists producing a wide range of products, such as textiles, adhesives, paper, food components, etc. Another maize variety resistant to maize blight is also being developed. Neal Gutterson stated: "We are going to continue to work on other cereals, with a focus on resistance to diseases, yield, tolerance to drought, nutrient composition and maturation duration." With regard to herbicide tolerance, Neal Gutterson thought that it was not a priority target, because it may derail the feasibility and credibility of the CRISPR-Cas9 technique. While the latter permits the introduction of an alien gene into the plant genome, Pionner's researchers will avoid it (Herzberg, 2017a).

Another contribution of Calyxt, a startup from Minneapolis (Minnesota)

Calyxt is the agricultural scion of the French biotechnology company Cellectics, established in an area where the cereal yields are the highest in the world. At the Minneapolis-based startup 30 employees including 25 researchers are working on a new technology that "can change" the world, according to the company's president, Federico Tripodi. The startup was supposed to be listed on the Nasdaq, the second financial market of the United States. The technique mentioned by F. Tripodi was not CRISPR-Cas9 but Talen, restriction enzymes developed in 2009 which can also cut the DNA molecule. The development of CRISPR-Cas9, simpler and quicker, put a hold on the use of Talen. But Calyxt's researchers, which own a unique patent, do believe in the future of this technique (Herzberg, 2017a).

The startup bought a field in the suburban area of Minneapolis where its first field trials will be carried out, at the beginning manually and thereafter with the help of automation. "With their robot they can assemble a Talen experiment almost as quickly as a CRISPR-Cas9 one," according to Feng Zhang, in charge of field operations. Calyxt's objectives are the increase in yield as well as the development of drought resistance. Also, in order to mitigate or to control the spread of diabetes, allergies and obesity, Calyxt aims at producing healthier foodstuffs. According to F. Tripodi the US Department of Agriculture (USDA) has approved the following modified varieties that are being developed : a soybean that can produce a stable oil with trans-fatty acids (hence less harmful for the cardio-vascular system); potatoes which do not blacken when peeled, which also remain firm under cold and do not produce acrylamide when cooked (acrylamide is a carcinogenic compound); a wheat with a high content of fibers, and another wheat, developed in collaboration with a Chinese team, that is resistant to a specific disease; and even another one that is tolerant to some herbicides – but not to glyphosate (Herzberg, 2017a).

Consolidation of the seed business

Two decades ago the seed industry was far more fragmented. In 1994 the top four companies in the worldwide market for seeds and crop biotechnology had a combined share of 20%. By 2009 the top four's share was 54%. Similarly in agrochemicals the top four's share rose from just *ca.* a quarter to more than half over that period. But the presence of another consolidation of this bioindustry remains (*The Economist*, 2015a). Low commodity prices, which are beginning to curb farmers spending on supplies, are one reason for it. For instance the drop in cereal prices affected Monsanto who announced on 7 October 2015 the laying off of 2,600 employees, i.e. 12%

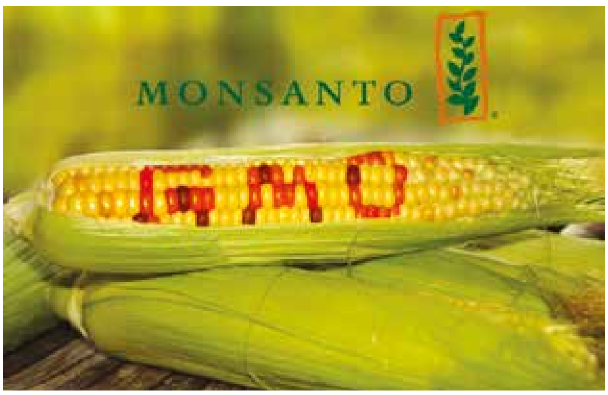
of its staff. This operation was to take place in two years and would cost the company between US$850 million and US$900 million (or between €750 million and €800 million). The former layoff of Monsanto's employees occured in 2009 and affected 900 salaried staff. The company had to acknowledge an 11% decrease in its profit, down to US$3.5 billion. Monsanto made it clear that the situation in 2016 will not be better (Girard, 2015).

For the third year in sequence maize harvests have been abundant; and the same situation prevailed for rice and wheat. Consequently the granaries were full and the trend for the prices was a downward one. American farmers tended to reduce their acreage planted with maize and thus reduced their expenses. In Brazil the devaluation of the national currency, the real, versus the dollar increased the cost of all inputs, particularly imported seeds, and thus decreased their use. Such a situation has been noted for soybeans. All these GM crop varieties which made up 40% of Monsanto's annual turnover and which were the most fruitful segment of the company's activity, were therefore affected by the low commodity prices (Girard, 2015).

Another reason is the diminishing reward brought in by Monsanto's weedkiller glyphosate, sold as Roundup, and by Roundup Ready seeds that were genetically altered to withstand the herbicide. In addition to a series of disputes about the potential effect of glyphosate on human and animal health, the weeds are fighting back. A study published in 2013 by the Union of Concerned Scientists found that weeds resistant to glyphosate were present in more than half of America's farms. Monsanto is developing crop seeds resistant to dicamba, another herbicide, and planned to spend perhaps US$1billion or more on a plant to produce the chemical. The overall end result is that Monsanto's annual turnover for 2015 was to be reduced by 5%, down to US$15 billion. Thus for Monsanto's chief executive officer (CEO) Hugh Grant, consolidation in the agroindustry has become unavoidable, particularly he said because of the increasing costs of research (Girard, 2015; *The Economist*, 2015a).

Those opposed to the industry getting even more concentrated fear it would mean less innovation, as a handful of global giants concentrate on defending their existing intellectual property rights. Since the mid-1990s the big six – Monsanto, Syngenta, Bayer, Dow Chemical, BASF and DuPont – have between them bought up more than 200 other companies and their patents. Some fret that research would become more focused on the most profitable crops, rather than seeking improvements to those that might feed the poor, such as cassava or sorghum in sub-Saharan Africa. The other big worry is that the fewer firms are producing seeds and herbicides, the more expensive these will be for farmers. In recent years American farmers' spending on fertilizer, seeds and other inputs has risen significantly, and the prices they have been able to charge have not kept pace with their increasing costs. That is why the American National Farmers Union opposed Monsanto's moves on Syngenta and welcomed the bid collapse (*The Economist*, 2015a).

Monsanto's bid on Syngenta



The world leader of seeds came to the conclusion that buying Syngenta – a world leader of herbicides, pesticides and fungicides – would create a giant in the agroindustry. Furthermore the merger would give the new gigantic company greater scale in underserved markets, with farmers gaining access to a broader variety of products. The merger would also combine the two firms' research pipelines and this would help speed up the development of new products. This failed to convince Syngenta's bosses, apparently, even though the final offer was around the level that a recent poll of Syngenta investors had indicated might sway them. The fact is that Syngenta rebuffed a bid of US$45 billion in June 2015. And another made on 18 August 2015, worth US$47 billion. So, on 26 August 2015, Monsanto walked away. But consolidation of the industry may be in prospect anyway. The takeover battle stimulated the interest of other big agricultural suppliers: BASF, another of the big six, had reportedly sought financing to make a rival offer for Syngenta. And Monsanto may not be unscathed: in 2016 the firm may be itself a target (*The Economist*, 2015a). Finally Syngenta was bought by ChemChina, the Chinese state-owned China National Chemical Corp. in a US$43-billion deal (Sasson, 2016).

Bayer-Monsanto merger

After four months of negotiations (starting on 19 May 2016) between the German pharmaceutical and agrochemical company Bayer AG and Monsanto Co. the two groups agreed to merge on Wednesday 14 September 2016. Bayer had to raise an opening bid of US$122 a share of Monsanto in May 2016 at least three times to clinch the takeover at US$128. Monsanto announced therefore that it would sell itself at an aggregate value of US$66 billion (or *ca.* €59 billion). The deal price of US$128 per share in cash is just 3% above Monsanto's post-financial crisis high reached in 2014. A failed bid for rival Syngenta along with recent weak results had sent Monsanto shares sliding. Analysts had speculated the deal would close for between US$140 and US$150 a share. By selling below Monsanto has telegraphed how little it thought of its standalone prospects (Massoudi, Fontanella-Khan and Chazan, 2016).

Bayer AG, Leverkusen, Germany, the discoverer of aspirin, had in 2015 an annual turnover of €46.4 billion (+12.1% compared with 2014), and a profit of €6.2 billion (+15.8% compared with 2014); the number of its employees was 117,000. In the case of Monsanto Co., the annual turnover reached in 2015 US$15 billion (or *ca.* €13.4 billion) or -5% compared with 2014; the profit was US$3.5 billion (-11% compared with 2014); the number of employees was 22,500 (Boutelet, 2016b). By mid-2016 the estimated stock value of Bayer AG was *ca.* €73 billion, i.e. about the double of Monsanto Co. (Boutelet, 2016a).

The transaction ranks as the largest all-cash deal and biggest foreign acquisition of an American company. Bayer's proposed acquisition of Monsanto values the target at US$66 billion including debt. Monsanto's equity value was about US$57 billion. Bayer's chief executive, Werner Baumann, will receive the support of five international banks for loans amounting to *ca.* €57 billion to fund the acquisition (De La Merced, 2016; Massoudi, Fontanella-Khan and Chazan, 2016). Hugh Grant, Monsanto chief executive, described "his company's tie-up with Bayer as a match made in heaven". Monsanto, he stated, produces seeds, while Bayer makes crop protection chemicals. "When you bring these two platforms together you unlock new products and you unlock innovation on a totally different scale." It is true that the industrial logic driving Bayer's proposed takeover of Monsanto, the largest overseas deal by a German company, is simple. A combined Bayer-Monsanto will be a one-stop shop selling seeds, crop sprays and advice to farmers across the world. Monsanto's dominance in seeds will now be paired with Bayer's crop chemicals unit to offer a supermarket to farmers. Bayer will continue to derive €23 billion of revenue from its health-care units, which sell pharmaceuticals, over-the-counter drugs and animal medicine (Massoudi, Fontanella-Khan and Chazan, 2016).

By improving agricultural yields the enlarged company will contribute to feed a world population that is expected to grow by 3 billion by 2050, to reach 10 billion people. Bayer stated the global market in agricultural inputs will be worth €120 billion by 2025. Bayer-Monsanto would command a huge chunk of that: their combined agricultural sales were €23.1 billion in 2015, compared with €14.8 billion for ChemChina-Syngenta, €14.6 billion for Dow Chemical-DuPont and €5.8 billion for BASF (another German big crop chemical company based in Ludwigshafen). It should be mentioned that two other blockbuster deals are due to transform the agrobusiness industry. These are Dow Chemical Co. planned takeover of DuPont Co. which has been billed as a merger of equals, and ChemChina's proposed acquisition of Syngenta of Switzerland (Alessi, 2016). The incentive for all these companies is the ability to sell seeds and chemicals as a package. Werner Baumann stated: "It is all about growth and innovation of two organizations that are highly complementary (in terms of) product portfolios and regional coverage" (Alessi, 2016; Boutelet, 2016a; Massoudi, Fontanella-Khan and Chazan, 2016).

Despite claims by W. Baumann and H. Grant that there is little overlap between their companies, Bayer and Monsanto do have similar products that could ring alarm bells with regulators. For instance Monsanto produces the weedkiller glyphosate, sold under the name of Roundup, as well as seeds that have been genetically modified to be resistant to glyphosate, called Roundup Ready. Bayer has similar products, called Liberty Link. The two franchises are often used in conjunction with each other. Some weeds have become resistant to Roundup over the years, so farmers complement it with Liberty Link. Therefore and according to Christian Faitz, an analyst at Kepler Cheuvreux, Bayer may have to sell Liberty Link to get the Monsanto deal past regulators. The tie-up would also create the largest supplier of cotton seeds in the United States, responsible for almost 70% of crop acreage, according to Verdant Partners, a consultancy C. Faitz believed Bayer would have to sell that part of its business too. However, Hugh Grant underscored what he sees as the beauty of the deal – the companies' complementarity. "Monsanto is a seed biotech, emerging data science business, while Bayer is pre-eminent in chemistry and when you sketch that out on a piece of paper, the overlaps are really very small" (Massoudi, Fontanella-Khan and Chazan, 2016).

Five banks are providing an extraordinary US$57 billion bridge loan to Bayer. The company stated it would eventually recover its A-credit rating by selling US$19 billion in equity in the four of convertibles and rights offerings. Bayer said furthermore that in three years there will be US$1.5 billion of annual combination savings to cover that premium. Indeed Bayer announced that the promised US$300 million in new annual sales will accelerate after three years. Investors and creditors found these explanations plausible, its credibility enhanced by its price discipline. Bayer will pay for Monsanto by raising US$19 billion in equity through a rights issue and convertible bonds, and the remainder by issuing debt. The Bayer-Monsanto deal includes a US$2 billion break-fee payable by Bayer should it walk away from the agreement, or if it is blocked by regulators. On the other hand, Hugh Grant stands to make more than US$226 million from the sale, according to the company's latest annual report, with a large amount of the sum coming from the vesting of shares and options he held, as well as a severance package if he leaves as a result of the sale (Massoudi, Fontanella-Kahn and Chazan, 2016). Werner Baumann, Bayer's chief executive, acknowledged that the company would have to file the deal with authorities in 30 different jurisdictions, the main ones being the United States, Canada, Brazil and the European Union. Yet he still expressed confidence that the deal should close by the end of 2017. But Jeremy Redenius, analyst at Bernstein, stated there was only a 50% probability that the deal would complete. "We expect significant antitrust and political hurdles," he said (Massoudi, Fontanella-Kahn and Chazan, 2016).

Scrutiny by politicians and regulators

Although the combined group will try to respond to feeding an evergrowing human and livestock population as well as to climate change and global warming, which affects all farmers across the world, through an approach "which systematically integrates an expertise in seeds and crop protection, including biotechnology, with a strong commitment in favour of innovation and sustainable agricultural practices" (as stated on 13 September 2016 by Liam Cordon, director of Bayer's Crop Science Division and member of the management of the company), the deal with Monsanto is expected to be closely scrutinized by politicians and regulators on both sides of the Atlantic. "Produce more with less" is the mantra of both groups, as well as an emphasis on their "sustainable" approach aimed at helping the farmers to overcome tomorrow's obstacles. Amid concerns are that the big players in the agrobusiness markets will have the power to raise prices for farmers – and potentially increase the cost of food for consumers (Boutelet, 2016; Massoudi, Fontanella-Kahn and Chazan, 2016).

