
REVIEW

A critical assessment of regulatory triggers for products of biotechnology: Product vs. process

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ABSTRACT. Regulatory policies governing the safety of genetic engineering (rDNA) and the resulting products (GMOs) have been contentious and divisive, especially in agricultural applications of the technologies. These tensions led to vastly different approaches to safety regulation in different jurisdictions, even though the intent of regulations—to assure public and environmental safety—are common worldwide, and even though the international scientific communities agree on the basic principles of risk assessment and risk management. So great are the political divisions that jurisdictions cannot even agree on the appropriate triggers for regulatory capture, whether product or process. This paper reviews the historical policy and scientific implications of agricultural biotechnology regulatory approaches taken by the European Union, USA and Canada, using their respective statutes and regulations, and then critically assesses the scientific underpinnings of each.

KEYWORDS. Biotechnology, GMOs, PNT, Product vs process, regulation, Regulatory Trigger, safety, policy

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INTRODUCTION

The Goal Of Regulation; Regulatory Theory And Policy

What does government regulation attempt to achieve? The primary goal of regulation is to protect our society, community and environment from harms. In a perfect world, all potential threats, whether to life, food and feed security or ecosystems, would be rendered ineffective by appropriately directed regulation and risk management interventions. In our imperfect world, however, practical realities demand prioritization in the allocation of resources— human, temporal and financial—to regulate and manage only a portion of the spectrum of potential hazards. No nation can afford to fully regulate everything for every risk, so a system of prioritization must be adopted everywhere. The distinctions described for differing jurisdictions in this study are largely a matter of differing prioritization policies and strategies.

Unfortunately, every thing and every activity carries some degree of risk. Getting out of bed in the morning carries a risk, as does the alternative, staying in bed. Some activities are more risky than others. Smoking tobacco is widely recognized as a much greater threat to health than breathing clean fresh mountain air. Sensible, then, is the policy of directing substantial regulatory resources to the major risks associated with tobacco smoking, and relatively few to the negligible risks of breathing fresh mountain air.

Broad anti-smoking policies support the maxim of regulatory theory that the degree of regulatory oversight should be commensurate with the degree of documented (*i.e.*, not hypothetical) risk posed.

To optimize the deployment of regulatory resources, effective prioritization demands accurately assessing the risks posed by various threats, then concentrating efforts to regulate and mitigate risks on those posing the greatest threats.

Failure to correctly identify risks and assign appropriate regulatory resources commensurate with degree of risk is an abdication of regulatory responsibility. It leads to errors both of commission (over-regulation of relatively lower risk threats) and also omission, (under-regulation of

relatively higher risk threats). Inappropriately expending resources – through inefficient prioritization – on lower risk threats necessarily means not only are resources being wasted, it means health and environment are left vulnerable to harms from higher risk but less threats.

Society depends on and, for the most part, trusts, government policy and regulators to be efficient and reasonably accurate in prioritization of regulatory resources. Witness the erosion of public trust in government regulators in the UK following the outbreak of BSE, “Mad Cow” disease in the 1980s. British government politicians and regulators reassured the public that the BSE matter was under control, and that there was nothing wrong with the beef supply. But then innocent humans contracted vCJD as a direct result of trusting government scientists in consuming neural tissue from beef “government certified safe,” but nevertheless contaminated from BSE prions. While the British government properly attempted to calm public anxiety and fear, it failed to prioritize the real threats to health and security of the food supply. The strategy employed was to calm public anxiety (a legitimate endeavor), but the British government failed to invoke a science based analysis of BSE in cattle and the connection of BSE to vCJD in humans. Public support, credibility and trust in the UK regulatory system plummeted, and it is only recently starting to rebuild. But beef consumption in the UK still has not recovered.

With scientifically sound prioritization of regulatory resources in the UK in the 1970s, the vCJD outbreaks in humans would probably not have occurred, and the threat from BSE itself would have been minimized. Clearly, efficient prioritization is crucial to effective regulation and maintenance of public trust in the regulatory system.

Confusing Terms and Ambiguous Definitions

One of the difficulties in discussing regulatory and safety issues is the imprecise definition of some common terms. Unlike technical jargon, which is usually unique and either the definition is known or unknown, terms like

“biotechnology” “genetic modification” or “substantial equivalence” have common but varied meanings. Thus, these terms are more likely to be confusing and ambiguous, as each listener knows and understands these terms, but the definitions can vary between speaker and listener. To provide some clarity and common understanding, the following terms are discussed and defined.

Biotechnology, Past and Present

Biotechnology, broadly defined, can refer to any application of biology to derive goods and services. Indeed, the official Canadian definition, codified in the Canadian Environmental Protection Act (CEPA) (Canadian Environmental Protection Act 1999), is “. . .the application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural and modified forms.” Like most other ‘official’ definitions of biotechnology, Canada’s derived from that first appearing in an OECD document from 1982: “. . .the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services” (Bull et al., 1982).

Clearly, using this definition, humans have practiced biotechnology since the dawn of civilization some 40,000 years ago. Even then, our earliest ancestors started manipulating biological systems such as yeast to make bread, wine and beer.

If we restrict the definition to genetic modification of biological systems to generate goods and services, then we can go back 10,000 years, when our ancestors first domesticated agriculture, intentionally selecting genetically suitable or preferable crops and animals for domestication. Unfortunately, any term with a variable or ambiguous definition is not very useful in discussions, particularly as they concern risks and regulations. The term “Genetic modification” has an official definition in the European Union, but is officially undefined and generally avoided in official US and Canadian statutes and policy documents. Popular usage of genetic modification, especially “GMO” (genetically modified

organism) can, depending on usage, limit the definition to rDNA or genetic engineering, or expanded more broadly to encompass things that fit no official definition, such as crops developed using non-traditional means of breeding (e.g., in vitro selection). Defining GMO in 90/220EEC 3 and clarified in 18/2001/EC 4 illustrates the problems with policymakers deciding scientific issues without heeding guidance from expert scientists. For example, in the EU, common food ingredients such as sugar or soybean oil is (legally) required to be labeled as a GMO, if the sugar or oil were derived from a genetically engineered sugarbeet or soybean plant, respectively. In reality, neither sugar nor soybean oil are organisms of any kind, let alone genetically modified, as these substances are not living entities – ‘organisms’ – and in any case have no genes to be modified.

Perhaps even more embarrassing (to EU policymakers), the concept of a gene transfer across the ‘species barrier’, as something in which ‘*the genetic material has been altered in a way that does not occur naturally*’ is both explicit and implicit in the EU definition of GMO. Scientists have known for years that genes can and do move from one species to another, using natural mechanisms. But if there was any argument from the policymakers, it was laid to rest by a 2015 publication by Kyndt et al (Kyndt et al., 2015). showing that all cultivars and some wild lines of sweet potato (*Ipomoea* ssp.) naturally carried bacterial genes inserted by *Agrobacterium tumefaciens* thousands of years ago, without any human involvement, proving that neither the transfer of genes across the so-called species barrier was unnatural, nor the DNA transfer mechanism used by many modern genetic engineers to develop new crop varieties, *Agrobacterium*, is in any way ‘unnatural’.

Modern Biotechnology

In the past hundred or so years, plant, animal and microbial geneticists applied several tools to modify the genetic makeup to derive ‘improved’ plants, animals and microbes.

This intentional genetic modification—i.e., breeding—became more sophisticated, involving

the intentional recombination of genes and genomes from judiciously chosen strains of plants or breeds of animals, in which desired traits are identified, recombined and then selected in progeny to derive a new population, one intended to displace a previous population with a less desirable complement of features.

This 'traditional' genetic modification of plants and animals to generate improved genotypes, also called breeding or sometimes husbandry, made use of a wide range of tools. These included simple selection out of a genetically near-homogenous population to the intentional mass mutation of genomes, using such vehicles as ionizing radiation or chemical mutagens, in an attempt to generate some mutant improvement.

Improvement, of course, is a purely human attribute and assigned by humans, intended for the betterment of humans, if not for the plant, animal or the environment. For example, as a natural protection mechanism, many plants naturally generate anti-feeding chemicals to stave off predation by animals intent of eating the plant. In Nature, humans are included in such predacious animals, so humans may find the natural plant compounds to be anything from distasteful or unpalatable to outright toxic. Plant breeders dealing with such a plant would 'improve' it by removing or reducing the amount of these antifeedant chemicals, thus making the plant safer and/or more palatable for human consumption. However, from the perspective of the plant or Nature, the genetic modification would hardly be an improvement, as the plant would then be more susceptible to consumption by one animal or another. Without the tender loving care and protection of a managed (farm or ranch) environment, such plants would be selected against due to predation by animals and quickly driven to extinction. Such is the observation of modern cultivated plants that happen to escape the farm; rarely do such escapees establish populations in feral circumstances.

Although all these new cultivars, strains, breeds, lines, etc. were, by almost any definition genetically modified, there was very little regulatory oversight concerned with

environmental or health risks of these new living entities. Indeed, the main regulatory review of new cultivars of crops focused on ensuring that the 'new' cultivar was indeed genetically modified, genetically distinct from preexisting crops of the same type. (Other requirements included genetic stability and superior agronomic performance). But there remains little or no required regulatory scrutiny for potential safety concerns.

This is unfortunate, because real environmental harm was done due to lack of regulatory oversight of the 'traditional' forms of breeding, which includes introductions of exotic germplasm or alien species. Under-regulated plant introductions have caused substantial ecological damage in communities around the world. Purple loosestrife, introduced as a garden ornamental, is now a major invasive weed in much of North America with its rapid escape from the garden and into the nonmanaged landscape (US National Academies of Science 2002). Most major weeds of North America were unintentional introductions brought along by European pioneers and visitors. The aggressive European weeds quickly established populations and spread rapidly throughout the North American landscape (US National Academies of Science 2002).

The publication in 1953 of the molecular structure of DNA by Watson and Crick, the genetic molecule carried in all living things, provided the opportunity for even more specific intentional genetic improvements.

One astonishing feature of molecular genetics was the discovery that the genetic 'code' as carried by DNA and translated by RNA, was common to all species. In essence, a gene is a specific segment of 4 chemical bases forming the DNA molecule. The genetic information is carried by the 4 chemical DNA bases much like alphabet letters carry information when compiled into words and sentences, but don't mean much in isolation. A gene is a set of instructions formed by the particular sequence of DNA bases, just as a sentence is a specific sequence of words. The discovery that the chemical composition of DNA is common to all species was not particularly surprising, but the discovery that the 'language' used by the

base sequence was common to all was indeed unexpected and unpredicted. This fact, that a gene from one species would be read and understood in the cells of other species, forms the basis for what came to be known as genetic engineering. For example, because of this common DNA language, the human insulin gene can be transferred into a bacterium, and the bacterium will read, understand and make human insulin, even though the bacterium has no need or use for the insulin protein. If different species used a different genetic language, for example by having the DNA triplet ATG code for some amino acid other than Methionine, genetic engineering as we know it would be impracticable.

Genetic engineering, called recombinant DNA (rDNA) technology (to yield *transgenic* organisms) grew out of the discovery of the molecular structure of DNA, the finding that all species use the same genetic language (or code), and the simultaneous development of restriction endonucleases, enzymes which recognize specific DNA base sequences and cut the DNA molecule precisely. The identification and purification of these restriction enzymes (REs) enabled specific DNA sequences, coding for specific genes, to be isolated by judicious use of REs with differing base recognition sites. That is, one RE might cut a long segment of DNA at the beginning of a base sequence for a given gene, and a second cuts at the end of the gene. In this manner, a relatively short segment of DNA coding for one specific gene can be isolated from the thousands of other genes, the isolated segment may then be used for ultimate transfer to another species. For further explanation of the process of genetic engineering, see ref (McHughen 2000).

