21 February 2018

The Regulations Review,
The Office of the Gene Technology Regulator (MDP 54);
GPO Box 9848,
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Re: 2016-17 Technical Review of the Gene Technology Regulations 2001

Please accept my following submission to the 2016-17 Technical Review of the Gene Technology Regulations 2001.

1. CRISPR techniques should be regulated

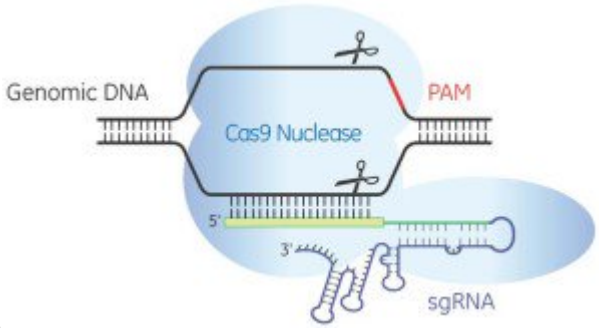
> Biohacker Josiah Zayden has a company that sells DIY CRISPR kits, and regrets publicly injecting himself with CRISPR.
>
> *"I wasn't trying to give myself bigger muscles. I wasn't trying necessarily to genetically modify myself. I don't want to genetically modify myself at the moment. So many people ask me to do it on camera, and I'm like, are you crazy? I'm not injecting myself for TV. I didn't intend for it to be this way."* *https://www.theatlantic.com/science/archive/2018/02/biohacking-stunts-crispr/553511/*

Even the Biohacker community names CRISPR techniques as GM techniques, and as such they should be regulated as gene technology under the Gene Technology Act 2000.

I submit this work by Dr Jonathan Latham

> **God's Red Pencil? CRISPR and The Three Myths of Precise Genome Editing**
>
> by Jonathan Latham, PhD
>
> For the benefit of those parts of the world where public acceptance of biotechnology is incomplete, a public relations blitz is at full tilt. It concerns an emerging set of methods for altering the DNA of living organisms. "*Easy DNA Editing Will Remake the World. Buckle Up*"; "*We Have the Technology to Destroy All Zika Mosquitoes*"; and "*CRISPR: gene editing is just the beginning"*. (CRISPR is short for CRISPR/cas9, which is short for Clustered Regularly-Interspaced Short Palindromic Repeats/CRISPR associated protein 9; Jinek et al., 2012. It is a combination of a guide RNA and a protein that can cut DNA.)
>
> The hubris is alarming; but the more subtle element of the propaganda campaign is the biggest and most dangerous improbability of them all: that CRISPR and related technologies are "genome editing" (

That is, they are capable of creating precise, accurate and specific alterations



to DNA.

Even the "serious" media is in on it. *Nature* magazine in July 2015 published "Super-muscly pigs created by small genetic tweak". Two value judgments in a seven word headline: "small" and "tweak", neither supported by the content of the article. Still enthralled, if not wholly original, just last week the *NY Times* opinion section offered: "*Tweaking genes to save species*".

How do I know this is a propaganda war? I heard it from the horse itself. In February I was at a UN meeting on biotechnology in Rome, Italy, where a senior representative of the Biotechnology Industry Organisation (BIO) explained to the assembled delegates the "exquisite specificity" and "precision" of genome editing.

Myth 1: Current genome editing technologies are not error prone

BIO's exposition is belied by the evidence. If CRISPR were already precise, accurate and specific there would, for example, be no publications in prominent scientific journals titled "*Improving CRISPR-Cas nuclease specificity using truncated guide RNAs*". And these would not begin by describing how ordinary CRISPR "can induce mutations at sites that differ by as many as five nucleotides from the intended target", i.e. CRISPR may act at unknown sites in the genome where it is not wanted (Fu et al., 2014).