"The regulatory risks [to the Bayer-Monsanto deal] are not insignificant," stated Peter Verdult, an analyst at Citi. "We are seeing rapid consolidation across the whole industry, and there is bound to be a lot of scrutiny about the world's food supply being held in so few hands." So far the messages from regulators have been mixed. In August 2016 ChemChina cleared by a big hurdle in the pursuit of Syngenta when the Committee on Foreign Investment, an American panel that can block deals, approved the transaction. But in Europe officials are taking a tough approach. In August 2016 the European Union competition commissioner Margrethe Vestager opened an investigation into the Dow Chemical-DuPont tie-up, refusing a proposed package of concessions to fast track the deal. Similar probes are likely into the ChemChina-Syngenta deal and Bayer's agreed offer for Monsanto (Massoudi, Fontanella-Kahn and Chazan, 2016).

Meanwhile, in the United States, Senate Judiciary Committee chairman Charles Grassley scheduled a hearing by the third week of September 2016 on consolidation in the agrobusiness sector, because of concerns about the implications for farmers. In a letter to the US Department of Justice's antitrust division in August 2016, he said the deals may "have an enhanced adverse impact on competition in the industry and raise barriers to entry for smaller companies by altering the industry structure for seeds and chemicals." Others also questioned Bayer's assertion that integrated solutions will benefit farmers. "Size on its own is not a recipe for success," said BASF head of crop protection Markus Heldt. "Farmers want the freedom to choose, they want choice and alternatives. They do not just want to be dependent on three to four [suppliers] on a global scale" (Massoudi, Fontanella-Kahn and Chazan, 2016).

A question of image

The takeover of Monsanto, the leader of GM seeds, may confer a negative image because it is one of the most unpopular corporations globally. During the campaign against the TransAtlantic Free Trade Agreement (TAFTA) which was carried out in Germany by various organizations, Monsanto was systematically quoted as the corporation which represents the excess of agricultural globalization. Bayer would suffer from an image of being tied up with the symbol of an unsustainable agriculture in a country where environmental protection is a major concern. But the German company considered that the risk in terms of image was less important than the other problem that threatened it: to be acquired by a bigger rival. The combination Bayer-Monsanto, if approved by the regulators, would enable Bayer to become big enough to escape a hostile acquisition, e.g. by Pfizer or ChemChina (Boutelet, 2016b).

Among the proponents of the deal, Bayer's chief executive Werner Baumann, 53-years old at the time of the takeover, has chaired all the mergers and acquisitions of Bayer over a decade. He wanted to be involved in this new high-risk transaction, which upgrades him among the most powerful CEOs of the German economy. In fact he was prepared to acquire Monsanto for a long time, but he had to wait for the departure of his predecessor in April 2016, Marijn Dekkers, who was opposed to the takeover. He had with his team to deploy its know-how regarding the acquisition of companies. For instance he was able to successfully manage the acquisition of its rival Schering based in Berlin. He also had to rebuild and reorganize the Health Care sector of Bayer after the scandal provoked by the anticholesterol drug Lipobay in 2002. It was also W. Baumann who organized the separation of Bayer's activities in plastics (€11 billion), which were successfully listed in the stock exchange under the name of Covestro in the fall of 2015 (Alessi, 2016; Boutelet, 2016b).

However, in a country such as Germany which is opposed to GMOs and very concerned about health and environment issues, the opponents to the combination Bayer-Monsanto among ecological movements and farmers' associations cannot be underestimated. In fact, as soon as the takeover was announced, they were going to do everything possible to block the transaction. That was the case of Anton Hofreiter, chairman of the parliamentary group Alliance 90/The Greens, who declared: "This transaction should not complete." The parliamentary group condemned the creation of a "superpower" group, which will "aggravate starvation across the world and not combat it." According to A. Hofreiter, the huge amount of money paid by Bayer to acquire Monsanto – almost 20 times the annual profit of the American corporation – would clearly indicate an increase in the price of seeds and agricultural inputs. He made a strong plea to the regulation authorities of the European Union and the United States to block the merger (Boutelet, 2016b).

Regarding the independent members of the big Federation of German Farmers, the deal Bayer-Monsanto is considered "a declaration of war" to all civic society. "We should not be fooled by a so-called fair enterprise like Bayer which buys back the reputation of the most unpopular corporations globally. Bayer also tried to bring GMOs in German fields, it failed to do so because we have resisted it," recalled Georg Jansen, director of the AbL Federation. Germans are opposed to GMOs and their use in cropland has been forbidden since 2009, with an exception for laboratory research. With respect to ecologists it was thought that the fact that Bayer was unscathed until now, would come to an end. "Bayer has the same business model as Monsanto, they also have GMOs, patents on living beings, glyphosate, but they have been less aggressive than Monsanto in their communication. Monsanto has been the tree which was hiding the forest. This will not last for long," declared Dirk Zimmermann of Greenpeace to the French daily newspaper *Le Monde* (Boutelet, 2016b).

But doubts remain about the results of this battle: can the non-governmental organizations struggle against a behemoth resulting from the combination Bayer-Monsanto? The combined company has a formidable lobbying power at international level. The forthcoming discussion at the level of the European Commission on the authorization of glyphosate at the end of 2017 would be a first illustration of the lobbying power of the new entity. The use of glyphosate in croplands beyond 2017 is an obvious objective from Monsanto's viewpoint, and the new company would struggle to achieve it thanks to its strength and lobbying power (Boutelet, 2016b).

Selected snapshots in a few developing countries

Overall benefits of GM crops

An informative report prepared by PG Economics, a consultancy, titled *Genetically Modified Crops: Global Socio-Economic and Environmental Impact, 1996-2012*, highlighted the contribution of GM crops, since the beginning of its large-scale cultivation, to a more productive and sustainable agriculture. Between 1996 and 2013, agricultural biotechnology contributed worldwide to an additional 138 million tons of soybeans and 274 million tons of maize. In addition 21.7 million tons of cotton and 8 million tons of canola have been produced during this period. It was estimated that in the absence of the contribution of agricultural biotechnology the 18 million farmers who have used GM crops in 2013, just maintaining the global production during that year would have needed additional planting of 5.8 million hectares of soybeans, 8.3 million ha of maize, 3.5 million ha of cotton and 0.5 million ha of canola. This additional area was equivalent to 11% of farmland in the United States, or to 29% of farmland in Brazil, or to 32% of cereal farmland in the European Union (28 countries). RR soybeans were planted in South America in 2013 (but before in Argentina), and the farmers harvested an average 10% increase in yield. It was estimated that the net economic benefit at the level of the farm was in 2013 US$20.5 million, equivalent to an increase in the average profit of US$122 per hectare. During the 18 years of the study (1996-2013) the increase in the global agricultural benefit has been US$133.5 billion.

GM crops have contributed to the reduction of greenhouse-effect gases emitted by agricultural activities, due to a lesser use of fuel and a storage of additional carbon in the soil further to no-tillage farming. It has been calculated that in 2013 *ca*. 8 billion kg of CO_2 were not emitted to the atmosphere (equivalent to the withdrawal of 12.4 millions of cars from the streets worldwide). GM crops have reduced the use of pesticides (1996-2013) by 550 million kg (-8.6%). This is considered equivalent to the total quantity of pesticides sprayed on crops in the European Union during two agricultural campaigns. As a result this has reduced the environmental impact associated with the use of herbicides and pesticides on the whole area cultivated with GM crops (-19%). The tolerance to herbicides in the case of soybeans and canola has contributed to an increase in production in some countries; it has enabled Argentina farmers to grow soybeans after wheat during the same period of farming with a better yield and a better weed control. The resistance to insect pests in cotton and maize resulted in an increase in yield of these crop species due to lesser losses from insect attacks. It has been estimated that this technology brought in during the period 1996-2013 an average increase in yield of +11.7% for insect-resistant maize and +17% for insect-resistant cotton.

Some benefits for animal and human health

In *Transgenic Research* (2015) Japanese researchers published their results on the development of GM rice, fortified on enriched with gamma-aminobutyric acid (GABA), which is a neurotransmitter in the central nervous system of mammals and which could be used in the regulation of cardiovascular mechanisms because of its role in hypertension. The researchers introduced the genes involved in the synthesis of GABA into a variety of *japonica* rice, called Koshihikari, and thereafter compared the GM rice with the controls in greenhouses; they found that the GM rice plants had the same yield as control plants, but contained significantly higher amounts of GABA. Moreover the feeding of hypertensive rats with this GM rice for two months had an antihypertension effect in the laboratory animals.

In *Plant Biotechnology Journal* (2015), a team of researchers from Spain and Germany published their results on feeding poultry with maize containing high amounts of carotenoids: beta-carotene, lycopene, zeaxanthin and lutein. Those animals fed with this GM maize had a better health and accumulated more carotenoids in peripheral tissues such as skin, muscle and fats, as well as more retinol in the liver, than control animals. Furthermore when these animals were challenged with the parasite *Eimeria tenella*, they found that their growth rate was normal, the symptoms of the disease were light and the number of oocysts in their feces was much lower than in control animals. These results demonstrated that a diet containing a GM-maize with high levels of carotenoids would improve the immune system of poultry; furthermore the carotenoids are present and available in the peripheric tissues of the animals, thus heightening their nutritional value.

Camelina sativa is a herbaceous plant belonging to the Brassicaceae, originally from North Europe and Central Asia. It has been introduced in North America. It is grown as an oil-producing crop, in order to produce soaps, painting ingredients, and meal (after oil extraction, as feed for livestock). Researchers at the Rothamsted Research Institute, England, carried out field trials with a variety of *Camelina sativa* genetically modified in order to produce higher amounts of omega-3 fatty acids in their seeds. The field trials carried out during one year were conclusive and they therefore opened a new way to obtain this kind of fatty acids from plants and not mainly from fish. The GM plants of *C. sativa* contained the genes for the synthesis of omega-3 fatty acids extracted from marine photosynthetic organisms, and their synthesis took place in the seeds. The research carried out at the Rothamsted Research Institute and the field trials performed there have confirmed the stable development of *Camelina sativa* transgenic plants that are able to synthesize fish omega-3 fatty acids and have the same features as control plants in terms of yield, growth rate, blossoming and formation of seeds. Nowadays the global consumption of fish oil is more than 1 million tons. One may hope that with the GM *Camelina sativa* plants there is a terrestrial way of producing these fatty acids.

Country review (selected examples)

• Tanzania

Hussein Mansoor, deputy-director of research at the ministry of agriculture, food security and cooperatives, stated that "the scientists will be able to carry out field trials with GM crops without any fear." This decision was made by mid-2015 when Tanzanian scientists were ready to make field trials with maize plants genetically engineered to be resistant to insects and tolerant to drought, within the framework of WEMA (Water Efficient Maize) programme, as well as with cassava varieties resistant to the mosaics virus. The coordinator of the WEMA programme in Tanzania, Aloise Kullaya, greeted this decision which could improve the income of Tanzanian farmers if the products (seeds) could be commercialized.

WEMA is a public-private programme which operates in Tanzania, Kenya, Uganda, Mozambique and South Africa. Its objective is to develop a drought and insect-resistant maize, using conventional breeding, selection assisted with biomarkers and biotechnology. The new varieties will be distributed freely to poor farmers in Africa. Field trials began in 2015 and commercialization of the new varieties will follow in about a few years. The coordinator of the African Agricultural Biotechnology Forum, Daniel Otunge, expressed his satisfaction regarding the field trials to be carried out in Tanzania; this, he considered, showed that the government of Tanzania was believing in the contribution of crop biotechnology to agricultural production.

• China

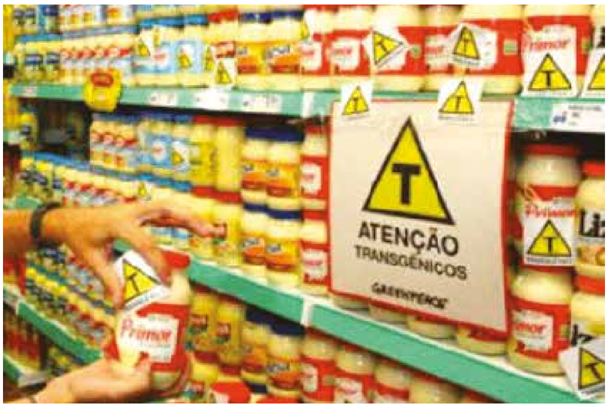
Several researchers belonging to the National Key Laboratory of Plant Molecular Genetics and National Center of Plant Gene Research, Institute of Plant Physiology and Ecology, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai, as well as to the College of Agriculture and Biotechnology, Zhejiang University, Hengzhou, the College of Life Sciences, Wuhan University, Hubei, the Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha, the Shanghai Center for Plant Stress Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, and the Collaborative Innovation Center of Genetics and Development, Institute of Plant Physiology and Ecology, Shanghai, have published in *Nature Biotechnology* on 17 August 2015 (Hui Shen et al., 2015) the results of their research on increasing thermotolerance in rice and tomato. They demonstrated that overexpression of the *Arabidopsis thaliana* receptor-like kinase ERECTA (ER) in *Arabidopsis*, rice and tomato conferred thermotolerance independent of water loss and that *Arabidopsis* ER mutants were hypersensitive to heat. Transgenic tomato and rice lines overexpressing *Arabidopsis* ER showed improved heat tolerance in the greenhouse and in field tests at multiple locations in China during several seasons. Moreover ER-overexpressing transgenic *Arabidopsis*, tomato and rice plants had increased biomass. These findings could contribute to engineering or breeding thermotolerant crops with no growth penalty.

With respect to biosafety of GMOs China established an overall system of surveillance that includes research, production and commercialization. In September 2015 the agriculture ministry of China announced that it was willing to work with other departments in order to improve the current biosafety system, so as to reinforce the safety of GMO consumption. The agriculture ministry responded to a request made by ten members of the highest-ranking consulting body of China, in charge of ensuring the safety of food derived from GM crops. In the agriculture ministry's response, published on the website of the ministry, it was indicated that China, like other countries, has carried out many research work on the safety of these GM foodstuffs which brought the demonstration that they were as safe for consumption as their conventional counterparts. Furthermore the ministry highlighted that GM foodstuffs had been submitted to an evaluation of their risks for human and animal health, and the result was that they are safe.

• Brazil

After a historic recession, characterized by the collapse of the Gross Domestic Product (GDP) down to -3.7% in 2015 and -3.5% in 2016, the economic growth has become positive during the first quarter of 2017(1%), which would lead to a modest growth of GDP in 2017 (+0.7%). One of the main driving forces behind this improvement was the agricultural sector (that contributed 0.8 point of a 1% growth during the 2017 first quarter). Consequently the Intellicom Institute was predicting an 8.5% annual growth of the sector, compared with 0.6% for the industry and -0.1% for services. This disparity was reflected geographically, with an annual 5.1% growth predicted for the State of Mato Grosso, compared with 0.5% for the State of São Paulo and - 1.4% for failed State of Rio (Gatinois, 2017).