Options in Regulatory Structures

Risk assessment and management is at essence a scientific endeavor. An effective risk assessment demands such data as it is required to inform risk management and mitigation strategies. Without scientific measurement and

analyses, the threat of, say, tobacco smoking would be a function of uninformed opinion and guesswork, which is not a reliable or credible foundation for sensible regulatory strategy.

With risk assessment essentially a scientific matter, it is not surprising that scientific studies of how to evaluate risk have been around for many years. Even before the specter of BSE or genetic engineering frightened citizens into demanding regulatory protection from perceived but not substantiated risks, various scientific bodies have investigated the appropriate means to properly and accurately conduct risk assessments, e.g., US National Academies of Science (1983).

Science must form the foundation for effective regulation but it is not and should not be the sole determinant of public regulatory policy. Other considerations, such as social policy, ethics, economics, etc, may be constructed upon the scientific foundation, but they should not drive public policy in the absence of a scientifically sound foundation, any more than science alone should direct policy in the absence of these other important aspects (McHughen 2007).

TYPES OF REGULATORY TRIGGERS

Allocating limited regulatory resources requires prioritization in making a decision on where to focus regulatory attention. Invoking the regulatory maxim that regulation should be commensurate with risk, and that all products and processes carry some degree of risk, sensible regulation involves a triage to sort higher risk products (which then face greater regulatory scrutiny) from lower risk ones (which would face lesser regulatory scrutiny). To be an effective dichotomy, there should be a clear demarcation between the 2 risk categories.

The Temporal Trigger

One common and expedient regulatory trigger is a simple temporal distinction. With this trigger, everything developed after a set date is captured. Everything already in place is

exempt, or ‘grandfathered’. Any number of new regulations use this dichotomy because it is as unequivocal as practically possible and easily understood and enforced. However, it does ignore the threats posed by the ‘grandfathered’ products, presumably the same threats stimulating the promulgation of the new regulations in the first place. In practical reality, the temporal dichotomy works best when the risks are not particularly great to begin with, and the products are of an ephemeral nature anyway, such that the exempt products or processes are soon rendered obsolete and displaced by those newer products and processes captured by the new regulations.

A legal perspective often recommends a simple dichotomy to serve as a trigger because of the clarity and expediency. Disregarding any risk factors, distinguishing black from white is a simple task and everyone can agree which is which. Such a simple and widely accepted dichotomy leads to a quick and correct decision— anyone can decide in an instant of observation if a given item is black or white, if those are the only 2 states. Temporal dichotomy is similarly simple—almost anyone can quickly discern whether today is before or after, say January 1, 2017. A high priority within the legal regulatory offices is a clear endpoint or ‘closure’ for a decision with a highly accurate dichotomization. Industry also appreciates a clear and simple distinction, with a reasonable certainty of outcome and closure. Even if they don’t like it, they know the rules and can either comply or not get involved. As Henry Ford is attributed to have said “I can deal with asinine rules, I can’t deal with uncertainty.”

The major conceptual and practical problem with the temporal dichotomy is that it is not based on addressing any actual risk, the foundation and objective of regulatory action.

The Process Trigger

Another common trigger is novelty of *process*. Most jurisdictions use the *process* of rDNA, (aka genetic engineering, rDNA or “modern biotechnology”), as an apparently simple dichotomy. Superficially, this fulfils the legal desire to invoke

a simple, clear distinction to capture certain things and exempt others. In the 1980s, when concerns about biotechnology were being raised and explored both in the scientific and regulatory communities (unfortunately in segregated venues, for the most part) it seemed clear—at least in the legal/regulatory venues—that a soybean plant, for example, containing a bacterial gene in its genome must have been derived using the *process* of rDNA, so it was a simple and clear dichotomy to invoke the *process* of rDNA/GE/modern biotechnology to capture this soybean with a bacterial gene for regulatory scrutiny. After all, it was commonly believed (at least among non-scientists) that nature does not transfer genes across the ‘species barrier,” so any violation of the species barrier itself provides a clear dichotomy and signal that the product (soybean with bacterial gene) must have undergone the process of rDNA, the only known mechanism to violate the species barrier. It was also expedient that popular (if not scientific) opinion was that the process of rDNA was inherently risky, so capturing all such organisms for safety regulation seemed to fulfill public demands and assuage public anxiety as well. It didn’t hurt that an assumption of increased risk also invoked the so-called ‘Precautionary Principle’, which itself is a political construct, not a scientific principle, and which has been used to support political agendas to obstruct deployment of potentially useful technologies (Miller, McHughen 2011; Tagliabue 2016). In fact, the ‘Precautionary Principle’— which is built into EU GMO regulations— can be used to deny deployment of virtually any new technology, which means we must maintain the traditional status quo products and processes, the same ones that created the problems of anthropogenic climate change and global pollution.

This process trigger fails both the legal desire to provide an objective and clear dichotomy and also the scientific objective to capture those things or processes posing the greatest risk.

PROBLEMS FROM THE LEGAL/REGULATORY PERSPECTIVE

The legal criteria quickly broke down, as scientists studying genetics and particularly the

rapidly expanding field of -omics destroyed the dichotomous concept of ‘species barrier’, as evidence mounted that what appeared to be distinct species actually shared considerable genetic homology and synteny. As well, the first plant gene transfer agent used by humans was itself a naturally occurring biological entity, *Agrobacterium tumefaciens*, which Nature herself endowed with the ability to transfer genetic material from its own bacterial genome into the genome of plants- not merely across the ‘species barrier’ but into the furthest reaches, a different biological kingdom.

Subsequently, the rDNA process trigger proved less dichotomous than expected; other new technical processes were being developed that didn’t fit the rDNA definition, yet caused some alarm because they were deemed ‘unnatural’. Certain forms of cell hybridization, for example, frightened some people who demanded regulation of those technologies. And now, with a range of new breeding techniques coming on stream that can circumvent rDNA processes entirely is causing considerable angst among those who wish to see all modern breeding methods and products regulated. For a review of these gene editing and related techniques, see Abdallah et al. (2015).

A practical and crucial deficiency of the process trigger is that processes will continue to advance, and with each technical advance, regulatory resources must be expended on investigating and determining whether or not a new process or modification should be captured and if so, how to approach the costly task of amending regulations for such changes, which may be incremental with little or no impact on risk.

Quite apart from triggering based on selected processes is the difficulty in enforcing and litigating when evidence may be lacking. That is, a given product may be created using either of 2 processes, one is a triggering process and the other is a non-triggering process. The resulting 2 near-identical products present near-equal threat, so public safety is jeopardized by regulating one and not the other. And, if neither process leaves an objective indicator or ‘fingerprint’ there are no detection features signifying that a regulated process was used in

making the item in question, how can the regulations be enforced, particularly if the developer claims trade secret confidentiality? If there is no probative evidence clearly and necessarily tying a regulated process to products resulting from the use of that regulated process, and only from that process, there can be no effective enforcement. And without effective enforcement, the regulations are meaningless and public resources are again wasted.

In all of these scenarios involving process-based triggers, limited regulatory resources are expended without any consideration of actual risk and without increasing the actual safety to the public or the environment.

PROBLEMS FROM THE SCIENTIFIC (RISK BASED CRITERIA) PERSPECTIVE

The scientific community had theorized for many years that the concept of a genetic ‘species barrier’ was simply wrong, in spite of its popularity among non-scientists.

But more importantly, the wider scientific community already knew from the studies conducted and published in the OECD ‘Blue Book,’ Organisation for Economic Cooperation and Development (OECD) 1986, the US White House, Office of Science and Technology Policy’s “Coordinated framework for regulation of biotechnology” (White House, OSTP, 1986) and the US National Academy of Sciences white paper (US NAS, 1987) that process was unrelated to risk, and that if the goal were to prioritize regulatory action and be scientifically sound, it must focus on products, regardless of the process used to create the products. An obvious example of a failure to capture a potentially high risk product, albeit in horticulture and not agriculture, is the simple introduction of alien species. Because such environmentally risky organisms as purple loosestrife are not captured under any *process-* based (not even from traditional breeding) dichotomy, the invasive plant was introduced without a risk assessment and inevitably ‘did what comes naturally’ – it spread

and caused, and continues to cause, considerable and irreparable ecosystem damage.⁶

Another logical flaw in the process-based trigger is the inappropriate regulatory treatment of the triggered item. If the concern rests with the *process*, then it is the *process* that should be regulated and assessed. That is, the triggering factor is the risk inherent in the process (in this case, rDNA), but the analyzed item is the resulting product. A risk assessment can of course be conducted on the resulting product, but the conclusions drawn address the risks associated with that product only; they do not address the underlying concern with the threat posed by the process that created that product. In logic, if the process is deemed risky (as it is in a process-based trigger system) then the risk analysis should be conducted on the process itself.

Similarly, a risk assessment on a product resulting from the use of a given process sheds no light on the risks inherent in using the process, unless large numbers of different products of the same process were risk assessed and all came to the same conclusions. What this means for risks inherent in using the process of biotechnology is that any or every product of that process should yield the same risk assessment conclusions, and that assessing the risks of the process need not analyze or risk assess every different product, as it invariably is now in those jurisdictions applying the process based trigger. In practical terms, if using rDNA was inherently hazardous, those hazards would appear in assessments of GE bacteria, GE plants and GE animals. To illustrate, some critics claim (without evidence) that the process of rDNA causes genetic instability, such that the genome with a foreign DNA inserted using rDNA spontaneously mutates with DNA excisions, chromosomal translocations, and other genetic aberrations. Well, such mutations should be evident in GE bacteria as clearly as in GE plants or GE animals. In which case, a risk assessment study of the simplest GE organisms, perhaps bacteria and lower plants, should suffice to conclude whether or not the process of rDNA does indeed cause genetic instability, and further

tests on higher organisms, say GE plants, would be superfluous and unnecessary. It should be obvious that if there are inherent risks with the process, such as genetic instability, then analyzing every product separately is not only scientifically irrational, it borders on the ludicrous. But such is the logical conclusion of the process based trigger. And this is remains the procedure followed in process-triggered jurisdictions. Even when their own scientists conclude the practice is scientifically unjustified (e.g., US National Academy of Science, US Institute of Medicine 2004; Kessler 2001). It should also be obvious that if the practice is scientifically unjustified, it is also economically unjustified, as it represents a waste of limited public resources and fails to assign resources to the higher risk priorities, which means that sooner or later, a hazardous but under-regulated product will cause damage, damage that could have been obviated if scientifically sound regulations were in place.

Recognizing the inherent failure of process based triggers, and adopting instead a product based trigger, the practical question then became how to sensibly invoke a product/trait based trigger to efficiently capture the highest risk products and tiering or even exempting the low risk ones.

Novel Breeding Method as Trigger

One contrivance of the process based trigger to try to circumvent the problems in capturing technical advances is to fuse “novelty” to breeding method. That is, this trigger would capture any products developed using any “new” (i.e. developed after a given date) genetic technique. This approach would capture all products of processes of rDNA (presuming the date were set early enough) as well as cell fusion, encapsulation, etc. without the need to continually revisit and adjust the list of captured breeding methods.

Such a contrivance may be politically expedient to serve a political goal of capturing all products of modern technology and only products of modern technology, but it fails in the primary objective to protect society and the environment from harms because it exempts some potentially

hazardous things and over-regulates some less risky things. In short, the prioritization fails. It also fails the scientific justification, as again it focuses on process, instead of product as the vector of hazard. Remember the primary purpose of regulation- to protect society and environment from food, feed and ecological threats. The greatest damage to the environment has been and continues to be from releases (intentional and unintentional) of unmodified organisms. By setting a *process* of breeding trigger, whether novel or not, fails to capture the most hazardous and most damaging products, i.e., those introductions that were not “bred” at all. Notwithstanding phytosanitary regulations, designed to limit microbial pathogen transmission, the introduction of alien seed and propagules continues apace. By failing to capture risky products (including prospective introduced species), the responsibility to society to protect commensurate with risk is abdicated. As there is no method or process involved in breeding these introduced species, no process-based trigger will capture them.