Thus CRISPR itself will need tweaking before it can be useful for safe commercial products, and that is the first error of the tweaking argument. So far, it is technically not possible to make a single (and only a single) genetic change to a genome using CRISPR and be sure one has done so (Fichtner et al., 2014). As Fichtner noted "in mammalian systems Cas9 causes a high degree of off-target effects". And at least until modified versions come into use, this will limit the safety, and hopefully limit the application, of CRISPR and related biotechnologies. There is, furthermore, no guarantee that more precise versions of CRISPR are even biologically possible. Technically therefore, precision is a myth: no form of genome editing can do what is currently being claimed.

Myth 2: Precision equals control

The second key error of CRISPR boosters is to assume that, even if we had complete precision, this would allow control over the consequences for the resulting organism.

Suppose, as a non-Chinese speaker, I were to precisely remove from a Chinese text one character, one line, or one page. I would have one hundred percent precision, but zero control over the change in meaning. Precision, therefore, is only as useful as the understanding that underlies it, and surely no DNA biologist would propose we understand DNA–or else why are we studying it?

A classic example of how DNA can still reveal unexpected functions decades after discovery is the CaMV 35S promoter, a DNA sequence used in commercialised GMO plants for almost twenty years. The CaMV 35S DNA is described in every application for commercial use as a simple DNA "promoter" (an "on" switch for gene expression).

In 1999, however, the CaMV 35S "promoter" was found to encode a recombinational hotspot (Kohli et al., 1999). In 2011 it was found to produce massive quantities of small RNAs. These RNAs probably function as decoys to neutralise the plant immune system (Blevins et al., 2011). One year later still, regulators found it to contain an overlapping viral gene whose functions are still being elucidated (Podevin and du Jardin 2012). Will we ever know enough about any DNA sequence to accurately describe changing it as "editing"?

Myth 3: DNA functions are modular and changes are predictable

The third error of CRISPR advocates is to imply that changes to gene functions can be presumed to be discrete and constrained.

The concept of the precise editing of a genome leading to a precise biological outcome depends heavily on the conception that genes give rise to simple outputs. This is the genetic paradigm taught in schools. It is also the paradigm presented to the public and that even plays a large role in the thinking of molecular genetic researchers.

However, a defined, discrete or simple pathway from gene to trait probably never exists. Most gene function is mediated murkily through highly complex biochemical and other networks that depend on many conditional factors, such as the presence of other genes and their variants, on the environment, on the age of the organism, on chance, and so forth. Geneticists and molecular biologists, however, since the time of Gregor Mendel, have striven to find or create artificial experimental systems in which environmental or any other sources of variation are minimised so as not to distract from the more "important" business of genetic discovery.

But by discarding organisms or traits that do not follow their expectations, geneticists and molecular biologists have built themselves a circular argument in favour of a naive deterministic account of gene function. Their paradigm habitually downplays the enormous complexities by which information passes (in both directions) between organisms and their genomes. It has created an immense and mostly unexamined bias in the default public understanding of genes and DNA.

This is not my argument. It belongs to Richard Lewontin of Harvard University, probably the most famous geneticist of our time.

The benefits of naive genetic determinism to the architects of the genome-industrial complex are very great. Since it pretty much requires that organisms be seen as robots being operated by mini-dictators (rather than, for example, as systems with emergent properties) and those genes as having effects that are narrow and clearly defined rather than being diffuse and unpredictable, it simplifies their sales pitch and frames risk assessment as unnecessary.

The problem comes to a head, however, when this narrow conceptualisation of genetics is applied to the real world and situations that have not been, as it were, set up in advance. In the case of the "Super-muscly" pigs reported by *Nature*, strength is not their only feature. They must also have more skin to cover their bodies and stronger bones to carry themselves. They also, apparently, have difficulty giving birth; and if they were ever released into the wild, they would presumably have to eat more. Thus a supposedly simple genetic tweak can have wide effects on the organism throughout its lifecycle.