The agroindustrial sector, now considered strategic more than ever for the Brazilian economic recovery, has been fostered during the presidency of Luiz Inacio Lula da Silva (in 2003) and has benefited from the high increase in the prices of raw materials, including those of agrifood products. The development of Brazilian agrifood sector was so impressive that the country was dubbed the "farm of the world", while China was considered the "world's toolshed" and India its "office" (Gatinois, 2017).



Plant and agricultural biotechnology, as well as the progress in livestock husbandry, have played a key role in the steep growth of the agroindustrial sector. Brazil is among the top three nations which grow and transform transgenic crops into food and feed. In 2017, the "harvest was perfect," claimed Marcos Fava Neves, an agricultural engineer and professor at the University of São Paulo (USP). But ideal temperatures and rainfall were not the only reasons. "The agroindustry uses advanced technologies and is very competitive, it exports to China and Africa, it creates jobs and can help develop cities which are locked inland and far from the main transport infrastructures," he added (Gatinois, 2017).

The importance of the agroindustrial sector for the overall economy and the increasing political representation of the farming sector in the Brazilian Congress through the "Bancada ruralista" – the agrobusiness lobbying body – partly explain the complacency of Brazil's president, Michel Temer. The latter, concerned about its possible impeachment and in order to avoid being caught up in dubious deals, has been touting the large-scale farmers or "fazendeiros" through renegotiating their debts at the expense of budget restraint, offering them more cropland or pastures at the expense of protected areas and indigenous lands. He even lessened the repression against the so-called "slavery work" (Gatinois, 2017).

During a conference organized by the economic journal *Valor*, on 5 October 2017, Martin Wolf, editor in the British daily newspaper *Financial Times*, had underlined the dependence of Brazil on the cycle of raw materials. That vulnerability associated with the "reprimarization" of Brazilian economy (i.e. the increased importance of raw materials at the expense of industry) was witnessed through the commercial balance. While in the early 1980s the industry contributed to more than 30% of the GDP, in 2017 the transformation industry contributed to only 11%-12% of GDP, according to André Nassif, professor at the Federal University Fluminense of Rio de Janeiro. "The agricultural sector alone cannot support the whole economic growth. There is a need for a regrowth of the industrial sector so as to make economic growth sustainable," underlined the Brazilian economist. But the economy minister, Henrique Meirelles, retorted: "Brazil is undergoing a solid recovery and is on the threshold of a growth cycle which may be the longest during the last decade," he tweeted on 10 October 2017. It seems that "the recovery is spreading through all sectors," according to Gesner Oliveira, an economy professor at the São Paulo Getulio Vargas Foundation. However the political turmoil created by the multiplication of corruption scandals shed to light by the national anticorruption enquiry known as *Lava Jato* (express cleansing), does not intice private investment – a key element in the improvement of industrial competitivity. "*Lava Jato* is a good thing. For the first time, everybody knows about what was hidden," estimated Gesner Oliveira. "In the longer term, that cleansing should make the market healthier and stimulate investments, especially the foreign ones." Experts considered that this might happen after the presidential elections scheduled for 2018 (Gatinois, 2017).

• Argentina

Argentina comes behind the United States and Brazil in terms of area where genetically modified crops are cultivated, mainly soybeans, maize, canola and cotton. In an official act, the president of Argentina, Cristina Fernández de Kirchner, on 5 October 2015, highlighted that with the approval of drought-tolerant soybeans – the first in the world – and also with that of PVY-virus-resistant potato, Argentina has become member of the select group of countries which are able to produce their own GM crops. The drought-tolerant soybean was developed as the result of a private-public partnership: the team working under the leadership of Raquel Lia Chan and belonging to the "National Universidad del Litoral" and the National Scientific and Technological Research Council (CONICET); and the biotechnology company Bioceres.

Potato is attacked by several viruses which cause great losses in the harvests made in the south, centre and north of the country. The virus PVY (potato virus Y) is one of the main viral diseases and can cause losses up to 80% of the hervest; the farmers have to buy new seeds every year. The transformation technology was developed by the researchers of the Institute for Genetic Engineering and Biotechnology – INGEBI – of the CONICET: Fernando Bravo Almonacid and Alejandro Mentaberry. It is worth mentioning that it is the same group of researchers and those of INTA (National Institute for Agricultural Technology, near Buenos Aires) under the leadership of Esteban Hopp, who were able to develop several other potato varieties that will become available to the farmers in a short lapse of time. The national biotechnology company that will be in charge of commercializing the PVY-resistant-potato is Technoplant, a subsidiary of the pharmaceutical and biotechnology group Sidus.

Argentina has therefore become part of the countries which not only grow transgenic plants, but will develop them in order to meet their needs and thereafter to commercialize them. Raquel Lia Chan, from the Agrobiotechnology Institute of Litoral (Universidad del Litoral) and National Science and Technology Research Council (CONICET, Spanish acronym), Santa Fe, Argentina, Eduardo Blumwald of the University of California (Davis) Department of Plant Sciences, Songhu Wang of the Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, Jessica Raineri and Zvi Peleg of the Hebrew University of Jerusalem Robert H. Smith Institute of Plant Sciences and Genetics in Agriculture (Rehovot, Israel), published in the July-2015 issue of Plant Molecular Biology (Raineri et al., 2015) the results of their collaborative research on the transcriptomic analysis of the drought response of transgenic rice plants expressing PSARK::IPT, validated by qPCR; the analysis indicated that a divergent rice transcription factor OsWRKY47 was induced under drought stress in these rice plants. Using OsWRKY47, knockout mutants and transgenic rice overexpressing OsWRKY47, they showed that the transcription of these putative targets (e.g. two genes encoding a Calmodulin binding protein and a Cys-rich secretory protein) were regulated by OsWRKY47. Phenotypic analysis carried out with transgenic rice plants showed that OsWRKY47 mutants displayed higher sensitivity to drought and reduced yield, while plants overexpressing OsWRKY47 were more tolerant. Raquel Lia Chan, director of the Agrobiotechnology Institute of the Littoral (IAL) and a renowned researcher at CONICET, declared in the city of Santa Fe (near Rosario) that she hoped to proceed with field trials and thereafter with the commercialization of the seeds of this GM rice. Raquel Lia Chan was in 2013 among the 10 women in Latin America who have been leading advanced scientific research, according to an evaluation made by the London BBC and the InterAmerican Network of Academies of Science.

The biotechnology company Bioceres was created in 2001 and its capital is divided among 260 shareholders, some of them being big farmers such as Gustavo Grobocopatel, dubbed the "king of soybeans," and a former president of Monsanto's local subsidiary. "Argentina was among the first countries who adopted GM seeds in 1995 combined with no-tillage farming," explained Martín Vásquez, the scientific director of Bioceres. He added: "The shareholders realized that much research was performed in the academic world, but there were no products developed," and thought that Bioceres could be a place where research and development could take place. The founders of Bioceres, most of them from Buenos Aires, made the decision not to centralize the company in the country's capital, but in Rosario, the heart of Argentine agriculture. Rosario had specialists in agronomy, biotechnology, biology and business management and finance. The premises of Bioceres were ubicated on a land which was obtained gratis for 20 years from the CONICET. The staff, most of them around 30 years of age, was taking care of a company that received over €40 million per year, partly in the form of a subsidy from the science ministry as well as a support from the European Union and Spain (Rebossio, 2015).

Bioceres has participated in the national development of seeds of crops resistant to drought and to salinity. In 2017 Bioceres planned to start commercializing its first soybean seeds, HB4. "This variety produces 15% more in arid zones than conventional plants, while in more fertile zones and less prone to drought, it can be used by the farmer as an insurance against an eventual drought, explained M. Vásquez. Bioceres has patented some 50 events (i.e. transformed plants or the process leading to them), and it will be the first in its specialty to be listed in Wall Street: it will be the third to be listed in the NASDAQ, after Mercado Libre (an electronic commerce enterprise) and Globant (a software company) [Rebossio, 2015]. Bioceres is also involved in industrial biotechnology and lends services of high quality. For instance Bioceres' researchers were able to synthesize in an oil-producing plant, safflower, which grows in the north and south of the country, the enzyme chymosin which is used for clotting milk in the manufacture of cheese. The enzyme is produced in the seeds from where it is isolated in the aqueous phase, while the meal could be used as feed (Rebossio, 2015).

Argentina invests 0.65% of its gross domestic product (GDP) in research and development (R&D), just behind Brazil. During the presidence of Néstor Kirchner and thereafter that of Cristina Fernández de Kirchner, the investment in R&D was increased significantly from 0.40% of the GDP. That was acknowledged among the beneficial effects of this presidence; Rogelio Frigerio, economic adviser to the challenger of Cristina Fernández de Kirchner, Mauricio Macri, reckoned that the past economy had achieved the generalization of social benefits as well as a positive reevaluation of science, with not only an increase in the overall GDP dedicated to R&D, but also with substantial means (Rebossio, 2015).

Argentina was been a pioneer in no-tillage agriculture since the 1970s. Forty years later, this practice was carried out in more than 90% of agricultural land, according to the Argentine Association of Producers in No-Tillage Agriculture. During the 1990s this practice was applied in conjunction with transgenic Roundup Ready soybeans, i.e. resistant to the Monsanto's herbicide Roundup, whose main active component is glyphosate. Argentina became the world's leading exporter of soybean oil and meal, as well as the world's third-biggest producer of this oleaginous crop, just behind the United States and Brazil, where cropland was three times that of Argentina and whose respective populations were seven and four times larger. Most of Argentine soybeans and soybean products are sold to China, Europe and Russia (Cué and Centenera, 2017).

Biotechnology has therefore become an important tool for the expansion of agriculture in Argentina, as well as an area of innovation where a country can create its own GM crops. This could be a good example to follow by others who have adopted these crops. Argentina's share of the world's trade of grains was *ca*. 13% in 2015. Such an expansion of mechanized and intensified agriculture over large acreages displaced traditional agriculture with some deforestation of native woodlands and migration of small farmers involved in familiar production. Today the management of agricultural land in Argentina is increasingly in the hands of many young scientists, equipped with iPhones, portable computers and trained in the treatment of big data. Thus, agricultural engineers make decisions from their offices according to satellite-provided data and analyzed by Frontec, a programme designed by the public enterprise Invac, considered as the emblematic icon of Argentine technological development. "Frontec treats the satellite images made during the last 30 years and regarding the critical periods of crop development, and thus can determine the environments of higher and lower productivity in every cropland," according to Diego Collivignarelli, coordinator of the Buenos Aires central and southeastern region of the so-called group Los Grobo. The latter is one of the best-known Argentine agroindustrial groups, whose headquarters are ubicated in Carlos Casares, amidst the humid pampa – one of the most fertile agricultural regions of the world – 330 km from Buenos Aires (Cué and Centenera, 2017).

This agroindustrial group has been created by Gustavo Grobocopatel, and it managed in 2017 some 300,000 hectares of cropland distributed in Argentina, Brazil and Uruguay. All this land was rented and G. Grobocopatel was never the landlord. This businessman also thinks that the success of his group was due to the fact that it was ubicated far away from Buenos Aires. He stated in this regard: “Politicians were not aware of what was going on in the agricultural areas, the latter were developing by themselves!” Today agricultural engineers of the group Los Grobo are analyzing and distributing the data regarding the growth and development of the crop (mainly soybeans) to every farmer, with the prescriptions about how much fertilizer should be added to his/her cropland. The whole process is automated. Other employees of the group, called brokers, analyze the data concerning the prices of the crop at Chicago and Rosario stock exchanges, in order to sell the product at the right moment; and that enabled large-scale farmers to make big fortunes. It is finally this kind of agriculture that is supertechnologically managed – which some consider much more advanced than that of wealthier countries, e.g. in Europe – that once again saves Argentina from the economic crises it has been going through on several occasions (Cué and Centenera, 2017).

“Argentina will be able in a few years to produce food for 800 million people,” stated Daniel G. Pelegrina, of the Argentine Rural Society, while in 2017 the country was producing enough food for 400 million people. By contrast to the lower competitivity of a large part of Argentine industry, which has enjoyed protectionism established by the government, Argentine agriculture has maintained its efficiency for decades. The president of Rosario’s Commercial Stock Exchange, Alberto Padoán, remembered that his Spanish partners considered “it was unbelievable that agriculture and livestock husbandry could function, despite the high export taxes that were so important for the State’s coffers. Mauricio Macri, Argentina’s re-elected president in October 2017 with a substantial majority, has been obliged to leave his farming activities two years before due to his political commitment. Nevertheless the president was considered a great ally of the farmers. He stated in this regard: “In Europe the governments promote agricultural exports thanks to subsidies, while in Argentina taxes of 35% were imposed on these exports. Now the pressure on the agricultural sector has been much lower and, for this reason, we have reached 130 million tons of exports.” Indeed the decrease in taxes, the announcements regarding new transport infrastructures and the appointment as agroindustry minister of the man in charge of the largest rural association have been received with great optimism by Argentine farmers (Cué and Centenera, 2017).

• Mexico

Mexico is the world’s fifth-biggest maize producer with 23 million tons per year, but its consumption is 33 million tons. This deficit should be imported, mainly from the United States, and that makes Mexico the world’s second-biggest importer of maize behind Japan. Imports were estimated at 40,000 million of pesos (equivalent of *ca*. US$4 billion) by the end of 2015. A legal decision cancelled the precautionary measure which impeded the experimental cultivation of GM maize. Consequently both the agriculture secretariat and that of environment and natural resources could deliver permits to continue the experimental planting of GM maize, which in fact started in 2009 and was interrupted in 2013. Alejandro Monteagudo, director general of AgroBio México, highlighted the need to abide by the law and plant GM maize in areas which are not considered the centers of origin and genetic diversity of the crop. Furthermore he mentioned that once GM maize is commercialized, the native varieties of this crop species will not be threatened, because they are very distant from the cultivation areas of GM maize (in the north). GM maize (mainly yellow maize, cultivated for feed), if properly managed, far from the criollo maize in South and Central Mexico, would contribute to seriously reduce the imports of yellow maize from the United States.

GENETICALLY MODIFIED ANIMALS

Approval of a genetically modified salmon for consumers in the United States

The AquAdvantage salmon, as it is known, is an Atlantic salmon (Salmo salar) that has been genetically modified so that it grows to market size faster than a conventional farmed salmon. It was developed in 1982 by AquaBounty Technologies, which is now majority-owned by the Intrexon Corporation. AquaBounty Technologies first applied for approval of the salmon in the 1990s, but it took years to determine what data would be needed and how the GM salmon would be regulated. In 2010 the Food and Drug Administration (FDA) tentatively concluded the fish would be safe for consumption and for the environment. In September 2010 an advisory committee found some fault with the FDA's analysis but did not in general challenge the overall conclusions. Then in December 2012 the FDA released a draft assessment that also concluded that GM salmon would pose little risk to the environment (Pollack, 2015b).

