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Genome Editing and the Future of Farming

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Genome editing: The promise and the politics

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ABSTRACT

Efficient and sustainable agriculture depends on a high degree of predictability. Both in the short-term, for growers and agronomists to make informed management decisions for the immediate upcoming seasons, but also in the long term to establish future agricultural policy and trade agreements, to define crop and livestock breeding goals, and to stimulate innovation in new products with transparent regulatory frameworks for pesticides and biotechnology; all of which require decade-long timeframes or longer. However, there are many factors with implications for world agriculture that are becoming increasingly unpredictable and which pose significant challenges for sustainable future food production. I will highlight two major areas of uncertainty, one which is environmental and beyond the control of humankind in the medium-term and the other, involving regulatory policy that is absolutely with in our short-term grasp. I will argue that providing certainty and transparency in the latter will make a significant contribution to global food security by ameliorating the effects of the former.

INTRODUCTION

If the World Meteorological Organization predictions for 2016 are correct, the last three years will have each broken records for high global mean temperatures (WMO 2016) and 16

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of the 17 hottest years on record will have occurred since 2000. Of course, increasing average global temperatures are in themselves challenging for agriculture, however, they mask the frequent and often extreme local climate anomalies that, along with associated abiotic and biotic stressors, have a more immediate negative effect on agricultural production. The 2007/8 and 2011/12 price spikes in commodity grains were directly related to prolonged extreme weather (Global Food Security 2016) and were a contributing factor in the social unrest seen in Egypt and elsewhere in 2008 (The Telegraph 2008). Additionally, the Oceanic Niño Index, shows the 2015/16 El Niño was one of the strongest ever recorded (Climate Prediction Centre 2016) leading to the FAO estimating that it affected more than 60 million people around the world (FAO 2016). They also claim that many more people will have their lives disrupted by the likely upcoming La Niña. Drought, flooding and extremes of temperature are becoming locally more frequent which make disease forecasting and crop and livestock management increasingly challenging. To secure a safe and nutritious food supply, a wide range of strategies to actively mitigate these effects are urgently required.

Plant and animal breeding is one such strategy and must be a central part of an integrated approach to efficient and sustainable food production. Biotechnology is an important facet of modern breeding and as such, a full spectrum of laboratory- and field-based science must be available and fully integrated into that process. The timely production of nutritious, well-adapted, high-yielding, pest and disease-resistant crops and farmed animal breeds needs all the tools we have at our disposal. It is thus ironic that badly needed applied research and innovation in modern breeding technologies is currently hampered by confused policy on innovation and regulatory affairs and also by the uncertainty and unpredictability inherent in current 'safety' regulations for breeding and agrichemicals. The lack of predictability and consistency in regulatory oversight for pesticides and biotechnology applies both for the same products between countries and for new technologies and products where existing regulations are not equipped to deal with them. The design and production of new active ingredients as well as the development of new crop varieties and animal breeds takes decades. The agrichemical industries, plant and animal breeders and growers all need predictability to plan, invest and innovate. The current uncertainty surrounding the

regulation of gene editing, a new and powerful tool to generate targeted mutations in plant and animal genomes, starkly exemplifies this challenge.

THE PROMISE

Conventional breeding is a forward genetic exercise that utilises the random assortment and independent segregation of DNA during meiosis to recombine alleles from different parents in unique but unpredictable ways. The offspring, often many thousands of individuals, must then be screened by phenotype and perhaps also by genotype if specific genetic markers are available. A sub-set of progeny that possess desired characteristics and, just as importantly, do not possess undesired ones, are selected for further crossing. The selection steps are often repeated for each generation and, depending on the species, time from the first cross to a new variety is between ten and twenty years. Thus we are only two or three breeding cycles away from 2050, 9 billion people and a significantly altered climate and we are making crosses today that largely delimit the variation of alleles in breeding populations used to generate the varieties of the future when the many of the climatic and biotic stressors still cannot be predicted (Jones 2016).

These significant challenges are best met by maximising the use of the many tools and technologies available to ensure breeding is more predictable and directed. There are two fields of science that have each made massive leaps forward over the last decade that, when brought together, are synergistic and will be pivotal in meeting our future breeding goals. One is the exponential rise in genome and expressed RNA data driven by the low cost and high throughput of current sequencing platforms; genes really do grow on trees! The rate of growth over the last decade has been truly astonishing, with the total amount of sequence data doubling approximately every seven months (Stephens 2015). For example, on the 10th Oct 2016, the Sequence Read Archive (a main repository for nucleotide sequence data) held records of sequences containing 3.4 quadrillion bases (3.4 x10^{15}) and is currently increasing at a rate of over 200 million bases per second. The other scientific discipline moving rapidly is that of in-vitro cellular technologies, particularly the ability to perform targeted gene editing and to recover normal, fertile adult animals and plants free of any recombinant DNA

but that possess the intended edit to a native gene. The platform that is proving most useful for gene editing research is CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), although other site-directed nucleases (SDN) that can cut or otherwise modifying predetermined DNA sequences in the genome include: zinc-finger nucleases (ZFN), transcription activator-like effector nuclease (TALEN) and meganucleases (MN). Other techniques such as oligonucleotide-directed mutagenesis (ODM) also exist along with yet unpublished molecules with genome-editing potential. All these methods give the researcher or breeder that ability to do 'reverse genetics' ie. to achieve improvements in the phenotype by making pre-determined and targeted edits in the genome. These technologies require a detailed knowledge of the genome at sequence level and the parallel, timely exponential growth in nucleotide databases outlined above are fuelling a rapid advance in gene editing for pure research and applications in human therapeutics as well as for animal and plant breeding.