Nature also revealed that thirty of the thirty two experimentally-edited pigs died prematurely and only one animal was still considered healthy at the time the study authors were interviewed. So much for precision.

The neverending story

Why is this discussion of precision important? Because for the last seventy years all chemical and biological technologies, from genetic engineering to pesticides, have been built on a myth of precision and specificity. They have all been adopted under the pretense that they would function without side effects or unexpected complications. Yet the extraordinary disasters and repercussions of DDT, leaded paint, agent orange, atrazine, C8, asbestos, chlordane, PCBs, and so on, when all is said and done, have been stories of the steady unraveling of a founding myth of precision and specificity.

Nevertheless, with the help of industry propagandists, their friends in the media, even the United Nations, we are once again being preached the gospel of precision. But no matter how you look at it, precision is a fable and should be treated as such.

The issues of CRISPR and other related new "genome editing" biotechnologies are the subject of intense activity behind the scenes. The US Department of Agriculture has just explained that it will not be regulating organisms whose genomes have been edited since it doesn't consider them to be GMOs at all. The EU was about to call them GMOs but the US has caused them to blink, meanwhile the US is in the process of revisiting its GMO regulatory environment entirely. Will future safety regulations of GMOs be based on a schoolboy version of genetics and an interpretation of genome editing crafted in a corporate public relations department? If history is any guide it will.

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Further reading (added April 26): Are new biotechnologies GMOs?

2. RNAi techniques should be regulated

RNAi techniques are also GM techniques, and as such they should be regulated as gene technology under the Gene Technology Act 2000. I attach the work of Heinemann, Agapito-Tenfen and Carman (2013).

You should have regulated these techniques before FSANZ approved the food. I've got nothing much more to say about that. I hold the Health Department wholly responsible for any adverse outcomes. I will remember, and if it takes too long, my children will be there to remember.

For Immediate Release: 29 March 2011
Monsanto's Newest GM Crop:

All aboard the Hindenburg!

Our food regulator FSANZ has decided that a new Monsanto GM crop represents no risk to human health.

MADGE is alerting Australians to the fact that FSANZ has decided this without any reported investigation into the safety of Monsanto's latest genetic construct. Monsanto has engineered the crop to produce pieces of its own genetic material in a virus form (double - stranded RNA).

The plant then seems to be fooled Into taking action against itself. The plant cells chop up this material into small pieces and use It to silence the plant's own natural genes.

What if some of these small pieces of dsRNA are actually perfect matches for some of our own genes? Will our own cells be fooled into self-silencing after eating material from this crop, in a sort of auto-immune response?

There is no indication that FSANZ has done Anything to investigate this and other possibilities.

We're not even sure they understand the science since they only cited one study on the topic, though there are thousands.

This form of genetic manipulation was only discovered in 1998, and the work was recognized to be useful with a Nobel prize in 2006. However the Codex Alimentarius safety assessment guidelines were written in 2003, and give no reference to this sort of genetic construct.

"Allowing this GM crop to enter our food supply is like strapping our entire society including our children into one of the first aircraft prototypes to be used in a trial" said Madeleine Love of MADGE.

"GM must emerge from the rubber stamping of FSANZ and into real public informed decision making. Our public health is at stake" said MADGE spokesperson Fran Murrell.

All aboard the Hindenburg says our food regulator.

Contact: Madeleine Love 0447 762 284
Fran Murrell 0401 407 944

3. Gene Drives and other such inventions should be regulated

You're thinking of deregulating gene drives et al. Are you joking? Are you psychopaths? It's a serious question.

I submit this work by Dr Jonathan Latham:

Gene Drives: A Scientific Case for a Complete and Perpetual Ban

by Jonathan Latham, PhD

One of the central issues of our day is how to safely manage the outputs of industrial innovation. Novel products incorporating nanotechnology, biotechnology, rare metals, microwaves, novel chemicals, and more, enter the market on a daily basis. Yet none of these products come with an adequate data set of scientific information. Nor do they come with a clear intellectual framework within which their risks can be placed, as disputes over the precautionary principle show. The majority of products receive no regulatory

supervision at all. How will the product be disposed of? What populations and which ecosystems will be exposed in the course of its advertised uses? What will be the consequences of accidental, off-label or illegal uses? Typically, none of these kinds of questions are adequately asked by government regulatory agencies unless citizens actively prod them to do so.