The FDA regulates genetically engineered animals as veterinary drugs, using the argument that the gene inserted into the animal meets the definition of a drug. Critics have branded this as an inadequate solution intended to squeeze a new technology into an old regulatory framework. They said the FDA is not as qualified as other government agencies to do environment assessments. The FDA retorted that to approve the Atlantic salmon (GM) it determined that the fish was safe to eat, that the inserted genetic elements did not harm the fish itself, and that AquaBounty Technologies had adequately proved that the salmon grew faster (Pollack, 2015b).

The AquAdvantage salmon contains a growth-hormone gene from the Pacific king salmon called chinook salmon and a genetic switch from the ocean pout, an eel-like creature, that keeps the transplanted gene continuously active, whereas the salmon own growth-hormone gene is active only during parts of the year. The company stated the fish could grow to market weight in as little as half the time of a conventionally farmed salmon (in 16 to 18 months instead of 30 months). Moreover the transgenic fish needs 75% less feed than its normal relatives to reach the adult size, so that its carbon imprint was reduced by a factor of 25. Opponents of the GM fish made the point that if the bigger fish were to escape, they could outcompete wild salmon for food and mates. Other scientists dismissed these concerns. The FDA stated that there were multiple physical barriers in the Canada and Panama facilities to prevent this. The GM salmon is also made sterile to prevent reproduction in the event they do escape. However the sterilization technique did not seem to be accurate (Pollack, 2015b).

On Thursday 19 November 2015 federal regulators approved the genetically engineered salmon as fit for consumption, clearing the way for the first genetically altered animal species to reach American supermarkets. Five years had elapsed since the FDA reviewers made their initial determination that the fish would be safe for consumers and for the environment, an unusually long period between preliminary and final approval. "The FDA has thoroughly analyzed and evaluated the data and information submitted by AquaBounty Technologies regarding the AquAdvantage salmon and determined that they have met the regulatory requirements for approval, including that food from the fish is safe to eat," stated Bernadette Dunham, director of the Center for Veterinary Medicine, an arm of the agency (Pollack, 2015b).

It was not immediately clear whether the GM salmon would be labeled so that consumers would know its origins. The FDA indicated that labeling would not be mandatory, a decision that is consistent with its position on foods derived from GM crops: genetic engineering in and of itself does not necessarily make a material change in the food. But on 19 November 2015 the FDA issued two documents providing guidance to companies on how to voluntarily label their foods to indicate whether they were made using genetic engineering. One is a draft guidance aimed at GM salmon and the other is the final guidance for GM crops (Pollack, 2015b).

The GM fish are supposed to be raised indoor to lessen the chances that they will escape in the wild. AquaBounty Technologies commented that this will also be less stressful on the environment and could eventually allow the fish to be raised in the United States, rather than being imported, as most farmed Atlantic salmon is. "Using land-based aquaculture systems, this rich source of protein and other nutrients can be farmed close to major consumer markets in a more sustainable manner," stated Ronald L. Stotish, chief executive of AquaBounty Technologies, on 19 November 2015. For now the GM fish are being raised in Panama, from eggs produced in Prince Edward Island, Canada. Approval to breed or raise the salmon elsewhere, for marketing to Americans, would require separate approvals (Pollack, 2015b).

On Friday 4th of August 2017 AquaBounty Technologies announced that it had delivered 4.5 tons of its transgenic salmon to various Canadian stores during the year-period that elapsed. Ronald L. Stotish, the chief executive of the company based in Maynard, Massachusetts, stated that "the sales of the transgenic fish and the discussions held with potential buyers of it clearly demonstrate that the clients wanted that kind of fish, and that the company was eager to increase its production capacity in order to meet the demand." It should be recalled that 25 years elapsed before the Canadian health ministry and the Canadian Agency for the Survey of Food Safety approved in May 2016 the possible marketing of the transgenic fish. After four years of tests the two institutions claimed that this new type of fish was as safe and nutritive as the non-transformed fish. Furthermore the Canadian agriculture ministry, Laurence MacAulay, expressed his trust in the new food product, and that he was willing to eat it (and he seized this occasion to mention that in Canada several crop species have been genetically transformed and foods derived from them were eaten by Canadian consumers) [Mougeot, 2017a].

However the ecologists and the associations for the protection of consumers denounced the fact that the transgenic salmon was not labeled as such. It is true that the Canadian agencies impose labeling on only products that may represent a risk for health, such as those foods which contain an allergenic substance. The Canadian regulation takes only into account the nutritive features or characteristics as well as the safety standards required during the whole production and farming processes. The environmental associations and opponents of transgenic salmon have since then tried to convince the big food distribution companies not to market such a transgenic fish. For instance some wholesale dealers and retailers such as Sobeys, Loblaws and the North American giant Cosco announced that they will not sell transgenic salmon, nicknamed “Frankenfish” (Mougeot, 2017a).

Another difficulty arose when the Canada - European Union Trade Agreement was to become effective as of 30 October 2016 (although its full operation was still dependent on the votes of the parliaments of the EU’s 28 member states): could the transgenic salmon be commercialized in Europe, whereas there are European States which are fierce opponents of transgenic organisms. For instance, in the report delivered on 8 September 2017 to the government of France, it was stated: “With regard to genetically-modified organisms and products derived from them or based on them, it is absolutely necessary that these products be clearly labeled as such, including the transformed products derived from them… This raises the issue of traceability of these products, bearing in mind that in Canada a specific labeling of these products is not required” (Mougeot, 2017b).

Consequently the traceability of these products imported from Canada is an issue. “The multiplication of health scandals related with food imports underlines the fact that the competent authorities cannot really undertake the necessary controls in order to make sure that these genetically modified organisms-derived products do not reach the French or European markets,” stated an expert of the Foundation for Nature and Man (*Fondation pour la nature et l’homme*, FNH). In fact to make a difference between a transgenic salmon and non-transgenic one, the competent authorities should make a genetic test “that costs between €5 and €15, a rather expensive one” (Mougeot, 2017b).

The issue of labeling is even more difficult to solve when the trade agreement between Canada and the European Union aims at reducing or even eliminating tariff barriers (i.e. tariffs and quotas), as well as non-tariff obstacles, e.g. the standards and regulations of goods and services produced in Canada and the European Union. Thus the tariff on Canadian salmon would have to decrease from 15% to 0%. In addition both partners “have committed themselves to drastically limit the labeling rules which are being considered as obstacles to trade,” stated Samuel Leré, in charge of environment and globalization within the FNH (Mougeot, 2017b).

Moreover for those institutions that would aim at finding the uniformization of norms and standards, courts would be set up in order to analyze and decide about litigation cases between both parties, as well as between a company and one of both parties. “In this respect, the precautionary principle which is followed in the European Union, would be challenged by Canada, because the latter requires the proof of a health risk before forbidding the marketing of a food item,” underlined S. Leré. The company AquaBounty Technologies was interviewed by the French daily newspaper *Le Monde* and it replied that “the approval of its transgenic salmon by the European competent authorities was not yet relevant in its development plan” (Mougeot, 2017b).

Salmon farming is the answer to sinking stocks at sea and to the fact that a large percentage of salmon that returned to their breeding rivers to spawn the next generation never made it. For instance, in Britain 20 years ago, 30% of wild salmon managed to complete the trip up their home river; today, the figure is 5%. At the Bushmills monitoring station in Northern Ireland, less than 3% of tagged fish returned to spawn in 2011, the lowest level since recording began in 1987. Fewer than 3,000 salmon made it back to the River Eden in north-west England in 2014, short of its “conservation level” of 5,000. Most of those that do make it have spent two years at sea, whereas in the past the majority came back after a single year (*The Economist*, 2015c).

There is no consensus over the cause. Warming seas may be one. But these do not seem to be harming herring or mackerel, which have been caught in record numbers. Another theory is that salmon farms, which rear most of the fish that are consumed, are crowding out the wild kind by releasing large amounts of salmon lice – a parasite that can kill juveniles – into their surrounding waters. In October 2015 Salmon and Trout Conservation Scotland, a trade group, called for a freeze on farm expansion; farmers, unsurprisingly, denied any link. Even if scientists are unclear why stocks are declining, they have ideas about how to bolster them. Our step is to construct more “fish passes,” ladders that enable migrating salmon to bypass the trickiest obstacles; since 2009 the government has built 63, opening up 3,700 km of salmon-friendly waters. Salmon were recently found on the River Dearne in Yorkshire for the first time in 150 years. Cutting the numbers of salmon-fishing licenses would also help (*The Economist*, 2015c).

Genetically transformed animals using the new genome-editing techniques

Besides salmon there has been a surge of interest in developing genetically engineered farm animals and pets, because the new genome-editing techniques allow the scientists to edit animal genomes rather than add genes from other species. That has made it far easier to create altered animals. On 30 January 2014 the journal *Cell* published the results about the first two primates whose genome was modified using the Crispr-Cas9 technique. The research work was carried out at the University of Nankin, and Huang and this team hoped to modify three targeted genes. They were able to genetically modify 180 embryos, and to implant 83 of them in surrogate macaque mothers. Ten pregnancies were obtained and only one gave birth to both primates with only two mutated genes instead of the three that were initially targeted. The pictures on the cover of the Cell issue of Linglin and Mingming, the newborn macaques, heralded the CRISPR-Cas9 technique worldwide (Niu et *al.*, 2014). According to Weizhi Ji, the former director of the zoo of Kunming (Yunnan) and member of China’s National Academy of Sciences, who participated in that experience which aimed to develop more realistic models of human neurodegenerative diseases, both monkeys were doing well and they are “closely under observation in order to detect any deleterious effect of the Crispr-Cas9 in the long term” (Leplâtre, Herzberg and Morin, 2016).

The new genome-editing techniques seemed therefore ready to be used in animals. For instance Chinese scientists were able to create goats with more muscle and longer hair. Researchers in Scotland used gene editing to create pigs resistant to African swine fever (Pollack, 2015b). In the French city of Nantes (centre-west of the country) the team led by Ignacio Anegon, director of the Research Centre for Transplantation and Immunology (UMR 1064), has collaborated with the Pasteur Institute of Montevideo (IPM), Uruguay, to develop the first sheep obtained through the use of Crispr-Cas9. This transformed sheep had much more muscle due to a mutation of the gene encoding myostatin, a growth factor which usually inhibits muscle development. “This mutation exists in natural conditions, in sheep living on a Danish island but also in a Belgian breed of cows,” explained I. Anegon. “Crispr has allowed the geneticists to obtain the mutation in the sheep studied much more rapidly than going through conventional selection schemes,” he added. This kind of genetically engineered animals are not yet authorized for commercialization. “They cannot be qualified as transgenic, because they have not inherited a gene coming from another species. But they have been nevertheless genetically modified," stated I. Anegon. There is also the issue of intellectual property regarding the patents filed for CRISPR-Cas9 and the dispute about them; and, according to I. Anegon, this is a factor that does not encourage industrialists in developing and patenting such kind of animals (Leplâtre, Herzberg and Morin, 2016).

Jennifer A. Doudna, professor at the University of California, Berkeley, who is considered with the French microbiologist Emmanuelle Charpentier as the co-discoverers of the genome-editing technique CRISPR-Cas9, created a startup Caribou Biosciences in 2011 so as to draw the profits from the patents on the technique and its applications. This startup raised initially US$11 million in funding and focuses on cell engineering for drug screening, agricultural and industrial biotechnology. Caribou Biosciences signed agreements with DuPont and Pioneer; it engaged into a partnership with Genus, specialized in animal genetics, with a view to developing pigs resistant to a virus causing a respiratory and reproductive syndrome (in this case again, there was no transfer of a gene from one species to another). Caribou Biosciences has also formed, with the big pharma Novartis and a venture-capital firm, a startup called Intellia Therapeutics (J.A. Doudna and L. Marraffini). With US$15 million raised in 2014 and an estimated value on the stock exchange of *ca*. US$900 million in 2016, Intellia Therapeutics will focus its work on gene therapies where cells are taken from patients, edited and put back into them (*The Economist*, 2015b).

Use of genome-editing techniques in the eradication of insect vectors of pathogens

When the technique CRISPR-Cas9 was discovered and used in plant and animal cells (and even in human embryos which were not transplanted into the womb), the genetic transformation of insect vectors of pathogens changed gears.

Gene drives

Animals have two versions of any given gene on two different chromosomes and the two versions or alleles can have important differences. Offspring normally inherit only one of each pair of chromosomes from each parent, and thus each version of the gene typically is found in only half of them. Techniques like CRISPR-Cas9 make it possible to break this rule with what is called a *gene drive* – a gene that uses gene-editing techniques to copy itself from one chromosome to the other, so that whichever chromosome the offspring inherits, they have the same version. The same will then apply to their offspring, too. In the case of normal inheritance (a gene on only one chromosome gets into only some offspring) the mating of a wild-type mosquito with a mosquito with a modified gene gives an offspring which have a 50% chance of inheriting the modified gene; in the case of gene drive inserted into one chromosome that copies itself into the other, the mating of a wild-type mosquito with a mosquito with gene drive gives an offspring where nearly 100% of the individuals inherit the modified gene.

Normally genes can only spread through a population if they confer an advantage. Gene drives can spread genes faster than the process of natural selection. A gene drive indeed should be able to spread through a population even if it is bad for its possessors. In 2003 Austin Burt – professor of evolutionary genetics at Imperial College London – suggested that this might be a way of altering wild animals so that they stop, for instance, to spread disease. As mentioned above, if mosquitoes were given a gene drive that makes them unable to transmit the malaria Protozoan (*Plasmodium* spp.) and then are released, the new trait's quick spread through the population at large would lower the burden of disease. See Sasson (2016, pp. 147-148; 224-227; 270-271).

Gene drive and eradication of insect vectors of pathogens

Gene drives remained theoretical until the beginning of 2015 when researchers tested Crispr-Cas9-based implementation of the idea in yeast and fruit flies. In January 2015 Ethan Brier and Valentino Gantz of the University of California, San Diego, used the technique to transform germinal cells of fruit flies (*Drosophila*) and they informed Anthony A. James of the University of California, Irvine, about their results. Eric Marois, a researcher at the French National Institute for Health and Medical Research (INSERM) and the University of Strasbourg, who works with the team of Andrea Crisanti and Tony Nolan, at Imperial College, London, on the genetic transformation of *Anopheles* stated: "The new technique has made an upheaval and we all tried to grab it." The team of Anthony A. James was the first to publish at the end of November 2015 in the *Proceedings of the National Academy of Sciences (PNAS)* USA an article where they described how to integrate a gene for resistance to *Plasmodium falciparum* – the Protozoan causing the deadliest form of malaria – into the genome of *Anopheles stephensi* – the main vector of the disease in the Indian subcontinent (Gantz et *al*. and James, 2015).

