

Now may be an opportune time for Australia to examine whether the trigger for regulatory review should be those products that fall into the ill-defined category of GMOs as defined by the National Gene Technology Scheme, or whether a more scientifically-defensible system would be triggered by product risk and novelty. Genetically modified, or, more correctly, genetically engineered (GE) plants have and will continue to contribute to food production and sustainability in the future. The current regulatory system for the products of gene technologies, so called GMOs, is lengthy and prohibitively expensive for all but large, multinational corporations. This level of regulatory scrutiny is often not supported by the risk posed by these products, and is prohibiting the commercialization of many public sector applications of this technology. No unique risks have been associated with the commercialized varieties of GE crops over the past 20 years, however the regulatory hurdles have all but precluded the development of GE specialty crops, and GE food animals globally, with but a single approval and retail sales in a single country (AquAdvantage salmon, Canada) in 2016, more than a quarter of a century after the founder fish of this line of salmon was produced in 1989.

Regulatory effort should be proportional to the risk posed by the product being evaluated – not what technology was used to produce that product. Currently, identical products produced using different breeding methods are subject to vastly different levels of regulatory scrutiny. The current “GMO”-based trigger for regulatory evaluation of GE plants and animals is disincentivizing the development of beneficial GE applications to the detriment of global food security and agricultural sustainability. Given 20 years of experience with GE crops and the burgeoning developments in gene technologies, now is an opportune time to consider whether a more workable and sensible approach would be to focus regulatory evaluations on the risks and benefits posed by novel traits in new varieties of crops and animals, irrespective of the breeding method that was used to introduce those traits.

Current realities

Regulatory systems provide a way for society to find a balance among the potential benefits, risks, and concerns associated with new technologies. Presumably oversight should be exercised only when the value of the reduction in risk obtained by additional oversight is greater than the costs of regulation. It is hard to argue that this has been the case with GMO crops to date where each event is associated with a multimillion dollar regulatory package. Regulatory agencies globally have had to develop convoluted and arbitrary language to specifically regulate “GMO” crops while exempting identical products produced using gene technologies like radiation mutagenesis and polyploidy. To the amazement of biologists, geneticists and scientists globally artificial distinctions have been drawn to distinguish between, for example, the risks associated with fast-growing salmon produced using conventional breeding methods and those associated with fast-growing GMO salmon produced with gene technologies. This unfounded distinction based on an imprecisely defined class of “GMO” organisms is tying the hands of plant and animal breeders globally, many working in the public sector, by precluding their access to a useful suite of tools to introduce beneficial genetic variation into breeding programs.

This problem of what constitutes a GMO is only going to become more difficult with the advent of site-directed nucleases and precision gene editing. And this highlights the problems associated with regulating based on an ill-defined notion of a GMO, rather than product risk. Gene technologies are going to continue to evolve, and it is becoming increasingly difficult to draw a clear distinction between GMOs, breeding, and evolution. At the end of the day, if the intent of the National Gene Technology Scheme is to enable safe genetic innovation, the focus of regulation has to move away from the outdated concept of a “GMO” to one based on the unique risks and benefits resulting from any novel attributes associated with the products of breeding programs, irrespective of the breeding methods used to achieve genetic change.

The current regulatory scheme is slow to respond to change and is stifling breeding innovation globally. Despite the prohibitively expensive global regulatory costs associated with GMO crops developed using certain “gene technologies” which has effectively limited their implementation to all but a few large field crops, their environmental benefit to date has been significant. Globally there has been a dramatic reduction in insecticide use with the *B.t.* crops including cotton in Australia, and more generally a shift to less toxic pesticides and adoption of no-till practices. If groups opposed to GMOs had been successful in their fearmongering campaign to keep these crops off the market indefinitely, the demonstrated environmental benefits as summarized below, (let alone the yield and farmer benefits), would be unrealized.

“The adoption of GE insect resistant and herbicide tolerant technology has reduced GLOBAL pesticide spraying by 618.7 million kg (~8.1%) and, as a result, decreased the environmental impact associated with (less toxic) herbicide and insecticide use on these crops by 18.6%. The technology has also facilitated important cuts in fuel use and tillage changes, resulting in a significant reduction in the release of greenhouse gas emissions from the GM cropping area. In 2015, this was equivalent to removing 11.9 million cars from the roads.¹”

The opportunity cost of precluding access to safe breeding methods must be part of the consideration of the costs and benefits associated with any regulatory evaluations. At its heart, the Gene Technology Act has a process-based trigger with no rationale as to WHY the trigger of gene technologies need additional regulatory oversight above that associated with conventional breeding, and ignores the now 20-year history of safe use. Scientific uncertainty is informed by more information, and while the absence of evidence of harm is not evidence of harm’s absence, it surely at this juncture there is a very large data set from which findings of relative safety can be drawn with a fair degree of confidence. Perhaps it is time to ask: Have the benefits resulting from the National Gene Technology Scheme outweighed the direct costs and commercialization delays associated with the scheme? Has the 20 year experience with commercialized GMO crops documented any actual human or environmental health risks?, and how do they compare to the realized human or environmental health benefits?