Canada and the Novel Trait/Product Trigger (PNT)

The trigger used in most Canadian regulatory agencies combines both the functional practicality of novelty with the scientifically sound assessment of *product*. In choosing how to allocate limited regulatory resources, Canadian scientists, regulators and policy-makers recognized the primacy of regulating on the basis of degree of risk, and recognized that risk is invariably a function of product. With plants, the novel product was characterized by plant species and trait. For example, a new frost tolerant canola might presents risks to health (if the new trait results in a new allergen or increased toxicant in the food) and also to the environment, (if the frost tolerance trait confers an increase in ecological fitness, the plant could become an invasive pest). To capture the highest risk products, Canada chose to prioritize regulatory action with a novel *product* dichotomy. While this distinction sacrifices some of the clarity and certainty of a purely temporal dichotomy, it gains by better

protecting the health of society, community and environment of Canada, the primary goal of regulation. Thus, the novel product/trait approach is not only scientifically sound, it addresses practical prioritization of real (as opposed to hypothetical or speculative) risk.

PROBLEMS WITH CANADA’S NOVELTY OF PRODUCT/TRAIT TRIGGER

The imperfections with the novelty of trait or product based trigger approach include situations where novelty is not quantal, or is not clearly ‘novel’. When considering a new food product, for example, basic human physiology is global; a foodborne toxin in Japanese tofu will cause as much damage to Japanese consumers as to Canadian consumers. So should a ‘novel’ food intended for introduction to Canadian markets be viewed as novel to the Canadian diet, or to the diet of populations worldwide? And, once we’re there, we need to consider that dietary exposure also influences impact. The average Japanese consumer eats much more tofu than the average Canadian (near nil). And there may be other ‘at risk’ populations also, such as pregnant women, or children, or the elderly or immunocompromised consumers.

On the ecological side, consider a plan for a horticulturalist to introduce a plant native to the intermountain region of British Columbia as an ornamental to gardens in Nova Scotia’s Annapolis Valley, over 5,000 km away, where the plant species is unknown. Is the plant considered ‘novel’ to the region of introduction, and subject to regulatory review? Or should it be considered exempt because it is native to one part of Canada and therefore deemed non-novel throughout the entire country? Both of these examples are realistic scenarios and the concept of novelty must address them.

CHANGING SOCIETY NORMS AND EXPECTATIONS

Coinciding with the development of genetic technologies in the 1970s and ‘80s,

Western society started taking a greater interest in scientific and medical progress, particularly progress supported with taxpayers' money. High profile scientific disasters, both real (e.g., Thalidomide, BSE) or exaggerated (e.g., DDT) stimulated greater public demand for accountability and involvement in regulatory policy surrounding developments in science and medicine. This demand for public accountability from the people who actually pay the bills, as reasonable as it seems, was a novel concept in the scientific and even regulatory community, a culture met historically with indifference from a public largely uninterested in esoteric technical research and humdrum regulatory bureaucracy.

Meeting the demand for greater public accountability and transparency required a sea change in the regulatory structure. While the public had no interest in directly participating in the scientific research process, and especially not in the bureaucratic procedures, they did demand greater knowledge of what was going on in the labs and behind office doors. This not unreasonable demand was met by adding a new function to the risk analysis paradigm, risk communication.

Up to this point, the risk analysis components included risk assessments and risk management. Risk assessment is largely a scientific function to determine the kind of risks associated with a given product or activity, along with a calculation of the likelihood of an undesirable event and the degree of threat posed. Risk management was largely the domain of regulators, who took the scientific data from the risk assessors and determined the management strategies to minimize the risks while allowing the benefits of deployment, if appropriate. The roles and responsibilities of each component are clear: risk assessment is a scientific endeavor conducted by competent scientists, risk management is a threat mitigation function conducted by scientifically trained regulators. Neither group had particular expertise in the new component, risk communication, and no one claimed responsibility. Although risk assessment and management are both fairly mature and function for the most part with capable and qualified personnel, risk communication remains the weakest link in the regulatory system to measure,

manage and assure the safety of products and activities (McHughen 2012).

SOCIETAL CONCERNS VS. SCIENTIFIC CONCERNS

The scientific and medical communities place threats associated with agricultural biotechnology into 2 general categories: 1) threats to food and/or feed safety, and 2) threats to the environment. The concerns in the first category are that the new biotech food carries novel or unexpected toxicants or allergens. The concerns in category 2 that the biotech plant, animal or microbe carries some trait offering an ecological fitness advantage, such that the modified organism, when it escapes from the farm or factory, will establish populations in the environment and wreak havoc with other living organisms, thus negatively impacting biodiversity and the dynamics of the local ecosystems.

In wider society, the concerns with biotechnology go beyond the scientific, encompassing ethical concerns (e.g., "We have no business messing in God's domain"), socioeconomic threats (e.g. "Biotech benefits only the big companies and threatens small family farmers"), and political (e.g., covert trade issues: "the US/Canada/Argentina is advancing beyond us with this technology, so we have to use any means available to slow them") (McHughen 2012)

REGULATORY PROBLEMS IN INTERNATIONAL TRADE

Each jurisdiction exercises the sovereign right to set their own priorities and regulatory systems; this is not unique to biotechnology. Nevertheless, because products of biotechnology, particularly agricultural products of biotechnology, are often components in international trade, the problems with differing regulatory approaches in different jurisdictions become much more acute than with less traded products.

Canada is unique in adopting the novelty trigger for regulatory scrutiny, and because of this, some call for Canada to conform to the rest of the world, in an effort to harmonize and facilitate

international trade. The problem with this facile suggestion is that while other jurisdictions share the process-based trigger, their definition of the triggering process varies widely, their interpretation of the trigger varies widely, and the practice of risk assessment of the triggered item varied widely. In the light of this scenario, Canada's acceding and reverting to a process-based trigger will do nothing to conform to international norms, because there is little conformity elsewhere. This is simple to illustrate: both the US and the EU have process based triggers for regulation of biotech products. But the "harmonized" trigger mechanism has not led to smooth, harmonized international trade in biotech commodities. Not only are there asynchronous approvals, where one jurisdiction (invariably the EU) is slower to approve a given product, there are also asymmetric approvals, where a product is approved in one place with no intent by the developer to seek approval elsewhere. The latter case might be appropriate for products intended solely for domestic production and consumption. But somehow, those products—if only in trace quantities—seem to find their way into shipments with international destinations, potentially wreaking havoc upon detection at the destination.

In addition, there are important distinctions in the way 'process trigger' is applied in the EU and USA. For example, if the US 'deregulates' (technically, 'non-regulated status') to a given transgenic event, that event may then become a parent in a breeding program, and crossed with a different deregulated 'event'. The progeny of the cross is considered non-regulated in the US and may enter commerce freely. However, the progeny in EU is considered a new event and is captured for regulatory approval, even if both parents have already been approved.

REGULATORY TRIGGERS FOR CAPTURING AGRICULTURAL BIOTECHNOLOGY IN EU, USA AND CANADA

European Union

The European Union is a purely process based trigger, although once triggered, it is the

resulting product that is regulated and scrutinized. The regulated item is subject to a wide range of technically valid tests and observations, which leads some to defend the claim for 'scientifically sound' regulation in the EU. One can admit the European procedure is detailed, rigorous and scientifically sound, but *only after the regulatory scrutiny is triggered*.

The main regulatory document covering genetically modified organisms (GMOs, as they are legally defined in Europe and much of the rest of the world) in the EU was, as previously mentioned, Directive 90/220/EEC (The Council of the European communities), which was updated and superseded by a newer legal framework Directive 2001/18/EC (Commission Directive 18/2001/EC), covering both the experimental release of GMOs into the environment and also the commercial release of GMOs, including importation, cultivation or as industrial products. In addition, the current primary Directive covering contained use is 2009/41/EC.

Curiously, while the EU policymakers had an opportunity to fix the problems with the definition of GMO, the only substantive change they made was to explicitly exempt *Homo sapiens*. They may have exempted humans because, depending on the interpretation of the definition in 90/220, Louise Brown and other 'test tube' babies would be legally designated as GMOs (products of *in vitro* fertilization – a laboratory process designed to overcome natural barriers to successful fertilization in the parents).

In the European Union, GM microbes in laboratories and other enclosed or contained environments are governed by the original Directive 90/219/EC (European Union), later amended by Directive 98/81/EC (European Union). Finally, GM product tracing and labeling under Regulations_{EC} 1829/2003 (pertaining to GMOs themselves) and 1830/2003 (for food or feed products produced from GMOs). The latter is particularly perplexing, as it requires labeling of products derived from a GMO plant, including refined sugars, oils, etc. with no DNA or protein present, so there's no scientific means to detect such derived substances, and therefore no means to enforce the regulation. We can carry this one step beyond and

mention that GMO plants photosynthesize to produce not only sugar, but oxygen as well. The ‘GMO’ oxygen produced from the millions of hectares of GE crops in North America waft across the Atlantic, unmolested and unlabeled, to be inhaled and ingested by unknowing Europeans in violation of their ‘right to know’ as promised by 1830/2003/EC. The complex and burdensome regulatory framework ensures the European populace that GMOs are indeed heavily regulated, in response to widespread public demand for such, but the regulations do little to actually identify, assess, manage or otherwise address real threats to the European environment or consumer.

The current EU definition of GMO (the basis of their regulatory trigger) is “*genetically modified organism (GMO) means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.*” This definition is not clear on at least one point, and some have argued that this wording excludes products resulting from the triggered processes IF the products could have been generated using traditional breeding methods. However, the EU has not explicitly clarified this and has not exempted any of the extant examples (such as Xa21 rice; see below). In addition to the various problems of being an exclusively process based trigger, the uncertainty afforded by the ambiguity of what is *natural* is daunting. By establishing processes that do “...not occur naturally...” as a trigger engenders great and probably intractable arguments over what nature does and does not do. Science cannot prove a negative, so science cannot prove categorically what nature cannot do. The EU approach to regulation, at least with regard to GMOs, is scientifically unjustified from the first definition, and founded on non-scientific principles. This problem is particularly profound considering the millions of dollars at stake, depending on the conclusion of the argument. Who can say (with credible support of scientifically valid evidence) that nature cannot, for example, transfer genes from one species to another, or would never confer herbicide resistance on a plant, when there are clear examples

of nature doing precisely those things? However, this perspective of EU regulations is not unanimous, as some give a more charitable interpretation (Sprink et al. 2016)

Scientists—if not European policymakers—know that genes are often moved from one species to another, and that herbicide resistance occurs naturally (every plant is naturally resistant to some herbicides) and naturally occurring HR genes are, like any other gene, subject to natural transfer to other plants, including other species.

Because of this vague dichotomy (of what nature could or could not do) and the large amount of money at stake, any proponent would and should argue vehemently that their product could or might be produced in nature, thus circumventing regulatory capture altogether and earning a free trip to the market. Scientifically, it would be very difficult to say nature could never develop any of the GMOs currently captured by the EU regulatory net. This is especially true when developers use *Agrobacterium* as the gene delivery vehicle, as Kyndt et al (2015) showed that all sweet potatoes are naturally genetically transformed by *Agrobacterium tumefaciens*.

The trigger criteria in the EU are entirely process based, essentially capturing all products and only products of “modern biotechnology (which includes all rDNA plus some other technologies)” going back to the start of regulation of products of biotechnology. Even here, there are exemptions for certain products of rDNA—namely foods produced *with*, as opposed to food produced *from*, products of rDNA. One of the first foods on the market anywhere was the so-called vegetarian cheese, produced with chymosin. Chymosin is a recombinant enzyme replacement for rennet, the native milk curdling enzyme from cow stomachs. As chymosin is produced from genetically engineered microbes, the resulting cheese was somewhat arbitrarily deemed non-GMO, because the rDNA ingredient was classified as a processing aid, not a true ingredient. With this simple semantic expedient, the EU managed to avoid having to regulate or label many of its own GMO food products, a contrivance not lost on the WTO dispute tribunal in 2008, which found the EU unable to

scientifically justify its de facto ban on approving new GMOs.