On 7 December 2015, A Crisanti, T. Nolan and co-workers published an article in *Nature Biotechnology: they targeted Anopheles gambiae* and wanted to spread a sterility-recessive gene. The trait is initially silently transmitted and thereafter it spreads at a huge speed. The insect vector is not just transformed, it is eradicated (Hammond et *al*. and Crisanti and Nolan, 2015). The Bill and Melinda Gates Foundation had supported A. James' research and also invested US$40 million in A. Burt's work on mosquito eradication. Each research team – the American and British – defends its technique. In both cases there are possible negative impacts on the environment and on the development of resistance among the mosquito populations. Kevin Esvelt, assistant professor at the Massachusetts Institute of Technology and also a pioneer in gene-drive research, made the following statement: "This bestows on us a formidable responsibility. We must assess all the risks and take all measures and precautions in order to minimize them." He published in *Science*, with several other scientists from the main international laboratories working in the area, a catalogue of recommendations concerning the use of gene drive, from the confinement of the laboratories to a set of rules. In his own view, there is no question to reject in principle gene drive. He was aware of the possible negative effects of this genetic technique, but, while he fully supported more research on these effects and ways to mitigate them, he recalled that working on the eradication of mosquito populations is a very relevant goal: "Do we forget that malaria still kills 1,000 children a day, despite the progress made?" (Oye et *al*. and Esvelt and Church, 2014).

It is true that the number of deaths caused by malaria has almost been halved between 2000 and 2015, due to the use of antimalaria drugs, of protective nets (with insecticide) and to better care provided to the patients. Austin Burt, however, did not set out to commit mosquito genocide. "Our target is malaria, not mosquitoes," he stated. "Mosquitoes are a means to an end." But once unleashed, Burt's mosquitoes have not kill switch; they will carry out their mission until there are no females left – it is the females which bite humans and transmit the pathogenic Protozoan. To some experts, it is a small sacrifice. But others worry about the implications of leaving a biological niche empty. As much as Anthony James would love to see a mosquito-free planet, he doubts we will ever get that far: "I just do not think there are enough, enough wills, to do this. There will always be small, isolated pockets of mosquitoes that will persist." We cannot afford to let up on the workaday methods that may not offer the promise of total extermination, but can still save lives – including clearing mosquito habitats, spraying walls and using bed nets (Sifferlin, 2016). "There is a potential that we are in trouble if all mosquitoes are gone," said Cameron Webb, a medical entomologist at the University of Sydney in Australia. Mosquitoes are an abundant snack for many kinds of birds, bats, fishes and frogs, and they may also play an important role as pollinators for some plants. Still, he said, the selective elimination of a species like the dengue or Zika viruses-carrying *Aedes aegypti* is not likely to do much harm, especially since it is largely an urban-dwelling creature. “If you were to eradicate *A. aegypti*, the ecological consequences are probably going to be quite low, and I think that is a fair trade-off given the incredible reduction in mosquito-borne-diseases,” admitted Cameron Webb (Sifferlin, 2016).

In October 2015 the French High Council for Biotechnology (HCB, French acronym) received a request for advice on “the advantages and weaknesses of the new techniques of genetic modification of insects.” On 7 June 2017 the council gave a well-balanced advice, mentioning an “interesting prospect” but not a “miracle solution.” The council’s president, Christine Noiville, stated that “taking advantage of genetically modified mosquitoes can be useful, and we should not be deprived of this tool,… but we must replace it within the existing techniques of combating the harmful insects, we also must take all legal precautions and make sure that local populations are involved.” These statements were interpreted as a sign of prudence and balance (Herzberg, 2017b).

It should be recalled that the British company Oxitec had been testing for the last seven years the techniques of spreading genetically modified mosquitoes across the world (e.g. Malaysia, Cayman Islands, Brazil). The results were uneven: in Malaysia the competent authorities had decided to interrupt the experiments, because they thought that the results of the tests were not convincing. In Brazil tests were carried out and resulted in a 80% to 95% local decrease of the “animal population” during two seasons. That decrease concerned Aedes populations and the method used was considered “selective,” as recalled by Catherine Golstein, the coordinator of the High Council’s scientific committee (Herzberg, 2017b).

“The positive effects regarding the impacts on epidemics remain to be determined,” stated the French High Council for Biotechnology. The method consists of spreading insects over several following seasons. Consequently, “if the genetically modified mosquitoes should be part of a prevention and control method, the position regarding this method should be on the long term and not as an emergency technique.” But in case of a “health crisis”, insecticides would be still “necessary”, the High Council’s report added. On the other hand, the High Council recommended to regulate these tests or experiments very carefully. “The regulatory framework that applies to GMOs in Europe seems to be relevant.” Nevertheless, it needs a “clarification” for other mosquitoes, modified through the infection by *Wolbachia* bacteria, that have similar impacts. Tests were carried out in French Polynesia, but within a poorly regulatory framework (Herzberg, 2017b).

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Genetically modified organisms: implications within the microbial and plant kingdoms

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Abstract

The progress accomplished during the last three decades concerning the knowledge of microbial and plant genomes, along with modern biotechnological tools, open prospects for some solutions of specific problems in such fields as: health, food production, agriculture and environment. Adoption of these approaches may find a compromise between productivity, transformation of added-value products, increase of yields for crops better adapted to stress and preservation of global ecological balances. Applications of GMOs – microorganisms and plants – in medical and therapeutic fields are of obvious interest. However, their use in agriculture, their presence in the food chain and in the environment raise many scientific issues that lead to controversy about environmental, health and ethical implications.

This paper presents in the first place the different fields for the use of microbial and plant GMOs. A balanced assessment of the economic and environmental challenges of GMO crops present on the world market is made while comparing the benefits, eventual fears, as well as ethical and social issues. Then, an overview of the relevant biosafety measures is presented.

Some unprecedented innovation prospects can be expected from the recent development of new revolutionary technologies. However, some issues are raised with regard to the risk-evaluation principles and procedures concerning these emerging genome engineering techniques.

Introduction

The modern biotechnological tools and the knowledge of microbial and plant genomes offer scientific solutions and opportunities, potential as well as unlimited areas of innovation. Some prospects are opened for the partial solution of certain specific problems when we are facing global changes and should respond to economic and environmental issues. The adoption indeed of these biotechnological approaches, which lead to the development of Genetically Modified Organisms «GMOs», could find a compromise between added-value productivity, yield increase of well adapted crops and the preservation of major ecological systems. However, basic health and environmental issues remain at the forefront of scientific debates. In order to understand in which way the products derived from modern biotechnologies could be adopted, it is first important to provide a general overview of their applications.

The relevant uses of GMOs (plants, animals and microorganisms) are relatively broad and related to several different fields, from fundamental research to applications in sectors such as medicine, food industry, agriculture and environmental protection. They are considered as part of the 21st century technology.

In this paper, we shall only address certain applications of GMOs (microorganisms and plants), as well as regulation measures and control of potential risks.

1. Use of genetically modified microorganisms (GMMs)

A number of products derived from GMMs are already authorized for use in the pharmaceutical and agrifood industries. Since 1980, the GMM bacteria, fungi and yeasts are considered as microorganisms having acquired new properties of producing molecules with therapeutic interest. Currently, they are utilized as producers of live vaccines, hormones (insulin, human growth hormone), antibodies, nutraceutics [1]. These bio-medicines represent 70% of the GMO market and play an important role compared with conventional drugs, and they are considered as the medicines of the future [2]. They are produced under tight and controlled confinement conditions in compliance with the requirements of optimal health safety. The procedures also require a purification of final products to be exempt from residual DNA or live GMM in the residues of fermentation processes in order to prevent any transfer of GMM genes to the autochtonous digestive microflora of humans, animals or in the environment.

New live GMMs may replace the active principle and might be consumed by humans via food preparations (medicines, enzymes, probiotics or others). The therapeutic applications are numerous:

- Delivery of medicines in the lower parts of the digestive tract without having to use complex galenic pharmaceutical preparations,
- Administer vaccines via oral, parenteral or nasal routes,
- Exposition of viral or tumoral antigens to neutralizing antibodies,
- Modulate immune reaction via the concomitant production of different interleukins and antigens,
- Desensitize, in the case of food allergies, via the oral route, using a modified allergen-producing GMM.

All these approaches need the consumption of live bacteria, some of which express eukaryotic proteins; henceforth the need of risk/benefit studies. The therapeutic use of GMM, in humans and animals, against severe diseases seems to be well accepted by the general public, since they help in the control and management of epidemics and health crises. In the agrifood sector, GMMs are also used as fermenting biomass for the production of enzymes, aromas, food additives or as technological auxiliaries in human food (production of wide-spectrum bacteriocins, improvement of organoleptic quality of dairy products) or in animal feeding (production of cellulase, xylanase, phytase; threonin, lysine, tryptophane; somatotropin, probiotics) [3].

Other uses of GMMs exist in:

- Agriculture: biopesticides, biofertilizers, growth promoters, nitrogen biological fixation [4];
- Animal husbandry : nutrition an animal growth,
- Industry: production of biofuels [5], biosurfactants [6], enzymes and organic acids;
- Environment: depollution, bioremediation [7] with a view to degrading such resistant products as organophosphorus compounds, polychlorobiphenyls (PCBs), heavy metals, pesticides, xenobiotics and products whose metabolic pathways do not exist [2].

2. Uses of Genetically Modified Plants (GMPs)

GMPs are also used to produce molecules of interest in various economic sectors. We will only address here the uses in the agricultural and industrial sectors.

Genetic engineering offers new plant-selection tools for such agronomic traits as: tolerance to herbicides, resistance to biotic stresses (pathogens), tolerance to environmental stress (drought, salinity and cold) and improvement of production. These GMPs present several advantages: higher yields, quality improvement of products, reduction in cropping costs, protection of crops and environment due to a lesser use of agricultural inputs.

The market of transgenic plants is rather small since it deals with only four industrial crops (soybeans, maize, cotton and colza or canola) and four transgenic traits such as: tolerance to herbicides (glyphosate), resistance to insect pests (Bt Cry gene), tolerance to viruses and fungi by means of different expression strategies of genes coding for proteins that inhibit different stages of the pathogen's life cycle.

Other industrial applications concern the:

- genetic transformation of forest trees used for paper industry, either by under-expressing certain genes coding for lignin biosynthesis or by over-expressing the same genes in order to increase the energetic value of wood [8];
- production of plant-derived polymers, e.g. biofuels and biodegradable plastics;
- production of molecules of pharmaceutical interest (human serum albumin, gastric lipase; hemoglobin, vaccines,) [9].

2.1. Economic and environmental issues of GMPs

GMO crops appeared at the beginning of the 1990s in the United States. In 1998, they were covering nearly 28 million hectares across nine countries, 75% of which were located in North America. Since then they witnessed an important growth rate, reaching in 2016 an area of 179.7 million hectares in 28 countries [10]. However, the GMO crops are mainly located in five countries (United States, Brazil, Argentina, India and Canada).

The impressive development of modern biotechnologies in various economic sectors (agrifood and pharmaceuticals) is a technological revolution that triggered a large debate relating to the scientific, economic, social and ethical issues. Opinions are diverging, some underlining the opportunities and others fears from GMOs. Some people put forward the advantages of these advanced technologies aimed at improving the productivity of various economic sectors (agriculture, health and environment), as well as nutrition and subsequently human and animal well-being – thus contributing to food security at the global level. Others insist on immediate or latent hazards, as well as on implications difficult to predict, such as threats to environmental balance and public health.

The potential risks linked to transgenesis are mainly of two types: health risks and environmental risks [11].

The health risks concern, in the first place, bioresistances associated with the use of marker genes of resistance to kanamycin (nptII) during transgenesis. This is a risk of horizontal transfer of genes to bacteria in the digestive system of human or animal consumers. It is a risk that is considered very low; however, the use of these marker genes in the 1st generation of GMOs, was discontinued by European directives since 2005. New transformation practices were developed, e.g. the use of genes for the selection/absorption of two non-assimilated carbon sources by the plant (mannose and xylose), or production of a fluorescent protein.

Secondly, the risk of the emergence of allergies is also taken into consideration. It can be linked to two factors, either the transfer of genes coding for allergens not-present in the original plant, or of genes that produce proteins that activate allergens present in the plants (rice, peanuts, nuts).

Other potential indirect health risks concern: residues from crop treatments (herbicides, adjuvants and metabolic residues); the use of viral sequences, such as the promoter P35S of the cauliflower mosaic virus, as a source of mutation or viral recombination in the human genome. It is a risk that is considered inexistent, since the virus replication cycle takes place in the cytoplasm.

The expected environmental risks are of three types: resistance to herbicides with the creation of new invasive species; transmission of resistance to insects either by diffusion of the resistance gene to crop relatives or through the selection of insect populations resistant to the toxin; and gene pollution due to the dissemination to non-GMO crops or due to the modification of the rhizosphere of GMPs.

Other possible risks of geopolitical or ethical nature may be foreseen, e.g. dependence of the agriculture of the South towards transgenic varieties of the North, therefore worsening North-South inequalities.

The risks of products derived from biotechnology are assessed case by case, using rigorous scientific evaluation studies regarding health and nutrition biosafety, and based on the concept of substantial equivalence (before being marketed).

Looking back over the last 20 years of GMOs use, national academies of sciences, of engineering and of medicine in the United States and Nobel Prize laureates have published a report in 2016 based on 900 risk-evaluation studies. This report confirms that GMO crops do not show more risks than conventional ones for human health and for the environment [12]. A strong, clear and vibrating message to the world indicated that biotechnology is safe and vital for the struggle against hunger, malnutrition, poverty and climate change.

2.2. Prospects for development and innovations

Since 1996, the GM crops have witnessed a global increase of their cultivated area from 1.7 millions hectares to 179.7 million hectares inn 2016 [10]. This increase in area is mainly due to the large adoption of GMPs by Brazil, China and India. New GM crops with «stacked traits» have been approved and/or commercialized in several countries, mainly United States, Brazil, Argentina, Canada and Myanmar.

Thanks to technological advances and innovation, 2nd and 3rd generations of crops have been developed by utilizing new gene selection techniques (NPBT : New Plant Breeding Techniques), based on new host systems and new modification approaches (from mutagenesis to gene insertion, using Nuclease without adding genes (S.A.G.E.), zinc-finger nuclease, meganuclease, TALEN, genome edition with CRISPR/Cas9). These approaches aim to silence genes or activate them, to mutate them or to replicate them, thus offering new modalities for genome modification [13]. In the case of CRISPR/Cas 9 system, gene editing allows the controlled and targeted gene correction, without the need for any external DNA nor for vectors. This powerful technology is a revolution that results in profound changes in genetic engineering and might lead to the development of optimized non-GMO seeds; and thus contributing to an intensification of sustainable agriculture and global food security.