In consequence of these defects, we expose our world to unique hazards with every product launch. In comparison with its tremendous importance, this is surely one of the least discussed issues of our day.

The spectrum of regulation

Regulation of the products of industrial processes comes in quite diverse forms. At one extreme is the U.S. airline industry. Commercial airplanes are intensively regulated throughout their lives, from design to production, maintenance and operation. When plane accidents occur, an intensive and independent investigation is carried out and little expense is spared searching for the parts, which may even be retrieved from the bottom of the ocean.


Mosquitos and DNA

When the investigation is concluded, recommendations are made. Not infrequently, aircraft design or maintenance is subsequently altered and planes already manufactured may be recalled.

This regulatory process is thus characterized by extensive and continuous feedback between all parts of the system: aircrew, regulators, maintenance crews, manufacturers, etc. This iterative type of regulatory supervision is widely viewed as successful and uncontroversial. Indeed, the airline industry has proportionately few deaths given the inherently hazardous and unnatural nature of flight.

In significant contrast is the regulation of the products of the chemical industry. The standard model for those synthetic chemicals that do not evade regulation entirely is to release them in a single decision. This decision is typically referred to as the ‘approval’ or ‘deregulation’ event. After the approval decision is made, further data are sometimes collected and chemical re-registration may sometimes be required, but the approval decision is in many senses irreversible — for example, because recall is a practical

impossibility. This type of regulation, which applies also to pharmaceuticals, crop biotechnology, and medical devices is thus characterized by only a minimal iterative component. The contrast with airplane safety, with its numerous systematized and formalized opportunities for feedback and learning with respect to each product, is significant.

The question of endpoints

A further contrast between airplane safety and chemical (or GMO) safety is in the number of endpoints — that is, potential specific hazards — that need to be taken into account. The relative simplicity and success of airline safety follows significantly from the fact that the number of potential negative outcomes are few and well defined. With the exception of hijacking, a plane crash is almost the sole endpoint of airplane safety.

Each product of the chemical and biotech industries, on the other hand, has a close to infinite list of potential negative outcomes. In 2007 the French government was presented with a report by professor Dominique Belpomme into the health of the population of the Caribbean islands of Martinique and Guadeloupe. According to that report, the 800,000 inhabitants faced a "health disaster" as a result of the spraying of the banana pesticide chlordecone. Half the male population would develop prostate cancer, infertility on the islands is rising, and all children on the islands are contaminated. Chlordecone will remain in the soil for up to a century.

Chlordecone was part of a pattern. Beginning with Lead-Arsenate, via DDT and other chlorinated hydrocarbons, and continuing successively through organophosphates and neonicotinoids, a long line of chemical insecticide families have entered widespread use only to be discarded or banned for their broad negative ecological and health consequences.

The primary reason for this pattern of insufficient foresight by regulators and experts is that any single synthetic chemical, such as a pesticide, may potentially cause an enormous number and diversity of harms. They may result in reproductive toxicity, neurotoxicity, or carcinogenicity, for example, to any of a very large (often unknown) number of species. Moreover, these harms may vary according to life stages, with environmental or dietary conditions, the presence of other pollutants, and so forth. Furthermore, these harms may occur near to or far from the places and times where the chemical was used. Even pharmaceuticals, where negative endpoints have historically been considered to be limited to individual patients, can yield surprises.

For example, contraceptives entering sewage systems may later contaminate water bodies and so disrupt the endocrine systems of fish (Fick et al. 2010).