Nevertheless, the apparently simple dichotomy of capturing products of rDNA technology and exempting all others became difficult to justify in light of the development of newer technologies that did not involve rDNA but that frightened some consumers anyway. One of the cultural distinctions in Europe (as opposed to much of North America) is the desire to promote and preserve what they perceive as 'natural' processes, as they are assumed safe and benign, if not entirely wholesome. In North America, in contrast, while there is an appreciation for nature and natural foods, most consumers are less negatively inclined toward or fearful of synthetic or processed crops and foods. The political response in Europe has been to amend the regulatory structure to capture not only rDNA but also products derived from other new processes to create crops and foods that "could not be created in Nature." Clearly, the driving motivation initially was rDNA itself, now extended to include other suspicious activities, i.e. anything 'unnatural'. The so-called new breeding technologies (NBTs) include several methods of altering the DNA base sequence, or gene expression, to achieve a new or altered trait without using rDNA. For a review of such methods, see Abdallah et al. (2015).

The problem with using the EU process based trigger should be apparent.

First, no one can argue exactly what nature can and cannot do. Nature can and does transfer genes across species. Nature can and does create highly hazardous toxins and allergens (Indeed, no human has ever synthesized anything remotely as potent as the most toxic substance created by nature, botulinum toxin, (now in commercialized preparation known as Botox[®]); and no human has successfully developed a new allergen. All known allergens are designed exclusively by Mother Nature). Nature is a wild and imaginative, unpredictable force. Establishing a regulatory dichotomy on 'what nature could or couldn't do' is fraught with uncertainty and inevitable mistakes.

The process based trigger also does not necessarily exclude products of rDNA that duplicate natural products- for example using rDNA to transfer genes from one variety to another to create a product that could readily be created using natural crossing alone. Some authorities argue that the EU will not capture a GMO for regulatory assessment if the same product could have been bred using traditional methods. However, there are no actual examples, and some counter examples to this interpretation. For one, the Xa21 disease resistance gene in rice has been bred into commercial rice cultivars using both rDNA and by traditional crossing. The traditional line can proceed to market with no regulatory scrutiny, while the essentially identical line produced using rDNA languishes (Tu et al. 1998; Khush et al. 2001; McHughen 2012).

Second, by setting the target based on a current process, the system has to be continually updated to capture recent advances in technologies. With genetic technologies under constant research and development, it is inevitable that any regulatory list will be outdated soon after it's compiled.

Because of these foundational errors, problems will continue to plague the EU regulatory system. These include conceptual errors ("*Do we regulate this new process or not? Do we have to change the definition to capture this process?*") and functional errors (dividing bureaucracy into "biotech" and traditional means 2 regulatory processes assessing the same risks, but with divided expertise. Maintaining two or more parallel regulatory structures is not only inefficient allocation of limited resources, it leads to technical errors (because the appropriate expertise always seems to be in the 'other' office, the regulated item gets a less expert assessment and the wrong regulatory conclusion is more likely reached) and 'turf' and expertise conflict between the 2 offices. Crucially, it leads to major socio-political errors (because the foundation is flawed, regulatory mistakes will continue, further eroding public confidence in the system, instead of bolstering it as intended).

UNITED STATES

Unlike Europe, the United States (and Canada) did not draft new legislation to capture and regulate biotechnology, but adapted existing statutes to cover the new products and use of new technologies, as they believed that already had sufficient legal authority and human expertise in their relevant agencies to provide sufficient protection to society and environment. Regulatory oversight, including trigger mechanisms, of agricultural biotech was addressed in the US by the White House Office of Science and Technology Policy's Coordinated Framework (OSTP, 1986) which assigned primary responsibility for regulating agricultural biotechnology to USDA, FDA and EPA.

The procedures for the 3 agencies and how they interpret the triggering mechanisms are summarized below. Comprehensive information on the US regulatory system for genetically engineered plants is available in Wozniak, McHughen (2012).

USDA

The Animal and Plant Health Inspection Service (APHIS) branch of USDA, through its Biotechnology Regulatory Service office, administers regulatory authority under the Plant Protection Act (PPA) of 2000 (US Plant Protection Act 2000). The primary goal is to ensure environmental safety (broadly defined and interpreted). USDA claims authority on the basis of "plant pest" characteristics, with the concern being that the genetically engineered plant is or will become a pest of agriculture. Their trigger is clearly the process of genetic engineering, combined with a plant pest feature; to date almost all plants developed using rDNA technologies and that carry a plant pest component have triggered regulatory action, while no plants of any other process have been so captured. The 'scientific' justification is that all commercialized genetically engineered plants until recently have been generated using either the plant pathogen *Agrobacterium tumefaciens* or carry genetic

elements, notably promoter segments, from the plant pathogen Cauliflower Mosaic Virus, CaMV or other known plant pathogens.

This spurious justification has repeatedly been challenged by scientific studies, including those of the National Academy of Sciences, who explicitly stated that the process based trigger is not scientifically justified and recommended as recently as 2016 that regulation should be based on characteristics of the final product instead of on the method of breeding (US National Academy of Science 2016). One major gap in applying the current USDA process based trigger is that it not only fails to capture potentially hazardous plants developed using methods other than rDNA, it actually exempts them. Another major gap is that, with the statutory stricture of "plant pest," potentially hazardous genetically engineered plants developed other than by *Agrobacterium* or those not carrying CaMV elements circumvent the trigger. That is, in addition to the rDNA trigger, there must also be some element from a known plant pest (such as *Agrobacterium* or CaMV). In the absence of such plant pest feature, even rDNA fails to trigger regulatory scrutiny. For example, in 2011, USDA declined to regulate a genetically engineered Kentucky Bluegrass from Scotts, as it lacked any DNA from plant pests, and the transformation occurred using a gene gun, not *Agrobacterium* (Waltz 2011). More recently, USDA declined to regulate a corn variety and mushrooms developed using CRISPR technology in the absence of any plant pest features (Waltz 2016).

A lesser gap or shortcoming in the process based USDA trigger system is that it continues to trigger regulatory action for identical plants engineered with the identical genetic construct. In both theory and in observable practice, the 2 plants should be identical or nearly so in their features, including risk profile. This dichotomy of regulatory action not only violates the maxim ("Products posing similar risk should receive similar regulatory scrutiny"). Capturing such subsequent transformation 'events', is an unnecessary duplication and waste of limited resources, as the risk assessment of the second

and subsequent plant is highly unlikely to result in a risk management decision differing from the first.

Like other agencies in the US and EU, once this process trigger captures what USDA calls a “regulated article,” the ensuing risk assessment and risk management is (appropriately) product oriented on a case-by-case basis. That is, the specific questions and concerns will depend on the traits or characteristics of the captured ‘regulated’ article. For example, a plant genetically engineered to withstand a herbicide treatment would face somewhat different questions and concerns than a plant genetically engineered with delayed ripening. The risk assessment focuses on the biology of the plant species and the features of the novel trait, with an emphasis on the likelihood that this species:trait combination will affect the environment. Usually, a small scale field trial is the first step on the several-year road to commercial release of a regulated article, and provides an opportunity to compile data relating to environmental release. To date, the USDA has authorized over 20,000 notifications or permits to conduct field trials with genetically engineered plants since 1986. Over 117 different transgenic ‘events’ have completed the full regulatory review, which concluded the plant is not likely to pose a risk to agriculture and viewed “as safe as” conventional counterparts, rendering the assessed plant and its progeny “unregulated status,” leading to potential commercial release. APHIS issues both an Environmental Assessment and a Determination of non-regulated Status for those genetically engineered plants successfully completing the review (Data searchable online, at <http://www.isb.vt.edu/>).

And like regulatory agencies in the EU and elsewhere, one triggered, the risk assessment procedures are properly science based and comprehensive, leading to a highly credible and scientifically sound conclusion for the products it assesses, even if the triggers for regulatory capture are politically motivated

FDA

The Food and Drug Administration, operating under the Department of Health and Human Services, is responsible for ensuring

safety and security of the food and animal feed supply. In FDA, the Center for Food Safety and Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM) review the new food or feed, respectively, focused on food/feed composition.

FDA takes a very Canadian approach to regulating products of biotechnology, in that the process of biotechnology does not trigger FDA regulatory scrutiny. Instead, it is the features or characteristics of the food that invoke interest from FDA, and then usually after the marketing fact. FDA exercises its authority when foods are altered in such a way that the food composition is substantially changed. The change could be an increase or decrease in the usual nutrients, minerals, fiber, toxicants, allergens or other usual components of the food in question. In any case, FDA does not trigger regulatory action due merely to the food coming from a biotechnological process.

In spite of this regulatory position, all food products on the US market from a biotechnology process have been through a FDA ‘consultation,’ during which FDA scientists review the compositional analyses, looking for any changes in the nutrients, antinutrients or other usual components of the foods. The proponent voluntarily engages in this activity, as it is prudent and not particularly onerous, in that any legitimate concerns would have been addressed by a responsible developer anyway. Because FDA is concerned primarily with food and feed safety, the questions asked during the consultation are the same questions any responsible developer would ask themselves about their new food or feed, and already have the data acquired and analyzed. Of course, FDA faces criticism from some quarters for having a “voluntary” system of biotechnology regulation, but so far, no harms have been documented due to FDA action or inaction on foods derived from biotechnology. FDA to date has “completed the consultation” in respect of over 150 genetically engineered foods and feeds (><http://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon>). FDA does not formally ‘approve’ the evaluated food/feed, but

instead evaluates whether the food/feed differs materially in composition or safety factors relative to the unmodified counterpart.

EPA

The Environmental Protection Agency (EPA) is primarily concerned with the environmental and health risks of pesticides, including herbicides, insecticides, fungicides, miticides, etc. a EPA was created by an Executive Order in 1970 and draws its broad authority from the National Environmental Policy Act of 1969 as well as, depending on details, from the Federal Insecticide, Fungicide and Rodenticide Act of 1972 (FIFRA) and Toxic Substances Control Act of 1976 (TSCA) (Wozniak, McHughen 2012).

Contrary to popular belief, EPA does not capture all genetically engineered organisms, but only those that effect a change in pesticide regime, such as a shift in the kind or amount of pesticide used. This includes the chemicals used on herbicide tolerant GE plants, as they are designed to be grown and protected with an herbicide not previously used on that crop. EPA also regulates nucleic acids and pesticidal compounds in plants engineered to generate their own pesticides, e.g. Bt corn, engineered to synthesize Bt pesticide within the plant. As the Bt corn plant alters the pesticide regime by synthesizing its own pesticidal substance, EPA refers to this as a plant incorporated protectant (PIP) and that triggers EPA regulatory oversight. EPA claims they do not regulate plants *per se*.

These three agencies carry the appropriate scientific and regulatory expertise to conduct the assessments, even if the trigger mechanism is not always entirely science based. Unlike the EU, US agencies enjoy a high degree of public trust and support, largely due to a lengthy and solid ‘track record’ of few mistakes, in terms of approving for release things that turned out more damaging than expected. In other words, US agencies have not made any serious errors in approving GE plants—none has been recalled for safety reasons—so they can justifiably claim a solid track record of success.