The new-generation GMPs, indeed, may respond to various concerns and global issues such as: tolerance to drought, tolerance to soil contamination by salt and/or heavy metals, a better utilization of phosphorus and nitrogen in poor soils, plants with high nutritive value (vitamin content, e.g. carotene-enriched rice, content in essential amino-acids), a better tolerance (hypoallergenic rice), a better control of transgene insertion, expression and stability, as well as the reliability of GMPs in the production of biofuels or bioplastics. Most of this new-generation GMPs are in the experimental stage in the laboratory, some are at the stage of field control trials and/or limited commercial distribution.

A retrospective study on the supervision of crops derived from the new technologies and under investigation by the European Commission was carried in 2016 by an independent body: the High Council of Biotechnologies «HCB» in France [14]. Following a description of the NPBT and an analysis of the issues linked to their development, the various commissions (scientific, legal and social) have not identified any risks at the health and environmental levels, nor at the socio-economic and ethical levels.

Other approaches are also in the experimental stage and they would offer future prospects for agricultural, medical or environmental biotechnologies, using plants and/or microorganisms. They rely on: i) epigenetics that changes gene expression without transformation of the nucleotide sequence; ii) xenobiology through modification of the chemical structure of nucleic acids; iii) «synthesis biology» through the creation of whole organisms using determined DNA sequences. The latter technique is used in two main areas: production of proteins through mechanisms that interfere with DNA, in order to correct certain mutations; secondly, the change of some metabolic pathways in a cell, towards other ends than their primary functions [15, 16]. This transformation may be directed to generate high-added-value products (e.g. biofuels, rubber, molecules of therapeutic interest, hydrogen to generate electricity), or towards the degradation, by developing biosensors or biocaptors of pollutants and contaminants that remain in the environment, such as plastics, petroleum products, pesticides and heavy metals.

These innovative approaches might lead to the development of organisms that are potentially much safer from the health and environmental viewpoints, since they are unable to exchange their genetic material with that of natural organisms present in the environment. In fact, having their own enzymes for their genome reproduction, they would not be up to exploit the biochemical pathways of natural organisms. They may also be an alternative to chemical industry, less polluting and less energy consuming, as well as to current GMOs that present genetic pollution risks. However, issues are being raised about the modalities and evaluation principles of risks associated with these emerging possibilities of genome engineering. The risk-evaluation studies are based on the comparison of the genetically-modified product with a non-modified natural equivalent product, which is not always easy to do. This is an important challenge that the institutions in charge of this evaluation will be confronted with in the near future.

Taking account of the economic and scientific issues, it will not be reasonable to put an end to research using these innovative technologies in various areas. However, it may be stated that scientific development is faster than the implementation of regulations across the world. There is also a need to adopt accompanying biosafety measures in order to manage possible risks associated with health and environment, and also to follow a case by case approach. National as well as regional biosafety regulatory frameworks should be established in all countries that have ratified the Cartagena Protocol, according to article 19 of this protocol. It is also necessary to put in place a health follow-up mechanism in the zones of production and consumption of biotechnology-derived products, as well as a regional risk-evaluation observatory, along with a mechanism for addressing ethical issues raised by these new technologies [17].

Conclusion

Biotechnologies have raised hopes for the diagnosis of human and animal diseases, targeted therapies through the development of biomedicines, as well as in agriculture within its sustainable-development pillars (social, economic and environmental). Furthermore, new advanced engineering techniques are being developed and may lead to rather radical genetic changes.

In this time of globalization, it is mandatory to possess the means of understanding the challenges linked to GMOs and to innovative approaches. Furthermore, the good knowledge of new genome-transformation technologies will allow the development of GMOs that will meet the needs of developing countries. However, a supervision via wise precaution and vigilance should be adopted with a view to safeguarding human and animal health, and preserving our environment.

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Genetically modified fish in aquaculture

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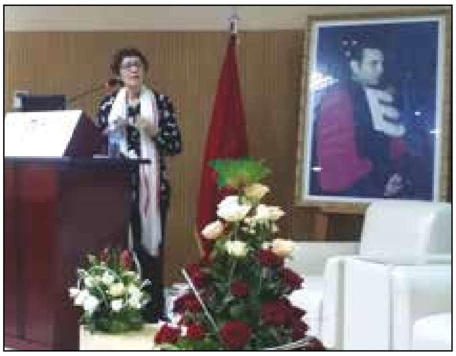
Introduction



Fish is recognized as a very healthy choice in human nutrition. Indeed, fish is a major source of high-quality protein and essential micronutrients, such as minerals and vitamins, which can contribute to alleviate diverse micronutrient deficiencies (Béné et al., 2015). In addition, fish have a unique lipid composition rich in omega-3 long-chain polyunsaturated fatty acids, which hasbeneficial effects in human health, including cardiovascular, inflammatory and neurological diseases (Tocher, 2009).

Fish consumption shows important regional differences in the world, as Asia accounts for more than 60% of total consumption while Africa shows the lowest rates with about 9 kg per capita and per year (Bene et al., 2015). Globally, fish consumption has considerably increased in the last decades, with an average annual rate of 3,2% from 1961 to 2013 (FAO, 2016).At the same time, capture of wild fish has remained relatively stable in the last 30 years,as most ocean fishery stocks are over or fully exploited. It is therefore fish farming that accounts for this increase in fish production, thanks tothe astonishing growth of the aquaculture industry known as the "blue revolution" (FAO, 2016). Indeed, aquaculture includes the farming of about 567 aquatic species including fish, molluscs, crustaceans and aquatic plants, from which around 220 species correspond to finfish and shellfish (Naylor et al., 2000). In the next future fish coming from aquaculture,which represent 44% of the total produced fish in these last few years (2013-2015), are expected to reach 52% in the year 2025 (FAO, 2016).

As outlined above,farmed fish are needed to meet the requirements of human consumption, but aquaculture should become a sustainable activity if we want to ensure a long-term supply of fish, as there are many factors related with the environment (water supply and quality, environmental impact, climate change, farming technologies) and also with the cultured organism itself (feed supply, diseases) thatcan affect its development.Improvement of certain characteristics of the fish can help to make aquaculture a more sustainable and profitable activity. It would be desirable to rear fish with fast somatic growth and efficient food-conversion rates, also animals that are healthy and illness-free with a safe and high nutritional meat quality. Ideally, fish should tolerate different environments;they should be easy to reproduce in captivity with short lifecycles and high fecundity, and preferably they should be species with low-trophic level (FAO, 2016; Naylor et al., 2000).

Despite all these challenges the contribution of biotechnology to aquaculture, and specifically to fish farming, has been very limited so far. Some of the best-known and commercially applied techniques include those of chromosome manipulation: the use of polyploidization, mainly triploidization, to produce sterile fish with increased somatic growth (Piferrer et al., 2009) or gynogenesis to produce all-female populations (Felip et al., 2001). Far behind stand all the approaches that include gene transfer in fish, which are nowadays only fully developed in a few model species dedicated to basic research, although considerable efforts have also been made in some cultured fish species (Dunham and Winn, 2014).

The contributions that gene transfer can make to aquaculture are related with the introduction of new characters and the improvement of characters of economic interest such as: animal health, growth rate, weight, food conversion rate, meat quality or control of reproductive cycle. Most of these processes are very complex and they involve the action of different genes, so that a more deep knowledge of the underlying mechanisms is previously needed. Following are the areas with significant advances, although they are at very different levels of development.

Growth hormone transgenic salmon

The ability of salmonids to respond to exogenously applied growth hormone is well known (Mc Lean and Donaldson, 1993). It is therefore logical that this is the application that has attracted most interest in the area of transgenic fish. In addition, this strategy was supported by the fact that the first stable transgenic animal was a mouse harbouring an exogenous GH gene that showed an extraordinary growth (Palmiter et al., 1982). This approach has been tried in quite a few numbers of fish species using very different DNA constructs regarding the origin of the GH gene and the promoter. In the first experiments performed in fish in the 1980s most of the constructs consisted of mammalian GH genes and viral promoters, but later the genes and promoters used were from fish origin. The response to transgene action has been very different, depending on the species and DNA constructs, and ranged from a 20-fold increase in size compared with the non-transgenic counterparts,to nearly no difference (Nam et al., 2001; Devlin et al., 1995). The best well known GH-transgenic fish is the so called *AquAdvantage* salmon. This genetically modifiedAtlantic salmon was developed by the group of G. Fletcher more than 25 years ago (Du et al., 1992). This modified line of Atlantic salmon harboursone copy per animal of an “all fish” DNA construct consisting of an antifreeze protein gene (AFP) promoter from ocean pout driving the expression of a Chinook salmon GH cDNA (opAFP-GHc2). In contrast to the seasonal expression of the own salmon GH gene, this transgenehas a continuous expression (FDA, 2015a). The AquAdvantge salmon is produced by a company named AquaBounty Technologies (Massachusetts, USA), and it grows to full size in 18 months compared with the three years for the wild type. In addition it needs 25% less feed than the wild type.

In 1995 the salmon producers applied to the Food and Drug Administration (FDA) to obtain its approval for human consumption. The agency completed its food safety assessment and statement of environmental impact in 2010 and 2012, respectively. But because it was the first product of its kind it still took another additional three years for its final approval as an “original animal drug application” on the 19th of November of 2015, becoming the first transgenic animal authorized as food in the USA (Ledford, 2015; FDA, 2015b). The FDA concluded that it was extremely unlikely that the fish could escape and establish themselves in the wild, as *AquAdvantage* salmon are all triploid females, and therefore sterile. In addition, they are grown in land-based tanks with multiple physical barriers to avoid escapes. Concerning their appropriateness for human consumption, the FDA after rigorous evaluation of extensive data concluded that the *AquAdvantage* salmon is as safe to eat as a non-genetically engineered salmon, as there are no meaningful differences in food composition between them (FDA, 2015b). See A. Sasson (2018) in this *Journal*.

During these years, significant growth enhancement has also been achieved in other fish species genetically modified withan exogenous GH gene,which include tilapia, common carp, mud loach, rainbow trout, coho and chinook salmon, and they are currently at different levels of development (Devlin et al., 2015).

Some opponents of this transgenic approach argue that growth enhancement can be achieved by traditional domestication/selection methods. Indeed, in an experiment performed with wild and domesticated rainbow trout lines harboring a GH-transgene, the researchers found that the response to the exogenous GH was greatly influenced by the intrinsic growth rate and genetic background, and that insertion of a GH gene in the domesticated line did not further enhance growth (Devlin et al., 2001). In a later study in coho salmon these authors found that domestication and GHtransgenesis are indeed modifying similar genetic pathways (Devlin et al., 2009).

Antifreeze proteins and cold resistance

However, if one aims to generate a fish with characteristics not previously present in their genetic pool, then genetic modification is the only approach to achieve that goal, this would be the case of the following strategy.

Many marine teleosts that inhabit in cold polar waters produce a series of proteins that enable them no to freeze. They are known as antifreeze proteins (AFP). So, the idea of producing transgenic fish expressing AFP proteins was initially motivated by the possibility to culture Atlantic salmon along the East coast of Canada. The first attempts to generate such transgenic salmons were not successful, as the exogenous AFP levels achieved were not enough to protect the animals from freezing (Hew et al., 1999). However, this same approach is being tried to confer cold resistance to carp or tilapia, what would protect these species from cold winters in some areas of China and Israel, respectively (Maclean, 2003; Wang et al., 1995; Wu et al., 1998).

Blocking sexual maturation

The gene overexpression approach is not always the right strategy, in some cases we may want to block a gene to get the desired phenotype. This would be the case of the gonadotropin-releasing hormone gene, whose product is a key regulator of reproduction. The aim was to knock-down this gene, by expressing its antisense mRNA, to get sterile animals or to exogenously control sexual maturation. This approach was first tried in rainbow trout but was not successful(Uzbekova et al., 2000); more recently it has been tried in common carp with better results, although not all the obtained fish were sterile (Xu et al., 2011).

Disease resistance

In intensive aquaculture fish are reared in high densities and these stressful conditions affect their immune system and lead to reduced disease resistance; besides, the risk of transmission of contagious illnesses is higher. For viral infections, the most advanced gene transfer approach is the use of DNA-vaccines containing the gene of a viral antigenic protein (Evensen and Leong, 2013), but these are not really genetically modified fish, as vaccines are injected in the muscle, so they are not transmitted to the offspring and are only transiently expressed. On the other hand, to increase resistance to bacterial infections the expression of a wide-spectrum antimicrobial molecules, such as lysozyme (Chengfei et al., 2015; Yazawa et al., 2006), cecropins (Dunham et al., 2002; Sarmasik et al., 2002) and others (Pan et al., 2011) has been tried in various species.

Metabolism modifications

One of the potential applications of gene transfer is to modify fish metabolism to make it more efficient. One example is phosphorus availability in the diet. The food pellets for fish have to be supplemented with expensive and polluting inorganic phosphorus because the fish cannot digest the phytate-phosphrorus present in the food pellets. Making fish able to digest phytate-phosphorus by the expression of an exogenous phytase gene is giving promising results in the model fish medaka (Hostetler et al., 2005). There are also attempts to increase the contents of omega-3 fatty acids in the meat by overexpressing some of the genes coding for enzymes of their synthetic route, such as delta5- and delta6-desaturases and elongase (Alimuddin et al., 2005; Cheng et al., 2014; Pang et al., 2014; Yoshizaki et al., 2007).

Environmental monitoring

Other applications of transgenic fish are being tried and that are different from those aimed at human consumption. They include, for example, the use of transgenic fish to monitor toxics in the environment. The idea is to use transgenic lines of model fish, or their embryos, containing an easily detectable reporter gene, whose expression is under the control of an element that can be induced by very low levels of a certain pollutant, suchas heavy metals or endocrine disrupting substances (Carvan et al., 2000; Legler et al., 2000; Mattingly et al., 2001; Seok et al., 2006; Zeng et al., 2005).

Biofactories

Although there are no significant results in this area, the use of transgenic fish to produce proteins with therapeutic or industrial value would broaden the interests of aquaculture. MacLean and collaborators have tried the use of transgenic tilapia to produce human coagulation factor VII. This would be a safe and cheaper alternative to the currentin *vitro* production of this factor (Hwang et al., 2004). Indeed, fish muscles have revealed as very good bioreactors when using appropriate promoters (Gong et al., 2003); this has already been applied to produce the first transgenic fish in the market, namely a series of zebra fish lines, containing different versions of fluorescent protein-coding genes, that are commercialized as ornamental fish under the name of *GloFish*.