A few authors have argued that the history of chemical regulation, from the point of view of protecting public health and ecological health, is better described as a long line of failure brought on unavoidably by the fact that such a myriad of endpoints greatly exceeds the practical and financial limitations of science. This is both because of the potential diversity and number of harmful

endpoints, and because each endpoint requires a specific scientific experiment—or at least specific data collection (3,4).

Thus, endpoints as exotic as the reproductive consequences for fish of contraceptive hormones filtered by the human kidney (and by a sewage system) need to be explicitly considered and experimentally measured as part of the regulatory system, in order to avoid major health and ecological harms. Yet regulators are faced with the genuine unavoidable conundrum of the sheer number of such potential outcomes. Listing them all is impossible and investigating them is inconceivable. There are, by many orders of magnitude, too many. The number of possible toxicological endpoints of a single chemical is enormous, yet failure to explicitly consider and measure each and every one of them could potentially lead to a public health disaster on the scale of Martinique and Guadeloupe or an ecological one on the scale of neonicotinoids (5).

In short, one can show that regulations covering industrial products vary along two main parameters. Those two parameters are:

1) *the iterative nature (or otherwise) of the regulatory process applied to them, and*

2) *the number of potential negative endpoints needing to be explicitly considered.*

Combining these two parameters with some relatively uncontroversial estimates of regulatory success suggests a simple hypothesis: that products having fewer endpoints and subjected to regulatory processes with more iterations are those most likely to be safe.

The underlying logic to this position is straightforward: Iterations allow mistakes to be corrected while fewer endpoints make regulation simpler and more manageable.

The endpoints of agricultural biotechnology

In comparison to synthetic chemicals, GMOs intended for agricultural use have a similarly large, perhaps greater, number of potential hazardous endpoints. They may harm human and other intended consumers, soils, other crops, non-target insects, and so forth.

Nevertheless, agricultural GMOs are in some sense relatively contained with respect to the harms they can cause for the reason that many GMO varieties used in

agriculture are restricted in their reproductive potential. Most commonly by virtue of their frost sensitivity. Such crops include maize and soybeans in most of the United States. This natural biological containment acts as a severe restriction on the possibility of harm by eliminating most long term

interactions outside of the agriculture/food system. Thus, the number of endpoints needing to be considered in risk assessment is greatly reduced.

There are some GMO crop varieties, however, which are not subject to such natural containment.

Creeping bentgrass (*Agrostis stolonifera)* is a turf grass for which the Scotts corporation (in collaboration with Monsanto) has created a GMO version resistant to the herbicide glyphosate.

The Scotts GMO bentgrass was open field-tested by the company in preparation for marketing between 2001 and 2003. However, it escaped from several company test sites. Whether mainly by pollen flow or by seed dispersal is not known, but glyphosate-tolerant *A. stolonifera* can currently (as of 2016) be found in several Oregon counties and in neighboring Idaho (6). The escape of this GMO grass has created problems for weed management of waterways. Since *A. stolonifera* is a wind- pollinated species, we can anticipate that, in the absence of a dramatic intervention, GMO *A. stolonifera* transgenes will spread globally to wherever this grass grows wild.

GMO herbicide-tolerant canola (Brassica *napus)* has been approved for agricultural use in Canada, the US, and Australia. Within those countries, herbicide-tolerant canola GMO populations have been found growing as feral populations. Feral GMO canola populations have also been found in Great Britain, Japan and France (7).

The third example of an uncontained GMO is corn in Mexico (8). The above countries might consider themselves lucky that creeping bentgrass and feral canola are (so far) largely agricultural annoyances. GMO corn often contains one or more members of the Cry family of insecticidal proteins. In much of Mexico, unlike most of the U.S., corn growth is not restricted by frost — which means that, in essence, self-replicating insecticides are spreading across the landscape. This corn arguably represents a degree of risk to ecological and food systems that exceeds the threat from chemical pesticides.