CANADA

In 1980, Canada created a federal task force to study report on the status of biotech in the country. The private sector task force, in its 1981 report, concluded that Canada’s biotechnology sector was weak and fragmented and recommended a publicly supported national strategy, which would include increasing research and investment. To respond to the criticisms made by the task force, Canada established a National Biotechnology Strategy to provide policy support and strategy to overcome the cited deficiencies, resulting in the creation of the National Biotechnology Advisory Committee, reporting to the Minister of State for Science and Technology. The committee quickly identified regulatory structure (or rather, the lack thereof) as a problem, as industry needed a clear regulatory route to the marketplace for their products, while society demanded clear regulations to protect health and environment from the real or perceived risks associated with the new genetic technologies. In addition to recommending various technical encouragements, regulatory affairs were also addressed. The Interdepartmental Committee on Biotechnology (ICB) appeared in 1985 to monitor federal biotechnology activities related to the National Strategy, including the encouragement of appropriate regulations. To achieve this, the ICB set up the Sub Group on Safety and Regulations, which commissioned a report, “Co-ordinated study on Government Processes in Safety and Regulation of Modern Biotechnology,” released in 1986 (Henley, 1987). Spurred by rapid developments in the technology, the Committee on Environmental Release brought regulators from 3 relevant departments, Agriculture, Environment and Health, together to discuss how to deal with the impending requests for release of genetically engineered organisms in Canada. They composed the manual “Bio-Tech regulations. A User’s Guide.” Biotech regulations - A user’s guide 1988 This document provided advice to industry on the scope of regulation and the Canadian legislative authority, as well as practical information on how and where to apply for permits, etc.

To this point, Food Production and Inspection (FP+I) Branch of Agriculture and Agri-Food Canada handled the regulatory affairs for agricultural products of biotechnology. Authorized field trials with transgenic (GE) plants in Canada started in 1988 (unofficial field trials were conducted in 1986 and 1987 (McHughen, unpublished) and numbers of both field trials and GE plants rapidly increased in subsequent years.

CARC 1988

From the outset of the technology, various Canadian agencies and committees conducted a number of studies on various aspects of agricultural biotechnology, focused on regulatory aspects at different levels of government and legal frameworks supporting the regulatory activities and jurisdictions. The landmark event was almost certainly the 1988 CARC workshop on regulation of agricultural products of biotechnology (1988). This workshop was instrumental in following shortly after the release of major international scientific analyses of the risks of biotechnology (*viz.* the previously cited OECD 'Blue Book,' Organisation for Economic Cooperation and Development (OECD) 1986 US White House, Office of Science and Technology Policy's "Coordinated framework for regulation of biotechnology" and the US National Academy of Sciences white paper (US National Academy of Science 1987).

It was also important for bringing together expert scientists, policymakers and regulators. Previously, these groups tended to meet separately (if at all) and so the cross communication across these diverse groups was instrumental in informing subsequent Canadian policy and scientific research. It also was astute in inviting international scientific and regulatory experts to provide perspectives from their home countries, especially the US (Terry Medley, USDA-APHIS) and the EU (Nigel Poole) (Poole, 1988). Many of the papers presented, and even the comments recorded during the discussion periods, were seminal in influencing not only Canadian but, indeed, international agricultural biotechnology regulatory policy.

Salient arguments raised at this workshop included the anticipation of potential cisgenics transfer, a term not coined until a dozen years later: "*I know of a group interested in isolating a rust resistance gene from one cultivar of flax and inserting it (using rDNA) into a presently susceptible line of flax. They could achieve an identical result by crossing the two lines and backcrossing in the conventional way. The end product in each case is the same, but one can freely be grown anywhere, the other is very strictly controlled.*" and also anticipated the potential problem with transferring an allergenic protein: "*...make legumes nutritionally better by introducing a high methionine/cysteine containing protein from Brazil nut. Superficially, this is a good idea because legumes do not provide enough of these nutrients and a lot of people in the world consume a lot of legumes. This (GE) is a way to more easily balance their diet. However, many people are lethally allergic to Brazil nut (anaphylaxis) proteins and do not expect to have a potentially fatal attack after eating peas. I don't care whether the Brazil nut gene is put into peas by genetic engineering or by some advance in conventional crossing. It is the gene product that represents a far greater danger to society than the way the trait was transferred.*" (McHughen, 1988). The now-famous Nordlee paper documenting exactly this transfer of allergenicity from Brazil nut to legumes (albeit in soybean, not peas) was published 8 years later (Nordlee et al., 1996). And finally, emphasizing the theme subsequently carried by scientific societies worldwide: "*This means that regulations should be based, in my opinion, on the gene product (trait) rather than on the means of introduction.*" (McHughen, 1988). Such comparative examples were powerful in illustrating how product, not process, is the key to regulatory oversight, and this argument was not lost on Canadian regulators and policymakers. Clearly, if a plant carries a new trait such as rust resistance, or herbicide tolerance, or a new allergenic protein or toxic metabolite, new risks are associated with the presence (or absence) of the trait itself, not the means by which the trait was acquired. In subsequent regulatory policy, Canada recognized the scientific legitimacy of

triggering regulatory priority based on product characteristics.

The European Union, as an affluent and civilized state, is often looked to for guidance on regulation for environmental protection and the very strict EU regulations covering agricultural biotechnology were often cited as a standard. However, the scientific reports (including representation from the EU scientific community) unanimously concluded that risk resides in products, not in the process used to make the product. But EU biotechnology regulations, in contradiction, focused on the process (i.e., “genetic modification”). In questioning the scientific validity of the EU focus on process, EU representative Nigel Poole replied “*It seems to me that we are not dealing entirely with logic in this development (of regulating biotechnology) in Europe.*” Indeed, the EU regulations continue today to be process based, in spite of pleas from their own scientific communities—such as from UK (ACRE) in 2013 and Czech Republic in 2009 that regulation to protect health and environment is necessarily product triggered and focused.

The Canadian CARC 1988 workshop deliberations concluded with a report, including recommendations, to the respective Ministers of Agriculture, Environment, Health and Welfare, and the Minister of state for Science and Technology. The relevant recommendations included (numbers as *per original*): 38

1. The product should be regulated, not the process producing them;

6. International harmonization is important provided that Canadian uniqueness is addressed first, and

9. Education of the public is an extremely important mission.

It should be noted that the scientific legitimacy of protecting health and environment by focusing on product as opposed to process did not originate in Canada, as this recognition or concept was present and emphasized in the scientific reports of the OECD “Blue Book” of 1986, US OSTP coordinated framework report of 1986 and US NAS white paper of 1987. The Canadian position, however, was alone in explicitly recognizing the scientific legitimacy and

inserting it into the regulatory structure. Canada is unique in having a novelty, product based trigger for regulation. While virtually all nations claim to have a science-based regulatory policy, Canada is the only one to be able to actually defend that position to the scientific community.

Several departments and agencies had an interest in biotechnology in the early days. The Canadian Medical Research Council (MRC) issued guidelines for handling rDNA materials as early as 1977 on the heels of the US NIH guidelines for handling rDNA, (reviewed in Talbot), like NIH, gradually but steadily relaxed the guidelines in ensuing years as familiarity and comfort with the categorical safety of rDNA grew.

Agriculture and AgriFood Canada was the primary federal office dealing with agricultural biotechnology, acting in the late 1980s with authority of at least 6 Acts (Animal Disease and Protection Act, for veterinary biologics; Feeds Act, for animal feed; Fertilizer Act, for fertilizers, including supplements; Pest Control Products Act, for pesticides; Plant Quarantine Act, covering introduction and spread of plant pests; Seeds Act, for crop varieties; and other food acts, giving authority for inspection of food products Hollebhone, 1988), Agriculture Canada’s Food Production and Inspection Branch (FP+I), as mentioned above, was already handling field trials with transgenic plants and, in 1987, appointed a Biotechnology Working Group to coordinate the various offices administering biotechnology regulatory actions under the different Acts. This group also recognized the legitimacy of the ‘product, not process’ concept of regulating products of biotechnology, but perhaps more importantly for Canada, determined that regulation of biotechnology can be accommodated under existing legislation, even if it means, as in the US, some adaptation or flexibility in interpretation was necessary to ensure capturing potential targets (Hollebone, 1988).

Hollebone also noted that the major constraint or limitation in Agriculture Canada’s regulatory system for biotechnology was the lack of adequate resources. Nevertheless, generally good working relationships with other

departments and agencies and appropriate MoUs allowed a sensible interaction to get the necessary work done. One efficiency borne of the parsimonious necessity was the “single desk” or “one window shopping” concept, in which a proponent would bring an application to one department or agency, and that agency would then be responsible for communication with any other agency to complete the regulatory review for that product.

Directive 94–08

Agriculture and AgriFood Canada released directive 94–08, in December of 1994 (Canadian Food Inspection Agency 1994). It was the first practical guideline to developers of genetically new plants. Updated several times since, the original and revised guidelines continue to carry considerable influence in Canada and elsewhere.

In 1997, Canadian Food Inspection Agency (CFIA) was separated out of Agriculture Canada to consolidate the food inspection regulatory functions previously distributed within FP+I of Agriculture and Agri-Food Canada, as well as some functions of other federal departments, Health Canada, Industry Canada and Fisheries and Oceans Canada (Auditor General of Canada, March 2004).

Canada still coordinates regulatory functions across several federal departments drawing authority from several Acts: CFIA remains the primary agency regulating novel products of biotechnology (and other methods) under Feeds Act, Seeds Act, Fertilizers Act, and Health of Animals Act (Canadian Food Inspection Agency). Health Canada draws its main authority under the Food and Drugs Act (Health Canada). Environment Canada operates with authority of Canadian Environmental Protection Act (Environment Canada). Interestingly, CEPA provides a residual clause (Schedule 4), meaning that it will capture any novel products of biotechnology not already captured and regulated under other Acts, and this feature dates back to the original CEPA of 1988. In practice, CFIA regulates environmental impacts of plants with novel traits (PNTs) under the Seeds

Act, while Health Canada regulates the actual food, pharmaceutical or industrial substance produced by the PNT. In contrast to the US, where FDA regulates both food and feed, counterpart Health Canada regulates food, but not feed, which is regulated by CFIA under the Feeds Act.

CFIA administers products of biotechnology primarily under the Plant Protection Act, Seeds Act, Feeds Act Fertilizers Act, Plant Protection Act and Health of Animals Act. CFIA triggers novelty based on a new or substantially altered trait or characteristic, or a new use of an older product.

Environment Canada regulates “new substances” (which captures novel organisms) under CEPA 1999. The Environment Canada regulatory definition of ‘living organism’ captures plants animals and microbes “that have been developed through the application of science and engineering.” Clearly, this is a process trigger, in contrast to the other agencies and unfortunately fails to discriminate- that is, it captures all newly modified organisms (exempting only those already regulated under other acts listed in CEPA Schedule 4), regardless of risk level. At the same time, the definition fails to capture the highest risk organisms, genetically unmodified but potentially invasive or otherwise hazardous to the environment. This process based definition is a crucial flaw in Environment Canada’s regulations that must be corrected before damage is done to the environment and, consequently, to EC’s public credibility.

Health Canada regulates threats to human safety posed by novel foods, human and veterinary drugs, cosmetics, medical devices and pest control products. Health Canada defines a novel food to include (among other things):

“... **foods that result from genetic modification** and exhibit new or modified characteristics that have previously not been identified in those foods, or that result from production by organisms exhibiting such new or modified characteristics” (emphasis added).

Clearly, “foods that result from genetic modification” is a process trigger and therefore scientifically unjustified. The main

conceptual problem with invoking this phrase is that it could exempt potentially hazardous foods that do not “result from genetic modification.” A good example that arose during discussion was a new feeding regime in pigs resulting in a higher omega-3 fatty acid profile, or a new UV treatment for apple juice. Although these ‘processes’ do not entail genetic changes, they do change the composition of the food and should therefore be unequivocally subject to regulatory review by Health Canada. The disharmony, uncertainty, and ambiguity (not to mention potential legal liability) can be eliminated by simply deleting this offending phrase from the HC definition. Deleting the phrase will still allow Health Canada to capture every novel food posing potential risk to health, and there should be no downside, as it would exempt only those genetically modified products that show no material change in the composition of the food, and therefore pose no risk to human health.