Xenotransplantation

Finally, a model of islet xenotransplantion to treat type-1diabetes is being developed using tilapia as donor. Strains of transgenic tilapia expressing human insulin in their islets have been developed. In fish, these islets are grouped in the so-called Brockmann bodies; this structure can be easily isolated and transplanted, and in addition they can be encapsulated in order to be isolated from the recipient's immune system as they are very resistant to hypoxia. So far, promising results have been obtained in treating type-1diabetes in mice by using this approach (Alexander et al., 2006).

Conclusions

Most of the applications of transgenesis in fish are still under development, and exclusively relegated to the research level. This is basically due to two reasons: the need to have a deeper understanding of the action of genes in fish, and the lack of a truly effective technique for transgenic production in most commercial species.In addition to these intrinsic bottlenecks, there are two exogenous factors that have to be considered, if more transgenic fish are to be developed, namely environmental risk and human safety perception.

Environmental risk of transgenic fish is related to their possible escape in the wild. The strategies proposed so far, and applied in *AquAdvantage* salmon, consist of using inland farms and sterile animals. All these measures have also to take into account animal welfare, an important matter for farmers and consumers, the animals being transgenic or not. Food-safety issues are handled by regulatory agencies and these may vary in their approaches on how to consider a transgenic animal. Some of these agencies, as in Canada, are supposed to apply the concept of substantial equivalence that compares in extreme detail the modified food with its unmodified counterpart, while the FDA in USA has considered the GH-transgenic salmon as a new animal drug (Fletcher et al., 2005).

But, in the long term, it is the consumer who will determine the fate of transgenic fish for human consumption. The benefits that the consumer would appreciate in these foods must be greater than the risks. It is also important to gain the trust of consumers.Their concerns have to be considered and incorporated in the regulatory process, in addition to education and information campaigns from scientists and trustworthy technological promoters explaining how these animals are generated, and how they have gone through deep analysis, in order to demonstrate that they are safe to eat (MacLean 2003; Fletcher et al., 2005; Aerni 2004).

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Genetically modified organisms in Africa

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Introduction

Africa did not take advantage of technologies that were developed and adopted from the mid 1940s to late 1960s that led to the green revolution in many Latin America and Asian countries. Hence the agricultural sector on the African continent did notprogress much, though its potential is enormous due to the diversity of crops that it can grow to become self-sufficient in food production. There are many challenges that African agriculture is facing including availability of new plant varieties, know-how, technology transfer, water supply and climate change. Also, mainly small farmers lead the African agriculture and women provide the bulk of inputs up to 60-80% (www.worldbank.org).

In the 1990s genetically modified (GM) crops, also known as biotech crops or genetically modified organisms (GMOs) developed through the adoption of genetic transformation technology, paved their way in United States, which is today the leading country in such adoption. This new technology consists of transferring a gene from one organism to another mainly through two major methods; either with the help of an *Agrobacterium* species or through microprojectile bombardment. The first commercial GM food product, a delayed ripening tomato, was marketed

in 1994 in the United States. Thereafter major crops like maize, soybeans, cotton and sugar beet were genetically transformed for herbicide and insect tolerance and had a fast adoption in the United States. Later on countries like Brazil and Argentina took advantage of the GM technology and farmers started to exploit large-scale cultivation of GM maize, soybeans and cotton. In 2015, these two countries grew nearly 37% of the total global acreage under GM crops (ISAAA, 2015). Although a fast adoption of GM crops took place in a few countries, the numerous critics expressed in the marketing and acceptance of such crops, did not allow its progress worldwide and once again Africa was left behind in taking advantage of the GM technology at the end of the last century.

Global and African situation

From 1996 to 2012, there has been a 100-fold increase, from 1.7 million ha to 170 million ha of GM crops planted in 20 developing and 8 industrial countries. In 2014, the global area under GM crops reached about 181.5 million ha. The top ten countries, in 2014, growing at least one million ha of GM crops each were: United States, Brazil, Argentina, Canada, India, China, Paraguay, Pakistan, South Africa, and Uruguay. Only South Africa figured in the top ten countries andit was the first country in Africa to commercially cultivate GM crops and is today the leading developing country growing such crops. GM maize and cotton have been planted in South Africa since 1997. In 2015, nearly 2.3 million ha were under GM crops in the country, with maize grown on 1.8 million ha and representing nearly 90% of the total area under this crop; for soybeans, out of 535 000 ha cultivated, 508 000 were GM and as for cotton 100% of the 12 000 ha were GM. It is estimated that the economic gains from soybeans only, for South Africa, for the period 2001 to 2014 was US$18.1 million and US$ 4.9 million for 2014 alone (Brookes and Barfoot, 2016), hence showing the growing interest of farmers in its cultivation.

Recently, other African countries namely, Burkina Faso and Sudan have been exploiting GM cotton (ISAAA, 2015) and the two countries, in 2015, account for 0.22% of the total global acreage under GM crops.Burkina Faso started to exploit insect-resistant *Bt* cotton (a gene inserted from the soil bacterium *Bacillus thuringiensis*) in 2009 and in 2015 the area under GM cotton reached 300 000 ha, representing nearly 57% of the total area under cotton production. Sudan increased the *Bt* cotton hectareage to 100% in 2015. The production cost of non-*Bt* cotton was much higher at US$ 372 for 0.42 ha compared to US$ 246 for *Bt* cotton (www.isaaa.org). However, in 2016, Burkina Faso announced the phasing out of *Bt* cotton (http://dw.com/p/1JF1e).

Egypt approved commercial production of *Bt* maize in 2008 following a private and public partnership collaboration, and in 2011 some 1700 ha were cultivated. However this did not last long, as in 2012 it suspended both *Bt* maize and cotton cultivation (NASAC, 2015). In the very same year, Kenya decided to ban all GM foods in its market until it could build the capacity to test and certify for GMOs (NASAC, 2015). In these two countries the ban came after the publication of the study by Séraliniet al (2012), reporting that rats fed on GM foods developed cancer. However this controversial study was soon retracted (in Wikipedia).

The Water Efficient Maize for Africa (WEMA) project – an international private-public partnership, which started in 2008, aims at enhancing food security in sub-Saharan Africa through developing drought-tolerant and insect-protected maize hybrids. Maize is the most important staple food in Africa and production faces major problems such as drought and pests attacks. During drought periods, the maize plants become even more susceptible to insect pests attack and hence further reduce any potential grain harvest, thus leading to food scarcity and insecurity amongst the small farmers. The WEMA project addresses these issues through the use of biotechnology tools and involves a consortium of five African countries namely Kenya, Mozambique, South Africa, Tanzania and Uganda (wema.aatf-africa.org/), in collaboration with the African Agricultural Technology Foundation (AAFT) and the International Maize and Wheat Improvement Centre (CIMMYT). Hybrid maize developed through this programme is currently undergoing field evaluation in Kenya and the first hybridis being sold under the brand name 'DroughtTEGOTM' (www.monsanto.com).

Besides the cultivation of major GM crops such as maize, soybeans and cotton, other crops including rice, wheat, sorghum, cassava and sweet potato have been genetically modified and field trials have been carried out or are underway with them in several African countries includingCameroon, Ghana, Malawi, Nigeria and Uganda(https://southernafrican.news/).

A precautionary approach to the adoption of GM crops

For the development of biotech crops, well-regulated systems for genetically modified plants should be in place so that no harm is caused to human, animal and the environment. In Africa, the governance of biotech crops is characterized by a precautionary approach. The majority of African countries are parties to the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (CBD), an international agreement on biosafety that entered into force in 2003. In 2006, 37 African countries had signed and ratified the agreement (CBD, 2006). The last African country having ratified the protocol is Cote d'Ivoire, in 2015 (https://bch.cbd.int/protocol/parties/). Countries that have a Biosafety law in place in Africa include South Africa (1997), Mauritius (2004), Kenya (2009), Burkina Faso (2011), Nigeria (2011), Uganda (2012), although not fully promulgated or implemented in some countries. A number of other countries have also prepared biosafety regulations and guidelines so as to minimize any risks that could be associated with the development and commercialization of biotech crops.

Biotech crops have great potential to contribute to real socio-economic benefits to the African continent, given the need to enhance its agricultural productivity. With the growing world population, it is expected that the world population will reach some 9.6 billion by 2050, according to the United Nations. This also means an increase of the population in the African continent. With the forecasted demographic changes, there is no doubt that more food will be required in Africa in the coming decades. Africa is uniquely exposed to food and nutrition insecurity, climate change, lack of fertile arable land, rising soil salinity in some areas and a decline in sustainable agricultural productivity. It is therefore important that it takes advantage of new biotechnology technologies to address these challenges. However it is also important that the development of biotech crops in Africa takes place within well-regulated frameworks so that no harm is caused to human, animal and the environment.

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GM crops situation in Latin America

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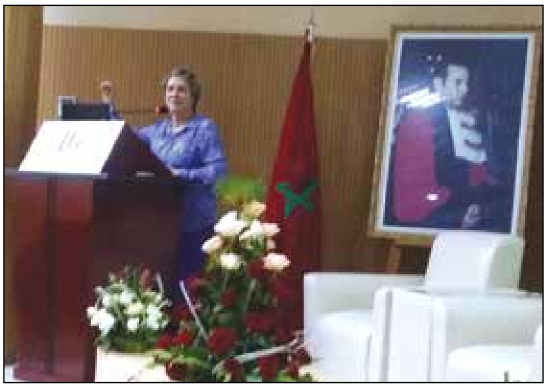
World requirements, sustainable development and agrobiotechnologies



One of the most formidable challenges humankind faces the present time, is to feed 9.7 billion people in 2050. The increase in crop productivity has declined following the important increase during the green revolution. It is clear that conventional crop technologies alone cannot contribute to fulfil the world requirements for food, feed and other uses. Additionally, climate change is one of the major challenges to face, with impacts in every field of human activity, and agriculture is strongly placed on the global climate change agenda.

There is considerable evidence that climate is changing and weather records are being broken more frequently, affecting severely people and their capacity to make a living and feed their families, and in many cases impact their vulnerability to extreme events. Most agriculture is climate dependent, therefore variability in weather will affect productivity. The requirement is to adapt agriculture production systems for a changing climate and to work in improvements in resilience, productivity and sustainability (*Global Food Security*, 2015).

Sustainable development is a global scale objective, evidenced in the Sustainable Development Goals (SDG) launched by the United Nations (UN) in 2015, and reaching the SDG targets will not be possible without a strong and sustainable global agriculture. (De Buck et al, 2016). Our option is to change our agricultural practices into more sustainable, balanced systems using the best of the different approaches and combining conventional crop breeding with more modern technologies looking forward to increase productivity with a minimum increase in the cultivated land. This means a sustainable intensification of crop productivity.

Several actions and diverse approaches are part of the alternatives looking forward more sustainable agricultural production, which include integrated pest management - IPM, efficient water and soil management, improved crop varieties, good agricultural practices - GAP, technology development and innovation, reduction of food waste and residues.

The elements required for agricultural sustainable production include:

- Higher productivity without increasing agricultural area
- Conservation/increase in biodiversity (adapted germplasm, use of new food sources)
- Reduction in pesticide use, or use of less persistent/toxic ones
- Improvement in product quality
- Decrease in the use of chemical fertilizers
- Reduction in post-harvest losses, reduction in food loss and waste
- Contribution to reduce desertification.

Sustainable agriculture and downstream processing industry are knowledge based ((De Buck et al, 2016). No one single tool, technology or approach will provide a complete solution for all the problems we have to face. There is a need to develop or to make more intensive use of new technologies that could make agricultural sectors more sustainable and these approaches must be useful and accessible for small farmers. During the International Symposium on "The Role of Agricultural Biotechnologies in Sustainable Food Systems and Nutrition" in February 2016, FAO's Director-General stated the need to discuss and analyze how agroecology and biotechnology can live together and, perhaps, be used as complementary options. Therefore, it is important to consider biotechnologies and agroecology as compatible schemes to obtain sustainable food and nutrition systems responding to climate change.

Agricultural biotechnologies (agrobiotechnologies) are much broader than Genetically Modified Organisms. Agrobiotechnologies are the best partner for sustainable agriculture because they contribute in several aspects such as: eco-intensification to improve environmental performance and reduce the greenhouse emissions, natural resources management and molecular characterization, biodiversity conservation and use, crop marker assisted selection (MAS), molecular based diagnostic systems, bioenergy supply, bioinoculant development such as production of biocontrol agents for pests and diseases, or the use of microorganisms as biofertilizers (mycorrhizae, biological nitrogen fixators, plant-growth promoting bacteria) among others (Hodson de Jaramillo, 2014).

Genetically modified crops (GM or biotech crops)

In 2015, 28 countries were cultivating genetically modified (GM) crops, with 179.7 million hectares planted by near 18 million farmers (James, 2015). An increasing number of companies, research institutions and universities around the world are working in the development of newly-bred crop varieties to face the world requirements for food, feed and industrial uses, and there has been an increase in the pipeline for GM crops. Nevertheless, as with any other technology, some economic, market and regulatory considerations are acting as barriers, and reducing the number of R&D products that eventually become commercial (Parisi et al., 2016).

Despite the controversy surrounding genetically modified crops, they are a very important tool for developing disease-resistant or tolerant crops that can reduce the use of pesticides and decrease crop losses. In a trio of papers published recently in *Nature Biotechnology*, researchers documented how new, faster methods of isolating genes – and looking in some unexpected places – led them to identify, clone, and transfer disease-resistant genes into soybeans, wheat, and potato plants (Parisi et al., 2016).Biotech crops areconsidered as the fastest adopted crop technologyin the history of modern agriculture, and have shown that they can contribute to a sustainable intensification strategy, which allows productivity/production to be increased only on the current 1.5 billion hectares of global crop land, thereby saving forests and biodiversity (James, 2015). It has been shown that GM technology has also contributed to reduce the agriculture's environmental footprint by facilitating environmentally friendly farming practices. GM technology has had a significant positive impact on farm income, derived from a combination of enhanced productivity and efficiency gains. The higher productivity of the currently commercialized GM crops alleviates the pressure to convert additional land for agriculture (Brookes & Barfoot, 2016). Biotech crops are one of several elements, and good farming practices, such as rotations and resistance management for insects, pathogens and weeds, are a must for biotech crops as they are for conventional crops. GM crops and foods have been consumed worldwide for 20 years, and not a single documented negative impact has been reported and verified. Instead, many scientific reports demonstrate that they have brought significant benefits to the farmers and to the environment reducing the use of pesticides and decreasing thus, the release of greenhouse gasses.

Crop biotechnology has reduced pesticide spraying (1996-2014) by 581 million kg (-8.2%). This is equivalent to the total amount of pesticide active ingredient applied to crops in China for more than a year. This has reduced the environmental impact related with herbicide and insecticide use on the area planted to biotech crops by 18.5% and has contributed to reducing the release of greenhouse gas emissions from agricultural practices. This results from less fuel use and additional soil carbon storage from reduced tillage with GM crops (Brookes & Barfoot, 2016).