Application to gene drives

Gene drives, as currently envisaged, and as explained elsewhere in this issue, are techniques to promote the inheritance of specific alleles. Gene drives typically rely on the introduction of CRISPR RNA and Cas9 type proteins from integrated transgenes to drive gene frequencies. Their ultimate goal is to alter the genetic composition of populations, including for the purposes of engineering population crashes or extinctions.

Because they rely on *in vitro* techniques to introduce foreign gene sequences, gene drives are technical extensions of biotechnology. From the present point of view of risk, however, the main distinction between gene driven organisms and most GMO crops is that gene drive organisms are explicitly designed to live and reproduce in the wild.

Conventional understanding is that gene drives can be regulated within standard frameworks (9). If we consider gene driven organisms in the terms of the framework outlined here, however, gene drive organisms approximate a perfect storm. They are 'products' that will likely not be able to be recalled, so any approval decision point must be presumed to be final and irreversible; and their reproductive and dispersal abilities imply the need to test a great number of endpoints, perhaps even more than either synthetic chemicals or agricultural GMOs.

Some sample questions can illustrate the diversity of endpoints relevant to gene drive organisms.

For example, will gene driven organisms, such as mice or mosquitoes, be hazardous to the predators that eat them, either as the prey species drive their own population extinct (if that is their intention), or if they fail to do so? The scientific grounds for posing this question are substantial. One is the documented unpredictability of genetic engineering processes. This unpredictability is especially a concern in the pest organisms for which gene drives are presumably intended since they are largely uncharacterized in comparison to the agricultural varieties that are the standard objects of genetic engineering.

The second scientific grounds for concern about the toxicity of gene drive organisms are the specific gene sequences that will be added. For instance, Oxitec's GMO (but not gene drive) diamond back moth (*Plutella xylostella)*, already planned for experimental releases in New York State, contains DNA from several viral pathogens including Herpes Simplex Virus (HSV) (10). Whether genes from viral pathogens can ever be safely inserted and used in other organisms is still an open question (11).

Other key questions center around whether gene drives will spread from the original species to others with which it may sometimes interbreed. The importance of this is firstly that the gene drive is likely to negatively impact these other species. More than that, any unwanted and unanticipated impacts of the gene drive will be felt outside the predicted impact zone if gene drives spread beyond the original species.

A third set of questions surely must center around whether the evolutionary trajectory of gene drive components can be adequately controlled and predicted given the complex assorting and mutating inherent in the concept of gene drives.

Posing such questions foregrounds the crucial underlying point: that the number of potential hazardous end-points needing to be investigated to establish the safety of a gene drive in the numerous conditions it will inevitably encounter will be vast. This is especially so when each question cannot be considered alone since none of them exist in isolation. The consequence is that no nation is financially or otherwise capable of operating such a science program, especially when these three questions represent the tip of an iceberg.

Compounding this main issue is that a large proportion of such endpoints cannot be credibly investigated outside of ecologically realistic environments, and such experiments are invariably expensive and laborious. Ideally, one would need a planet B.

It needs also to be considered that answering such questions would require unique and unprecedented scientific protocols. Imagine we wanted to test the toxicity of gene driven mosquitoes to bats, or test the behavioral characteristics of gene driven mosquitoes. There are unlikely to be scientific precedents, in terms of techniques and expertise, for such experiments.

These are the harsh realities that regulatory systems have long ignored. Having failed to protect the population against synthetic chemicals and failed to protect the environment from GMOs, it is illogical to expect that regulation organized on conventional lines will protect us from gene drives or any other wild GMO organisms.

This leads to just one conclusion. Unless a radically novel system of regulation can be invented, we should forget about gene drives. Just as we would have been better off foregoing agricultural pesticides and fungicides because regulatory systems lacked the rigor to oversee them. Gene driven organisms equally must never be released.

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(This article was originally published in GeneWatch Vol. 30, 2017)

Yours faithfully,

Madeleine Love