**REVIEW OF SCIENCE
UNDERPINNING AGRICULTURAL
BIOTECHNOLOGY REGULATIONS**

***US Office of Science and Technology
Policy (OSTP)***

Recombinant DNA technology was pioneered in the USA in the early 1970s, and concerns for potential risks followed shortly. It was the scientific community itself that first raised the specter of hazards associated with products of genetic engineering (rDNA) technologies. The 1975 Asilomar (California) Conference, organized by scientists, discussed various risk scenarios surrounding rDNA technology (Berg et al., 1975). This led to the NIH publishing Guidelines for research involving recombinant DNA Molecules in 1976 (Talbot, 1983). Although the NIH Guidelines (as they were known) were never codified in law, any US lab receiving federal funds were required to abide by them, and other labs, public and private, largely adhered to them voluntarily as

they were prudent, sensible and not overly onerous. Over the years, some of the restrictions were relaxed as the scientific and regulatory community became more familiar with the technology and the products of the technology, enabling greater comfort and confidence in the risk characterization and management. Biotechnology generated relatively little public concern until the early 1980s, when genetically engineered organisms were developed and proposed for release to the environment. Laboratory experiments hybridizing bits of DNA was one thing, but gene altered living organisms capable of self reproduction in the environment elicited much greater public concern, based (understandably) on the fear that the new organisms might reproduce uncontrollably and destroy life as we know it on the planet. To address this concern, the White House Executive Office convened an interagency working group to study the validity of the concerns and report on an appropriate regulatory policy to guard against any legitimate risks. The resulting “Coordinated framework for regulation of biotechnology” was released in draft in 1984 and final form in 1986 (White House, Office of Science and Technology Policy (OSTP), 1986).

Several conclusions reached in the framework document directed science and policy in the US and elsewhere in years to come (summarized from Medley, 1988):

1. The products of biotechnology do not differ fundamentally from unmodified organisms or from conventional products;
2. The product, rather than the process, should be regulated;
3. Regulation should be based on the end use of the product and conducted on a case-by-case basis;
4. The existing laws provide adequate authority for regulating products of biotechnology.

Notice that almost 30 years ago, before any genetically engineered organisms were released to the environment or consumed by humans, the crucial regulatory safety (1, 2, and 3) and legal (4) points were already predicted with remarkable prescience.

The scientific foundation was further secured with a follow-up position statement in 1992, in which OSTP documented a scientifically sound, risk based approach to products of biotechnology, with attention to be given to the features of the product and the environment into which it is to be released, and NOT of the process by which the product was created (Bromley, 1992).

**ORGANIZATION FOR ECONOMIC
COOPERATION AND DEVELOPMENT
(OECD)**

One of the first international scientific studies of risk from rDNA technologies was started in 1983 by the OECD and released as a report in 1986. Officially titled “Recombinant DNA safety considerations: safety considerations for industrial, agricultural and environmental applications of organisms derived by recombinant DNA techniques,” the oft-cited report became widely known by the simpler moniker “Blue Book.” The recommendations were prescient, as the panel of international scientists predicted, accurately as it turns out, that any risks raised by rDNA organisms can be expected to be of the same nature as those associated with conventional organisms, and so the procedures for risk assessment can be similar (Organisation for Economic Cooperation and Development (OECD) 1986).

The Blue Book also called for using the accumulated database of experience and familiarity of environmental and human health effects of conventional organisms as a starting point to guide evaluation of transgenic organisms, taking into account the features of the “host” modified organism, overlaid with the added novel features conferred by the genetic modification. This is the essence and origin of the concept of “substantial equivalence” (SE), which unfortunately has been misinterpreted in the intervening years to the point where SE is so ambiguous and misleading as to be not only unhelpful but actively reverses any positive direction to discussions. It is best not to use the expression at all. ‘Blue Book’ also made the point that ‘biotechnology’ is an ages-old set of

technologies applicable to all manner of food and agricultural and industrial production involving living things, but that the societal concerns were, for the most part, limited to rDNA methodologies. Another important contribution from the Blue Book is the active recognition that ethical issues, clearly important to overall policy development, played no part in a scientific assessment, and the panel explicitly chose not to consider ethical issues in their deliberations.

**NATIONAL ACADEMY OF SCIENCES
(NAS)**

The US National Academy of Sciences has conducted the most detailed analyses of the risks associated with biotechnology, starting with the seminal 24 page “White Paper” in 1987 (which concluded that there was no evidence of unique hazard in rDNA methods, or in moving genes across species) and the follow-up 1989 report on environmental release of genetically modified organisms. This latter report included the recommendation “The nature of the process (of breeding) is not a useful criterion for determining whether the product requires less or more oversight” (US National Academy of Science, 1989).

Subsequent studies from NAS focused increasingly detailed analyses, such as that on pest protected plants in 2000 (US National Academy of Science 2000), the environmental effects of transgenic plants in 2002 (US National Academies of Science 2002), the health effects of genetically engineered foods in 2004 (US National Academy of Science, US Institute of Medicine, 2004), and the impact of GE crops on sustainable agriculture (2010) US National Academy of Science 2010. All of these NAS studies progressively support and increasingly clarify, with additional evidence and data, the major conclusions of the earliest reports, viz. that the process of biotechnology poses no inherent or unique risk, implicitly or explicitly concluding that using the process of biotechnology as the trigger for regulatory oversight is not scientifically justified.

The 2004 study, although focused on food, included a comprehensive analysis and comparison of the risks from various plant and animal breeding methods, including ‘traditional’ or conventional methods and different biotechnological methods. This was a groundbreaking and influential study for at least 2 reasons:

- 1) for the first time, the risks associated with traditional breeding were evaluated (previously, traditional breeding was simply, and wrongly, assumed to be absolutely ‘safe’), and compared against the putative risks of processes of genetic engineering;
- 2) for the first time, different processes of genetic engineering were assessed separately (previously, all rDNA techniques were lumped together, as if they all carried identical risks).

This 2004 study also explicitly sought scientific evidence from all interested parties, including academia, industry, anti-biotechnology NGOs and private citizens, to weigh in on the question of risks associated with genetic engineering. As might be imagined, this exercise resulted in a large amount of documentation submitted by the various sources, as well as a public workshop with presentations from various and diverse stakeholders. A comprehensive analysis of all of these data and submissions failed to reveal any scientifically valid evidence to support the notion that breeding process contributed in any way to increased risk.

In 2016, the NAS released a comprehensive analysis of GE crop and food safety, reviewing the collective history going back to the beginning of the technology, including, (controversially) direct input from high profile GE skeptics. This move was criticized in the academic scientific community because it appeared to give credibility and scientific legitimacy to critics of science holding little or no scientific credentials. Nevertheless, the report evaluated not only these non-peer reviewed submissions but also over 700 peer reviewed scientific analyses covering every aspect of GE food and crop safety, and came to the same conclusion as all previous NAS studies going back to 1986- that genetic engineering (rDNA) as a process was

not inherently hazardous, and that to date, there were no verified cases of harm from the cultivation or consumption of GE crops and foods (US National Academy of Science, 2016).

EUROPEAN UNION

The member states of the European Union collectively enjoy both economic wealth and a deep and capable scientific community. With modern biotechnology being a more public and controversial issue in Europe, it is no surprise that the EU, through the European Commission (EC) provided considerable funding into the finding and documenting the risks associated with biotechnology. Clearly, some of this research was driven by legitimate scientific inquiry, but much of the activity was simply to satisfy the public demand for more research. Political expediency or not, well-funded EU scientific teams conducted solid scientific analyses of various aspects of biotechnology risk under a variety of funding programs since the earliest days of the technology. In addition to the current ongoing mandate of the European Food Safety Authority (established 2002). Four hundred teams of mainly public-sector EU scientists spent € 70 Million in conducting 81 different such projects over a period of 16 years. None of these projects were able to find any evidence that the process of rDNA posed any risk beyond that of conventional technologies (Kessler 2001). A subsequent compilation (2001–2010) similarly failed to show any novel risks associated with GMOs (European Commission). In total, the European Union spent 300 million Euros over a quarter century funding over 400 teams of public scientists to find scientific evidence of increased risk with GMOs. They came up empty handed.

THREATS TO HEALTH AND ENVIRONMENT

Clearly, there is increasing concern within both the public and the scientific communities for the impacts of climate change and the deteriorating state of the environment, from local to

global levels. Governments are under increasing pressure to promulgate laws and policies to protect and preserve the environment, and to reclaim damaged ecosystems as much as feasible. International support for various programs, including for example the Convention of Biological Diversity (CBD) and the Kyoto protocol are beyond the scope of this paper, but do serve to indicate the degree of worldwide interest and support for environmental and ecological preservation and protection.

Yes, there are real threats to the environment, including biodiversity in natural ecosystems and environmental sustainability of agricultural production systems. But political action to engage and contain the threats are at essence science based and require scientific analyses and direction if we are truly to reverse the degradation of the planet. Unfortunately, too few policies are sufficiently grounded in science to actually have much, if any, effect, because the policies seemed directed more to respond to public outcry than to overcome the actual threats. One good example of misguided international policy is the Cartagena Protocol on Biosafety, a subsidiary agreement under the Convention on Biological Diversity. In response to increasing public concern for (apparently) deteriorating biodiversity worldwide, Cartagena Protocol's objective, in the words of the background statement, is "... to protect biological diversity from the potential risks posed by living modified organisms resulting from modern biotechnology." (<http://www.biodiv.org/biosafety/background2.aspx>).

The protocol was negotiated at considerable time, energy and cost and now ratified by over 170 countries (<http://bch.cbd.int/protocol/>), but conspicuously absent are major grain exporters (Canada, the US, and Argentina). The implementation will also be very costly, particularly in terms of scarce human resources with appropriate professional expertise. The fallacy of Cartagena is that this costly but widely supported international accord has no scientific validity. The basic premise of Cartagena is that it will protect biodiversity from the threats posed by living products of biotechnology. Yet there is no scientific evidence presented anywhere that living products of biotechnology

pose any greater threat to biodiversity than living products of any other breeding process. The Cartagena protocol is disingenuous on 2 counts- first, it assumes a scientific foundation when there is none, and second, it misleads world citizens to believe 'something is being done to protect biodiversity', when in fact Cartagena does nothing to address the real and known threats to biodiversity.

There are indeed real threats to biodiversity, but Living Modified Organisms (LMOs) – how Cartagena refers to viable GMOs—are among the most benign. And by focusing all or almost all scant resources on biotechnology, the real threats are left to wreak havoc and continue to degrade the environment and pose risks to health.

No society can afford to waste limited resources on policies that don't work, are expensive (in terms of money, expertise and time) and fail to achieve the intent of the policy, especially when the goal is to protect health and safety of people and environment. No where is this more evident than in regulation of agricultural activities, with its immense environmental impact and on food production, so crucial to human (and other animal) health.

In addition to government agencies and scientific societies, scientists themselves have published papers on scientifically appropriate regulatory policies. Bradford et al, (2005) support the product (novel trait) approach to regulatory action. Their abstract is below:

The costs of meeting regulatory requirements and market restrictions guided by regulatory criteria are substantial impediments to the commercialization of transgenic crops. Although a cautious approach may have been prudent initially, we argue that some regulatory requirements can now be modified to reduce costs and uncertainty without compromising safety. Long-accepted plant breeding methods for incorporating new diversity into crop varieties, experience from two decades of research on and commercialization of transgenic crops, and expanding knowledge of plant genome structure and dynamics all indicate that if a gene or trait is safe, the genetic engineering process itself presents little potential for unexpected consequences that

would not be identified or eliminated in the variety development process before commercialization. We propose that as in conventional breeding, regulatory emphasis should be on phenotypic rather than genomic characteristics once a gene or trait has been shown to be safe. (Bradford et al., 2005).