The latest data for 1996 to 2014 showed that biotech crops contributed to Food Security, Sustainability and Climate Change by: increasing crop production valued at US$150 billion; providing a better environment, by saving 583.5 million kg of pesticides in 1996-2014; in 2014 alone reducing CO_2 emissions by 27 billion kg, equivalent to taking 12 million cars off the road for one year; conserving biodiversity in the period 1996-2014 by saving 152 million hectares of land (Brookes and Barfoot, 2016); and helped alleviate poverty by helping up to 16.5 million small farmers, and their families totalling >65 million people, who are some of the poorest people in the world. Biotech crops can increase productivity and income significantly and hence, can serve as an engine of rural economic growth that can contribute to the alleviation of poverty for the world's small and resource-poor farmers(James, 2015).

In their 2016 Report, Brookes & Barfoot point that "In the nineteenth year of widespread adoption, crop biotechnology has continued to provide substantial economic and environmental benefits, allowing farmers to grow more, with fewer resources, whilst delivering important environmental benefits for all citizens". They also show data related with how the insect resistant (IR) technology used has consistently delivered yield gains from reduced pest damage. The average yield gains over the 1996-2014 period across all users of this technology has been +13.1% for insect resistant corn and +17.3% for insect resistant cotton relative to conventional production systems. 2014 was also the second year IR soybeans were grown commercially in South America, where farmers have seen an average of +9.4% yield improvements. In relation with the herbicide tolerant (HT) technology, it has promoted increased production as well as weed control, with higher yields in some countries(Brookes & Barfoot, 2016).

A global meta-analysis conducted by Klumper and Qaim (2014) on 147 published biotech crop studies during the last 20 years, confirms significant and multiple benefits of GM crops. They concluded that "*on average, GM technology adoption has reduced chemical pesticide use by 37%, increased crop yields by 22%, and increased farmer profits by 68%. Yield gains and pesticide reductions are larger for insect-resistant crops than for herbicide-tolerant crops. Yield and profit gains are higher in developing countries than in developed countries*."These findings corroborate the findings of the annual global impact study by Brookes and Barfoot of PG Economics, annually referenced in the Annual ISAAA Briefs. The authors find dissimilar impacts, depending on the geographical region, the modified crops and even effects of seasonal variation. Despite this, the average agronomic and economic benefits of GM crops are large and significant. Yield increase and pesticide reduction have shown to be greater for insect resistant (IR) crops than for herbicide tolerant (HT) ones. Increases in yields and in farmer economic incomes are higher in developing countries than in developed countries.

Additionally, Qaim (2016) presented a more thorough description of the impacts of current and possible future GM crop applications, and their substantial contribution to sustainable agricultural development and food security, in his recent book, *Genetically Modified Crops and Agricultural Development*. He concluded that continued opposition to technologies that were shown to be beneficial and safe entails unnecessary human suffering and environmental degradation. He states that the difficult and politicized procedures required in many countries for biosafety and food safety delay the approval, commercialization and thus the adoption of the GM crops, and also are an obstacle for the development of new useful GM crops (Qaim, 2016).

The National Academies of Sciences, Engineering, and Medicine in an extensive study (900 research publications over 20 years) presented in May, 2016, stated that the study committee did not find substantiated evidence of a difference in risks to human health between currently commercialized GM crops and the conventionally bred ones. The committee concluded that GMOs are as safe as their conventional counterparts, and that there is no evidence of environmental problems.They consider that biotech crops have mostly produced favourable economic outcomes for farmers in early years of adoption, there has been a reduction in the use of chemical pesticides with benefits to human health, but they think that the gains will persist depending on institutional support and access to profitable local and global markets, especially for resource-poor farmers (NAS, 2016). See also Sasson (2018) in this *Journal*.

Latin America and the Caribbean

An interesting point is that in 2015, farmers in developing countries in Latin America, Asia and Africa grew 54% of global hectares in biotech crops. Currently there are now 10 countries in Latin America benefiting from the extensive adoption of biotech crops, planting mainly soybeans, maize, cotton, bean, canola, carnation and roses (Table 1). In order of hectares cultivated, they are Brazil, Argentina, Paraguay, Uruguay, Bolivia, Mexico, Colombia, Honduras, Chile, and Costa Rica (Table 2), with Cuba planning to resume planting in two years pending availability of their home-grown maize hybrids (James, 2015).

Table 1. GM crops in Latin America

Approved GM events by country				
Country	**Cotton Gossypiumhirsutum L.**	**Maize Zea mays L.**	Soybean Glycinemax L.	Other
Argentina	4 Events	35 Events	8 Events	
Bolivia			1 Event	
Brazil	12 Events	33 Events	10 Events	Bean - *Phaseolus vulgaris* – 1 Event *Eucalyptus* sp. - 1 Event
Chile	-	1 Event	1 Event	*Brassica napus* - 1 Event
Colombia	11 Events	44 Events	12 Events	Carnation - *Dianthus caryophyllus* - 8 Events Rose - *Rosa hybrida* - 2 Events Flax - *Linum usitatissimum* - 1 Event Rice - *Oryza sativa* - 2 Events Sugar beet - *Beta vulgaris* - 1 Event Wheat - *Triticum aestivum* 1 Event
Costa Rica	13 Events	2 Events	-	
Cuba	1 Event	-	-	
Honduras	7 Events	-	-	Rice - *Oryza sativa* - 1 Event
Mexico	30 Events	68 Events (Banned since 2013)	22 Events	Alfalfa - *Medicago sativa* - 5 Events Canola - *Brassica napus* - 13 Events Potato - *Solanum tuberosum* - 13 Events Rice - *Oryza sativa* - 1 Event Sugar beet - *Beta vulgaris* - 1 Event Tomato - *Lycopersicon esculentum* - 5 Events
Panama	-	1 Event	-	
Paraguay	3 Events	14 Events	3 Events	
Uruguay	-	10 Events	7 Events	

Source: Author generation, based on data from James (2015) and Brookes & Barfoot (2016).

Brazil, Argentina, Paraguay, Uruguay, Bolivia, Mexico and Colombia are considered mega countries for biotechnological crops, cultivating more than 100,000 has of GM crops per year. Brazil (44.2 mill ha) and Argentina (24.5 mill ha) ranked second and third places in the world, behind U.S.A which is the first crop planting Country (70.9 mill ha). These countries can be considered global food suppliers (James, 2015).

In 2015, Brazil, which has been the driving force for GM crop growth in the world during the last six years, ranked second only to the USA in biotech crop hectares cultivated in the world with 44.2 million hectares (up from 42.2 million in 2014); the increase in 2015 was 2 million hectares equivalent to a growth rate of 5%. In 2015, Brazil grew 25% (2% more than in 2014) of the global 179.7 million hectares. In the long term, Brazil is expected to close the gap with the US which has an efficient and science-based approval system that facilitates fast adoption. In 2015, Brazil commercially planted, for the third year, the stacked soybean with insect resistance and herbicide tolerance on 11.9 million hectares, a five-fold increase from 2.3 million hectares in 2013 and 5.2 million hectares in 2014. Additionally, in relation to GM trees, and also in Brazil, approval was gained by FuturaGene /Suzano for cultivation of a 20% higher-yielding home-grown biotech eucalyptus, plus commercialization of two home-grown crop products in 2016 – a virus resistant bean and a new herbicide tolerant soybean (James, 2015).

Table 2. Global area of biotech crops in 2015 by country, highlighting Latin America and the Caribbean countries

Rank	Country	Area (million hectares)	Area (acres)	Biotech crops
1	USA	70.9	175.2	Maize, soybean, cotton, canola, sugar beet, alfalfa, papaya, squash, potato
2	Brazil	44.2	109.2	Soybean, maize, cotton
3	Argentina	24.5	60.5	Soybean, maize, cotton
4	India	11.6	28.7	Cotton
5	Canada	11	27.2	Canola, maize, soybean, sugarbeet
6	China	3.7	9.1	Cotton, papaya, poplar
7	Paraguay	3.6	9.0	Soybean, maize, cotton
8	Pakistan	2.9	7.2	Cotton
9	South Africa	2.3	5.7	Maize, soybean, cotton
10	Uruguay	1.4	3.5	Soybean, maize
11	Bolivia	1.1	2.7	Soybean
12	Philippines	0.7	1.7	Maize
13	Australia	0.7	1.7	Cotton, canola
14	Burkina Faso	0.4	1.0	Cotton
15	Myanmar	0.3	0.7	Cotton
16	Mexico	0.1	0.3	Cotton, soybean
17	Spain	0.1	0.3	Maize
18	Colombia	0.1	0.3	Cotton, maize
19	Sudan	0.1	0.3	Cotton
20	Honduras	<0.1	<0.3	Maize
21	Chile	<0.1	<0.3	Maize, soybean, canola
22	Portugal	<0.1	<0.3	Maize
23	Vietnam	<0.1	<0.3	Maize
24	Czech Republic	<0.1	<0.3	Maize
25	Slovakia	<0.1	<0.3	Maize
26	Costa Rica	<0.1	<0.3	Cotton, soybean
27	Bangladesh	<0.1	<0.3	Brinjal/eggplant
28	Romania	<0.1	<0.3	Maize
	Total	**179.7**	**444.3**	

Source: Adaptation from James (2015).

Need for scientific biosafety systems

It is clear that biotechnological advances offer many possibilities to face some agricultural constraints. GM technology, in conjunction with conducive policies can increase significantly food production. Nevertheless, in order to support innovation in biotechnology and ensure the development of safe, sustainable biotech products, there is a need to establish a scientifically solid, efficient and reliable Biosafety system in each country. Many guidelines are available from different institutions/countries (FAO, CBD, UNEP, IFPRI, ICBGE, among others).

Currently, onerous regulation for transgenic biotech crops remains the principal constraint to adoption, which is particularly important for many developing countries. Unlike the onerous regulation that currently applies to the so-called GM crops, new developing technologies such as genome editing (such as CRISPR-Cas9) might be easier to science-based, balanced and appropriate regulation. Difficult and costly regulations are denying poor farmers in the developing countries access to the technologies. By using these technologies, small poor farmers will be able to survive and contribute to the doubling of food production to meet the needs of a growing population (James, 2015). In June, 2016 more than 120 Nobel laureates called upon the environmental groups to accept the safety approvals and to stop demonising biotechnology. The regulation framework should make it more practical for these crops to reach the farmers.

The report of the National Academies of Sciences (NAS, 2016) consider that all technologies for improving plant genetics-whether GE or conventional-can change foods in ways that could raise safety issues. Therefore, they conclude that is the product the one that should be regulated, not the process, and the analyses most be science-based. See also Sasson (2018) in this *Journal*.

Future prospects

Since the beginning of the 21st century, plant sciences have dramatically progressed in understanding the structure, function and regulation of the mechanisms that translate the plant genome into phenotypes. The latest discoveries have shown that genomes are much more dynamic entities than ever expected (De Buck et al., 2016). New genome-editing techniques such as Crispr offer timely and potent advantages over conventional and biotech crops in terms of precision, speed, cost and regulation (James, 2015). At the moment, several institutions (public and private), research centers, universities, foundations or local companies in various countries are developing GM crops, or using alternative systems such as CRISPR-Cas9 technology in order to produce plant material carrying desirable traits. These new technologies have the potential to increase the precision to make changes to plant genomes and expand the group of characters that can be changed or introduced, such as: improved tolerance to drought and thermal extremes; increased efficiency in photosynthesis and nitrogen use; and improved nutrient content. The number of crop species improved for insect and disease resistance will multiply, and the number of pests targeted will also likely increase. Nevertheless, the committee recommends balanced public investment in these emerging genetic-engineering technologies and other approaches to address food security (NAS, 2016).

In this way, new crop biotechnology developers are appearing in addition to the knownagrobiotech companies, especially in developing countries like India, China, Brazil, and Africa. Developing countries are showing a strong focus on a broader spectrum of crops, which could bring more specialty crops into the overall pipeline. However, so far, most of these crops have been developed mainly for domestic uses, especially in China and India (Parisi et al., 2016). An issue to take in account in these developments is the expiry of several patents of broadly cultivated and exported

GM crops GM crops, starting with MON810 maize (which expired in November 2014) and soybeans 40-3-2 (which expired in March 2015).

Some examples of advances in developing countries include the Water-Efficient Maize for Africa (WEMA) project, a public-private partnership that aims to improve food security and livelihoods for small farmers in sub-Saharan Africa by finding ways to double the maize yields (*http://wema.aatf-africa.org*). Drought tolerance has been recognised as one of the most important targets of crop improvement programs, and biotechnology has been identified as a powerful tool to achieve significant drought tolerance. FAO estimates that by 2025 approximately 480 million Africans could be living in areas of water scarcity. To face this challenge, plant scientists are developing drought-tolerant traits. In this project, GM and non-GM technology, including marker-assisted breeding (MAS), are combined to generate hybrid maize seeds with increased water use efficiency and resistance to insect pests. One of the goals is to add the *Bt* gene, whichwill be stacked with the drought-tolerance biotech trait (MON87460) that expresses the *Bacillus subtilis* cold-shock protein B (cspB), licensed from Monsanto. Another interesting example in a developing country is the biotech maize CIEA-9, which was developed with enhanced adaptation to severe drought and extreme temperatures in Mexico by CINVESTAV-IPN (Centro de Investigaciónes y Estudios Avanzados del Instituto Politécnico Nacional). The antisense RNA expression was used for silencing trehalase in the popular maize inbred line B73 (derived from Iowa Stiff Stalk Synthetic). This biotech maize requires 20% less water, endures high temperatures (up to 50°C), and the seeds germinates at 8°C, demonstrating their ability to withstand cold at early development stages (De Buck et al, 2016).

The regulation of new plant varieties is becoming more relevant. Technological progressis still taking place which can still be considered transgenesis, such as the use of the RNA interference technology to obtain a stable gene silencing effect (applied to commercial traits including pest resistance, disease resistance and crop composition). New technologies including zinc finger endonucleases, CRISPR-Cas9, or transcription activator-like effector nucleases (TALENs), could be considered differently because of the absence of foreign DNA sequences in the final products, despite the use of a biotech-based process. The impossibility of distinguishing these products from conventional ones using available detection methods represents an additional challenge at the regulatory level (Parisi et al., 2016).

Agrobiotechnological techniques including GM crops and gene editing are providing extraordinary opportunities to complement conventional selection, mutation breeding and molecular techniques for the modification of crops in order to obtain new characteristics and new traits of interest in crop varieties. In order to face the challenges of climate change and the requirement of sustainable agricultural production, a wise use of these scientific advances will allow developing countries to enhance productivity, increase yields and nutritional value of crops, which in turn can improve incomes and welfare of the producer.

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