So how should gene editing be regulated? Gene edited varieties possess targeted mutations to an existing gene as opposed to the insertion of a new one typical of GMOs. Thus, new varieties produced using gene editing are equivalent to those produced using induced or natural mutations, which have a history of safe use and are excluded from biotechnology regulations. Moreover, gene editing results in a single, targeted and well-characterised genetic change, whereas mutation breeding generates multiple, random and unknown genomic disruptions that are scatted throughout the genome. The Ruby Red grapefruit variety is part of our daily diets and is just one of the more than 3,000 crop varieties listed in the Joint FAO/IAEA Mutant Variety Database as resulting from mutation breeding. Despite several years of deliberation, it is disappointing that, at the time of writing, we still do not yet know whether products of gene editing would be regulated as a GMO in the EU or excluded from regulation like all induced mutations. We should use this opportunity to invigorate and democratise biotechnological innovation in the agricultural sector and devise a regulatory framework for gene editing that is proportionate to the risks (Jones 2015).

In addition to transforming molecular genetic science, the commercialisation of gene editing has exposed gaps in process-based regulatory definitions of biotechnology. Simple gene editing results in plants and animals that possess no recombinant DNA and as such, do not

give rise to a GMO. However, although the final product contains no transgenes, the current EU regulations are 'process-based' and there may well have been a temporary step in the process of developing a new gene-edited variety that did involve recombinant DNA. Thus, these plants do not fit neatly into either the GMO or non-GMO category and careful interpretation of the relevant EU law is currently underway by the European Commission and the European Court of Justice. However, as I will describe below from a risk assessment point of view, it is illogical to place all products of modern plant and animal breeding into one or another silo. Modern breeding utilises a spectrum of technologies, each with its own benefits and risks and should be regulated as such.

THE POLITICS

The research is clear; genome editing is set to be a valuable new tool for modern plant and animal breeding. By making targeted changes to existing genes in elite germplasm it has potential to rapidly generate step-changes in yield, resilience to biotic and abiotic stresses and nutritional quality required to meet future global food-supply demands. However, this can become reality only if all stakeholders are confident that these new crop varieties or animal breeds are nutritious and safe. The appropriateness and smooth-running of the regulatory processes that govern the cultivation and the placing of these food types into the market play a major part in building this confidence. For conventional GMOs in the EU this is clearly failing and there is a real danger that the promise of genome editing will also be lost to EU breeders, growers and consumers if it suffers from over-regulation or similar indecisive mechanisms for approval. The EU has one of the most stringent and robust risk assessment steps for GMOs in the world. However, when it comes to risk management and EU-wide decision-making for final approval, the member state bureaucrats, acting on behalf of their political leaders, consistently fail to reach a qualified majority one way or the other. Applications are left in limbo with no decision and the EU commissioner is understandably reluctant to make a unilateral authorisation on behalf of all the member states. Although for food and feed applications, thankfully he does, albeit significantly delayed compared to approvals in the exporting nations which creates extra costs to manage this lack of synchronicity. This indecision further undermines the science-based risk assessment,

confuses consumers and plays into the hand of organisations who campaign for the banning of all GMOs in principle, regardless of trait or safety issues. The 2015 opt-out clause gave member states the right to ban cultivation in their own country. I trust that some common sense will now prevail and that the 19 member states that have opted out of growing GMOs will now vote in favour of future cultivation approvals, given that de facto, they cannot be cultivated in their territories.

Regarding gene editing, the situation in the EU and many other territories, is currently unpredictable. To date, the USDA have ruled that at least five products generated using gene editing are not genetically engineered organisms; a low-phytate maize, a herbicide-tolerant canola, a mildew-resistant wheat, a non-browning mushroom and a waxy starch maize. These are either already in commercial production or probably soon will be. In addition, other countries including Argentina, Brazil and Japan either have, or are close to, formulating case-by-case guidance for gene edited crops. Canada has a trait-based system that should seamlessly accommodate new biotechnologies as they emerge. Meanwhile the EU has offered no guidance whatsoever as to how they plan to regulate gene edited products. Even though approximately 80% of its animal feed incorporates imported GMO soya or maize, it still has no plans for handling the import or cultivation of gene edited crops. This unhelpful vacuum is being filled with polarised views that serve to further confuse consumers. For example, there have been calls from vocal campaign groups for products of gene editing to be governed as a conventional GMO regardless of trait or whether there are already equivalent mutations already in the food supply (e.g. Natural News 2015, GM Watch 2014).

The EU trigger for biotechnology regulation is defined mainly by the process used to make the genetic improvement. While this situation remains, the dilemma over how to regulate gene editing will inevitably be repeated over and over as new breeding methodologies are developed. I propose a two-fold solution. To move away from a binary GMO or non-GMO definition of biotechnology to a more nuanced, scaled approach where the data requirements for assessment and procedures for risk management are proportional to the risks involved. For instance, products of simple gene editing would require a light-touch evaluation and management whereas those incorporating gene drives or some future

synthetic biotechnology would require a significantly higher level of regulatory oversight. Secondly, to elevate the concept of 'product' as a more important regulatory trigger. For example, when crops possessing herbicide tolerance (HT) to one or just a few active ingredients are widely cultivated, it is the HT trait that may poses a risk to the environment not the process by which it is made. There are currently commercially grown HT crops generated using three different basic breeding technologies; mutation breeding, gene editing and conventional GMOs. Only one, the latter, is currently regulated in the EU which is illogical. However, it would also be illogical to state that conventional GMOs and products of gene editing or mutation breeding all pose the same level of risk and require the same data requirements for risk assessment. Thus, we need to reverse the emphasis and place 'product' before 'process' and discard the all or nothing approach to regulation and devise a graduated process of assessment that uses as its basis the risks inherent in the product as the main trigger for regulation and data requirements.

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