Studies by professional scientific and medical bodies invariably support the product-based approach to regulatory action, as they all recognize the fundamental truth to risk being a function of the objective, measurable, physical features of a thing, rather than the subjective immeasurable ethereal process by which the thing was created.

PRACTICAL ISSUES

The scientific community has not endorsed the use of the process based trigger for risk assessment. The suggested alternative, using the traits of the product, is scientifically sound, justifiable and pragmatic. Further, adding *novelty* or familiarity of the product is a historically accepted means to focus and prioritize limited resources. The theoretical or conceptual issues aside, the process based regulatory trigger suffers numerous practical problems not encountered by the product based novel trait trigger.

For example, in the EU process based system the categories of process triggering mandatory regulatory capture must undergo constant revision to keep up with technical advances and new method to modify genes. The current EU contrivance is to define a GMO as something that “could not occur in nature.” But no one can prove, scientifically, what nature “can never do.” The statement itself is unscientific and categorically, irredeemably flawed. The recent revelation that sweet potato is a naturally occurring GMO, proving that nature can and indeed does transfer genes via genetic modification interspecifically, in spite of EU legislation claiming it ‘could not occur in nature’.

There is no standard international definition of what is covered even by such simple binary dichotomies as rDNA. Few policymakers have grappled with the question of whether the fruit of a tree grafted onto rDNA rootstock is

captured or not. Jurisdictions using the process based trigger will argue incessantly as to whether the fruit is captured, then possibly come to some rational but arbitrary decision—it may be yes, or it may be no. Any the neighboring jurisdiction might come to the opposite determination, using the same information and arguments. In a product based trigger, however, the answer is clear—Does the fruit itself carry any new traits, including toxins, nutrients, or whatever? If the answer is yes, the fruit is captured; if the answer is no, the fruit is exempted.

(A personal anecdote: When I raised this scenario to a European regulator a few years ago, his reply was “We don’t have to worry about such hypothetical situations. Food is not produced on grafted trees”).

Another plausible, if not common, scenario: A plant breeder uses a transgenic plant as one parent in conducting a regular pollen cross. The F1 hybrid of course carries the transgene, but the F2 will segregate, as some progeny will not have the transgene. If the breeder selects the non-transgenic segregant progeny and develops a new variety from it, is it captured by the process-based trigger? Clearly, rDNA was used in the breeding process, but there is no sign of the transgene in the new variety. Conceptually, it should be captured under a process based trigger regime. It clearly could not be captured under the product based regime, unless there were some other novel trait expressed.

The point is that such scenarios illustrate the difficulty faced by regulators working under a process based trigger. In addition to being scientifically unjustified, the process based trigger is also impracticable and cannot be rationally implemented.

SCIENTIFIC ANALYSES ON THE RISKS OF GENETIC MODIFICATION

An issue at the forefront of risks associated with biotechnology is the likelihood of unintended effects and that these unintended effects may be hazardous. A new crop variety, animal breed or microbial strain with novel features of known risk characteristics can be readily

evaluated and managed, but much of the fear of biotechnology is that the process will elicit some unintended effects, and these may carry unknown, potentially uncontrollable risks. Therefore, the appropriate scientific analysis focuses on unintended effects as an indicator of unpredicted hazard. Fortunately, the relatively long and well documented history of plant breeding provides a baseline upon which to compare different breeding methods, including various genetic engineering technologies.

The most comprehensive scientific analyses of the risks posed by plant breeding, including the comparison of both modern and traditional forms of genetic modification, is the 2004 report from the US National Academy of Sciences and Institute of Medicine (US National Academy of Science, 2004). Although it is focused on the health safety of genetically engineered food, the information and analyses are comprehensive, including both environmental and health safety, and on traditional as well as modern breeding methods. The sections of Chapter 3 of that report, *Unintended effects from Breeding* are particularly germane here, so provide the basis for the following text.

Any change to the DNA of a plant, animal or microbe can produce unintended effects, and these can include undesirable or hazardous features. Fortunately, the routine breeding practice, which entails several years of performance and safety evaluation of new genotypes, has a remarkably high (if imperfect) success rate at identifying and eliminating undesirable breeding lines prior to commercial release. Indeed, it is a truism that modern crop plants (and animal breeds) are optimized to grow and perform best in the managed environment of a farm, such that any major genetic perturbation as might cause an undesirable new feature would perform more poorly, and thus eliminated by the breeder, even if the undesirable manifestation of the feature itself goes undetected.

As a result, breeding technology for food, feed, fiber and other industrial uses has a remarkable history of safety, in that few new genotypes released to the market have caused harm, either to consumers or to the environment. Set against the backdrop of thousands of

new crop varieties, animal breeds and microbial strains, each of which is a product of genetic manipulation, the tiny proportion causing problems does not allow an accurate calculation of adverse events to emerge from the 'background noise' e.g., statistical error. Instead, the relative safety (or chance of unintended adverse effect) of various breeding methods can be calculated only conceptually.

Health Risks

All food and feed plants carry naturally occurring potential toxicants. Plant breeders, over the years, have bred much of these 'antinutritional substances' out of commercial varieties, but rarely are the toxins completely eliminated. Allergens are well known antinutritional factors in several of our most common foods; surely we would desire the complete elimination of allergens, but it has not happened even with considerable effort of traditional breeding (perhaps rDNA breeding will finally overcome the allergenicity problem). The highly toxic glycoalkaloid tomatine is a natural component of tomatoes, and breeders needed to reduce the tomatine content to make tomatoes safe for human consumption in the first place. Even with this effort of plant breeders, tomatine remains present in various tomatoes and can rise to hazardous levels in, for example, immature fruit, and the levels can also rise precipitously in plants grown under differential growing conditions. Thus, the cultivation conditions are more responsible for inherent food hazards than are the breeding methods.

Although rare, there are a few examples of problems arising from unintended effects in crops developed using traditional breeding methods. The most notorious is that of Lenape potato. Potatoes naturally produce the toxic glycoalkaloid solanine. Even modern cultivar potatoes generate substantial amounts of solanine, but typically the levels drop to 'safe' levels in the mature tuber humans use for food. However, the solanine levels can remain excessively high under certain circumstances, especially when light strikes a tuber exposed above soil level, or under certain storage conditions. Lenape was one potato variety especially

susceptible to solanine synthesis in cold conditions, and had to be removed from the market as this potentially hazardous feature was not noted during the breeding and evaluation process (Zitnak, Johnston, 1970). Other conventionally bred potato varieties producing unexpected toxicants also appeared over the years (Laurila et al., 1996).

One distinction drawn by those concerned with the rDNA breeding process relative to traditional breeding is the belief that transferring genes across species, as is often done with rDNA, does not occur with conventional breeding. The concern arises in the belief that 'foreign' genes may interact with the 'native' genes to destabilize or otherwise interfere with normal functioning, leading to the potentially hazardous unexpected effects. However, the starting premise is wrong. Both Nature and humans, using traditional breeding, can and do transfer genes from one species to another, without any of the hypothetical instabilities feared. For example, potato breeders make use of genes from foreign species (such as *S. brevifolius*, *S. acaule* or *S. chacoense*) to introduce and consolidate useful features in cultivated potato, *Solanum tuberosum*. And these non-GE, 'conventionally bred' potatoes can produce new toxins, unknown to the parental lines (Laurila et al., 1996).

Interestingly, those demanding greater regulatory restrictions for new crops developed using the process of rDNA on the basis of potential hazard of combining genes from different species do not make any exception for using rDNA to transfer genes *within* species, to generate crops in which there would be no 'foreign' genetic material, the so-called cis-genic or intra-genic transfer. For example, one claims "*Cisgenesis is transgenesis by another name. Cisgenic GMOs pose most of the same risks as transgenic GMOs*" (Earthopensource.org).

Unintended effects can and do arise with any breeding method, including traditional breeding such as ordinary pollen-based crossing and induced mutagenesis, as well as modern rDNA based methods. But the standard breeding efforts, including the safety and performance evaluation, effectively identify and eliminate almost all 'off-types' or other potentially hazardous lines. Even so, it

is rare for a breeding line to be eliminated for safety concerns. Even using induced mutagenesis, which entails deliberately scrambling the DNA to introduce mutations, has a remarkably safe history. Such mutant crops are even grown by certified Organic farmers. To date, over 3,000 crop varieties have been developed and used worldwide after induced mutagenesis (see data base of mutated plant varieties at <https://mvd.iaea.org/>) and none of these has been reported to have caused problems.

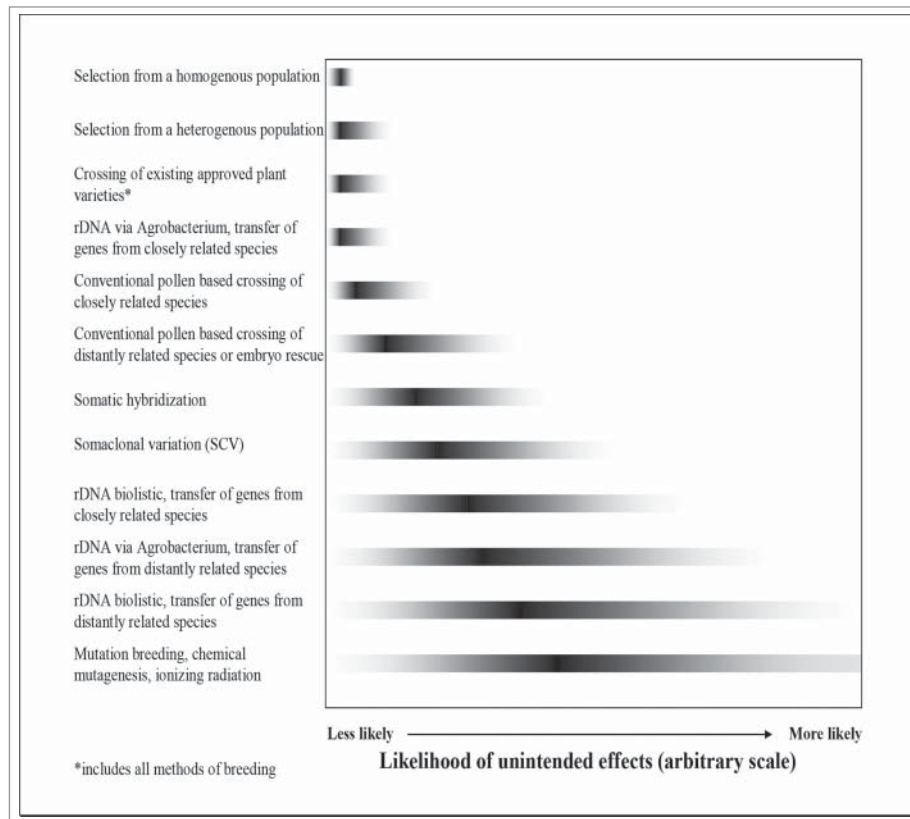
Because all breeding methods can, at least conceptually, generate unintended effects, the 2004 NAS panel attempted to illustrate the relative likelihood of a particular breeding method to produce potentially hazardous plants. In the analysis, several different breeding methods were compared, including the most common forms of breeding to generate food and feed crop varieties. The results were displayed as a bar chart, in which for each breeding method the length of the bar indicated the range of unintended effects most likely to appear from that method, with the intensity of the bar indicating the likely degree of differential phenotype from the parent (see Fig. 1). For example, selecting an off-type from a population of homogenous plants is least likely to show an unintended effect (short bar) and when it does, the likelihood is that the effect will not differ dramatically from the parental phenotype (intense portion of bar close to origin),

In contrast, the breeding method most likely to generate unintended effects is the induced mutagenesis (long bar) and it is also the most likely to produce something dramatically different from the parent phenotype) intense portion of bar furthest from origin).

Important to note here is that although the chart illustrates relative probability of unintended effects from breeding method, the incidence of actual unintended effects appearing in commercially released varieties is so low that the risks from all breeding methods can be considered equally negligible, especially in relation to true threats to health and safety.