The new methods of gene editing have the opportunity to introduce useful alterations into breeding programs. This technology must be considered in the context of the natural “gene editing” also known as *de novo* mutations (**dnm**) that occur every generation and which is the basis of evolution and genetic variation that is the foundations of all breeding programs. A 2016 a bioRxiv preprint (posted online Oct. 9, 2016) doi: <http://dx.doi.org/10.1101/079863> directly estimated the germ-line *de novo* mutation rate by sequencing the whole genome of 54 cattle from four pedigrees. Grand-parents, parents and offspring 30 (referred to as probands) were sequenced at average 26-fold depth (min = 21), and grand-offspring at average 21-fold depth (min = 10). These father-mother-offspring cattle trios identified candidate dnm’s as variants that were (i) detected in a proband, (ii) absent in both parents (and grand-parents when available), (iii) transmitted to at least one grand-offspring, and (iv) not previously reported in unrelated bulls. Two hundred and twenty of the 237 identified dnm’s were nucleotide substitutions, and 17 were small insertion-deletions. When accounting for genome coverage, **the estimated number of dnm’s per gamete averaged 46.6 for sperm cells and 18.1 for oocytes (male/female ratio of 2.6), corresponding to an average mutation rate of ~1.2x10⁻⁸ per base pair per gamete in cattle.**

¹ Graham Brookes & Peter Barfoot (2017): Environmental impacts of genetically modified (GM) crop use 1996–2015: Impacts on pesticide use and carbon emissions. GM Crops & Food, DOI: 10.1080/21645698.2017.1309490

Some activist groups are lobbying for the most precautionary approach to gene editing and suggest that there are unknowable risks associated with small mutations and deletions and therefore editing poses novel risks and should be regulated as GMOs – and ignore the fact that hundreds of these dnm alterations occur naturally every generation. Risk is not associated with the method used to introduce genomic changes – be it ionizing radiation mutagenesis, dnms, or nucleases.- it is associated with the end product. We have hundreds of years of breeding based on dnms and these are not regulated in conventional breeding programs. Blocking gene editing does not provide solutions to the problems that breeders would like to address with this tool.

There is no rationale for regulating varieties exhibiting a genetic trait and sequence produced using classical breeding techniques differently from those exhibiting the same trait produced using gene technologies, if the risks are the same. This is especially evident when no novel DNA has been introduced. As I discuss in my paper², when we used gene editing used to make a polled (hornless) Holstein dairy cow by editing the horned gene to exactly the same sequence as exists naturally in other breeds of cattle (e.g., polled Herefords), it is unclear why that polled animal should be subjected to a multimillion dollar regulatory review when an animal with exactly the same genotype and phenotype produced using crossbreeding and gene introgression would be subject to none. Likewise, it is difficult to envision how the food safety and environmental risks posed by the polled trait in the Holstein breed are different to those posed by the polled trait in the Hereford breed.

Perhaps Australia has an opportunity to develop a science-based, product focused regulatory system that:

- Is triggered by unreasonable unique risks associated with the novel trait(s) in that species (if any) in relation to known risks associated with growing existing varieties of that species and known spontaneous genetic changes associated with spontaneous *de novo* mutations;
- Required regulatory studies must be hypothesis-driven based upon the novel attributes of the product/variety, and not the breeding method used to develop the new variety;
- Potential benefits resulting from the novel variety/trait(s) must be explicitly quantified to enable an evaluation of the risk-to-benefit ratio posed by the introduction (or opportunity costs associated with the potential delay or prohibition) of the new variety (as is done with medical drugs);
- Specific novel attributes of the product (if any) such as the presence of a completely new substance in the food supply, changes in a macronutrient, an increase in a natural toxicant, or the presence of novel allergens should be the trigger for comprehensive food safety evaluation, not the gene technology used to produce that product.

Initial uncertainty about the safety of genetic technologies/GMOs was warranted 30 years ago. But since then, literally thousands of studies have contributed to the weight of evidence suggesting there are no unique risks associated with these breeding methods. A science-based regulatory system has to be proportional to, and focus on real risks, not perceived risks or hypothetical risks. Despite this history, regulatory review of GMOs has been getting ever more costly and taking a longer time to achieve. Globally there seems to be a collective case of regulatory group think, rather than critical analysis, and as of yet no country has been willing to decrease the regulatory burden based on these years of data, and evaluate products produced using gene technologies based on their actual risk and potential benefits. I hope the review of the National Gene Technology Scheme starts from first principles, and asks whether the existing system has achieved the appropriate societal balance among the potential benefits, risks, costs, and concerns for both public and private entities to use gene technologies to address agricultural problems.

² Carroll, D., Van Eenennaam, A., Taylor, J.R., Seger, J., Voytas, D. 2016. Regulate genome-edited products, not genome editing itself. *Nature Biotechnology*. 34(5):477-479.