The most important point of this chart to scientific justification of the trigger for regulatory action is the recognition that rDNA, as a breeding

FIGURE 1. Likelihood of unintended genetic effects associated with various methods of plant genetic modification. The gray tails indicate the relative degree of the range of potential unintended changes; the dark bar indicates the relative degree of genetic disruption for each method. For example, of the methods shown, a selection from a homogenous population is least likely to express unintended effects, and the range of those that do appear is also quite limited. In contrast, induced mutagenesis is the most genetically disruptive and, hence, most likely to display unintended effects from the widest potential range of phenotypic effects. Adapted from US National Academy of Science (2004).



method, cannot be segregated from other methods, including 'traditional' breeding methods. In fact, one form of rDNA is among the least likely to generate unintended effect, while another appear closer to mutagenesis as relatively more likely to generate unintended effects. No clear or even contrived dichotomy can draw a line between any form of breeding to demarcate 'safe' and 'unsafe'. No breeding process is inherently more hazardous than another, so breeding process cannot be used as a scientifically justified trigger for regulatory action.

Subsequent studies into unexpected effects of transgenesis in plants have verified the NAS 2004 findings and conclusions that rDNA is no more disruptive to the genome than other

methods of breeding. See, e.g. (Anderson et al., 2016), and references therein.

CANADIAN BACKGROUND AND PROBLEMS WITH IMPLEMENTATION OF THE NOVELTY (PNT) TRIGGER

Although Canada has adopted the scientifically sound policy of using novelty of product as the regulatory trigger, there remain some uncertainties and inconsistencies in interpretation and application of the principles. Over

several years, the various stakeholders were consulted through varied means, including sets of guidelines (e.g., Dir 94–08, *Assessment criteria for determining environmental safety of plants with novel traits*; the now defunct Dir 95–03, *Guidelines for the assessment of livestock feed from plants with novel traits*, replaced with Canadian Food Inspection Agency); and Health Canada’s *Guidelines for the safety assessment of novel foods* first published in 1994, updated in 2006). In addition to published guidelines, Canada also undertook several informal and unpublished public consultation workshops to discuss the prospects and potential problems with the novel plant regulatory trigger.

CFIA Public Consultation Workshops

To address some of the confusion over ‘novelty’ (at least as far as regulation of novel plants—PNTs—was concerned), CFIA conducted a series of workshops with relevant stakeholders between 2005 and 2008, as described in CFIA Directive (2009–09).

Administration of the definition of novel product (whether feed, food or plant) trigger is not quite as binary or dichotomous as one would like, because all new products are, by definition, *new*. This is not helpful in a regulatory setting, where limited resources demand a prioritization among ‘newness’ in products to capture for risk assessment only those posing the greatest risk. In this sense, novelty is not absolute; instead, prioritization involves a certain discretion on ‘where to draw the line’, between new but relatively low risk items and new but relatively higher risk items.

Legitimate differences in departmental or agency resources, expertise, approach, attitude, culture and practice means the line may be drawn at different points on the “riskiness” continuum, even when all agree on the meaning of novelty and trait based trigger.

But this differential can be confusing, if not frustrating, especially to stakeholders, who have one agency exempt a new product as non-novel and low risk, only to have another agency

capture the same product as being novel and potentially risky.

Some of these issues were raised and discussed at a workshop held February 6–7, 2006 in Ottawa. This workshop, organized by Wendy Shearer of CFIA and Jan Beardall of Department of Fisheries and Oceans (DFO), included representatives from CFIA, DFO, Environment Canada, and Health Canada, and discussed the novelty trigger and how to, as much as possible, harmonize interpretations and implementation of the novelty trigger across the varied regulatory offices. Discussion of the differences in interpretation and implementation of the triggers included analysis of the rationale and justifications—scientific or otherwise—of those differences and how harmonization could occur with a minimum of disturbance to all parties. One of the clear messages was the political and practical desire of harmonization, as a consistent interpretation and application of regulatory oversight would strengthen the scientific credibility or the regulatory system, obviate the practice of proponents “shopping” different regulatory offices to find the easiest route to marketing a new product, and, most important, provide greater assurance of protection from harm to Canadian society and environment. Another clear message from workshop participants was the need for greater harmonization to facilitate awareness, communication and interaction between and among departments and agencies. Such harmonization and communication also benefits stakeholders, both product proponents and society at large.

The first step toward harmonization is to identify the differences in interpretation in “novelty as a trigger” among the regulatory offices. The second step is to analyze each difference and determine whether they are superficial (and therefore easily harmonized) or more fundamental (and therefore requiring greater effort to achieve harmonization).

The 2006 workshop exposed and clarified 3 elements of the regulatory capture trigger common to all agencies and amenable to harmonization:

1. Novel trait/Altered characteristics/New features. The essential question- Is the

organism (including the complement of traits) new?

2. Novel use/New application/New environmental or dietary exposure. Is the (old) organism used in a new way, or to be released to a new ecosystem, or stimulate a substantial change in food consumption patterns?
3. Familiarity/equivalency. Has the agency sufficient familiarity with this product to warrant a lower risk priority? The concept here is that while everything poses some risk, resource limitations require prioritization of regulatory efforts to the products posing greatest risk. All agencies use familiarity (or a synonym such as equivalence) as a means to 'draw a line' on the prioritization list, to allow regulatory focus on those products not familiar, functionally equivalent, or for which there is no appropriate comparator.

(As an aside, the use of the expression "substantial equivalence" should be avoided due to widespread ambiguity and misinterpretation in the regulatory and public discourse resulting in uncertainty and confusion).

Another important outcome of the workshop discussion was the recognition that product novelty was both scientifically sound and most common trigger in Canada, but that process of derivation could be useful during the post-trigger risk assessment. For example, a new herbicide tolerant trait in crop species should trigger regulatory review regardless of the method of breeding. Once triggered, knowledge of the breeding method (process) will facilitate the risk analysis by guiding the questions and concerns. If rDNA is used, the proponent will have a considerable amount of probative information that would not be available if ionizing mutagenesis were the method of breeding.

Examples of uncertainty or disharmony in the Canadian regulatory landscape

- Development of a crop from a Canadian wildflower. Is a new crop considered novel if it is simply developed out of an indigenous, non-novel plant species?

Who should review this, CFIA or Environment Canada?

- A gamefish with enhanced growth features developed using conventional breeding methods.
- Introduction of an alien ornamental species.
- A virus infected perennial plant exhibiting a novel trait (which does not fall under CFIA/PBO trigger).
- Apple fruit with reduced polyphenols content is not novel to CFIA, as the levels are within 'normal' range for apples in Canada. But Environment Canada then captures the CFIA exempted product by default.
- A novel means of UV treatment of apple juice substantially reduces bacterial content. Health Canada wonders if this constitutes a novel product.
- An alien bait worm seems exempt from all regulatory offices. Such products are potentially hazardous (they may be invasive or pathogenic) but seem exempt from CEPA because they do not fall under the broad definition of 'biotechnology'

The discrepancies in interpretation of 'novelty' across agencies were, for the most part, superficial and therefore readily harmonized, both in legal documentation and in regulatory practice. The Canadian system for regulating products of biotechnology is a beacon worldwide for its founding principles of scientific credibility, sensibility and functionality, and for addressing the primary question—Are we protecting our people and environment in a cost effective manner? Most of the apparent differences discerned at CFIA workshops were trivial and therefore amenable to harmonization with little legalistic difficulty or practical disruption to day to day regulatory practice.

Overall, the public consultation workshops allowed a better understanding of issues and differences among the departments, and consensus recognition that harmonization in interpretation and application of the novelty concept trigger for regulatory action is both politically and scientifically desirable and practically feasible. As well, harmonization based

on a scientifically sound foundation enables a more consistent and justifiable science based, priority driven approach to protecting Canadian people and the environment from real threats.

Finally, and synthesizing the input from these various workshops, CFIA released a guidance document explaining PNT in 2009 (CFIA Directive 2009-09).

CONCLUSION

All nations claim to have “science-based” policies covering what are essentially scientific issues, such as those governing agricultural biotechnology. Most citizens demand scientific regulations be ‘science based’, because true science is politically neutral and a common standard. However, a scan of biotechnology regulations worldwide shows that most regulatory policies, although they include some scientific principles, are guided more by socioeconomics, philosophical or other interests. The more science is diluted by these other factors, the greater the jeopardy of not actually providing protection against real threats to safety and environment.

The first step in protecting the populace and environment is deciding what to regulate. Limited resources means prioritization, and setting priorities such that the highest risk products receive the greatest regulatory scrutiny should seem self evident.

Scientific studies from the earliest days of “modern biotechnology” recognized the risks posed by the technology were not lodged with the technology *per se*, but with the resulting products, and furthermore that these risks were no greater or lesser than the risks posed by products of traditional technologies. In short, the scientific analyses conducted by OECD, OSTP and NAS, in separate but near contemporaneous reports, all came to the same conclusion, that risks were a function of the product, not the process by which it was made.

The nation that most closely lives up to the claim of being ‘science based’ is Canada. The problems in Canada’s implementation and practice of regulatory oversight are not

fundamental or strategic, but of ‘nuts and bolts’ practicality at the level of the desk officers. In particular the lack of coordination and common interpretation across different departments and agencies are irritants and imperfections, but not fatal flaws. These problems do not indicate a fundamental flaw in the Canadian regulatory system; on the contrary, such problems can only exist where the system functions sufficiently to allow dossiers to proceed to that implementation desk level. Other jurisdictions, for example the EU, don’t know whether they have similar problems because their system does not, in practice, have any concrete examples of dossiers being processed at the level of the implementation officers. Their problems, instead, are more fundamental and strategic, which is why their system does not function (if “function” is defined as a sorting or filtering mechanisms, where higher risk items are caught and low risk items pass).

Castle et al. (2006) recommended that Canadian regulatory bodies could benefit from better communication and coordination, such that citizens, industry and regulators in different agencies would have a common understanding of the regulatory processes.

This point, that science policy must also recognize the legitimacy and benefit of better communication and transparency, both within the bureaucracy and with the wider public, was reiterated in the recent NAS report (US National Academy of Science, 2016). Public understanding and acceptance is an important factor in our democratic systems, and that can only be achieved by transparency and communication. At the same time, it must be recognized that scientific fact is not subject to the whim of democracy or popular opinion (McHughen, Porter, 2007). It does not matter if people deem DNA to be a protein, as they did in Mendocino County, California in a 2004 ballot initiative (http://www.co.mendocino.ca.us/agriculture/pdf/GMO_Ordinance.pdf). We can rest assured that Science ensures that DNA remains a nucleic acid, even in Mendocino County, regardless of what the wording of laws may assert.

Every scientific analysis of safety with GE crops and foods has reaffirmed what the OECD and US OSTP said in 1986 and 87, respectively- that the process of recombinant DNA is not inherently hazardous, so safety regulation should focus solely on the features of the product, regardless of process of breeding. To date, only the Canadian policy system has adopted the scientific foundation in formulating its regulatory policies. Thirty years later, the rest of the world is starting to recognize the validity of this ‘product trigger’ approach. A ‘product, not process’ regulatory trigger approach has been quietly discussed and even recommended explicitly in, for example, the UK (ACRE, 2013), Czech Republic (Sehnal & Drobnik, 2009) and in the United States (US National Academy of Science, 2016). It remains to be seen how long it will take policymakers in the US, Europe and elsewhere to amend their regulations – already claimed to be ‘science based’ – to conform to the advice offered by their own expert scientists. However, no matter how scientifically sound a regulatory system may be, it can be rendered dysfunctional by adverse political will, to the detriment of society at large.

ABBREVIATIONS

PNT	gPlant with Novel Trait
GMO	gGenetically Modified Organism
OECD	gOrganisation for Economic Cooperation and Development
rDNA Recombinant DNW	ggenetic engineering

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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