AgBioForum, 14(2): 61-70. ©2011 AgBioForum.

Risk of Regulation or Regulation of Risk? A *De Minimus* Framework for Genetically Modified Crops

Tim Durham
Florida Gulf Coast University

John Doucet
Nicholls State University

Lori Unruh Snyder
Purdue University

The precautionary principle places an impractical onus on science to demonstrate the absolute safety of genetically-modified (GM) crops. Conversely, traditionally bred articles receive little, if any, regulatory attention. Procedurally, GM certainly has the potential to create end products with deleterious (and thus regulatory actionable) characteristics. However, such risk is ultimately embodied in the end product and not the methodology, per se. Our proposal emphasizes a trait-based, end product model over the method-centric model. Using a *de minimus* framework, we propose a pragmatic, science-based rubric to assess GM crops. *De minimus* is designed to minimize regulatory bottlenecks for articles exhibiting nominal risk commensurate with antecedence, while reserving the amenities of precaution for those with an evidently higher risk index. Although GM may pose unique regulatory challenges, it is important that the regulation of risk not turn into the risk of regulation.

Key words: antecedence, biotechnology, cisgenic, *de minimus*, genetically modified, precautionary principle, regulation, transgenic.

Introduction

The Green Revolution was a watershed moment in agriculture and dramatically improved global food security. Unfortunately, this milestone foreshadowed future environmental costs, specifically, the overuse of pesticides, non-target effects, pest resistance, and environmental degradation.

One tool proposed to remedy these externalities is the use of genetic modification (GM). GM involves the precise transfer of DNA with advantageous traits from one organism to another. Typically these traits are agronomic in nature, though future developments are envisioned to be consumer oriented.

Proponents charge that GM is favorably positioned to be the new standard-bearer of crop improvement. Statistics appear to verify that claim: Since 1996, GM crops under cultivation have increased to over 1 billion hectares (James, 2010).

The adoption of GM is among the most rapid in history. Despite these statistics, the tenor among stakeholders is far from a consensus. Many skeptics are dismissive of the "gene revolution" and believe that such genetic interventions irrevocably alter crop physiology and by proxy, haphazardly introduce novel health and environmental risks. What has ensued is an often acrimonious debate on the appropriate level of regulatory rigor to comprehensively identify, quantify, and manage these risks.

Certainly, scientific and technological strides invariably bring risks to consumers and the environment (Sinclair, 1971-1972). Contemporary risk managers must demonstrate that they are reducing, mitigating, or minimizing a particular risk (Powell, 2000). Historical episodes such as the Starlink corn controversy have eroded trust in science and caused stakeholders to openly question the regulatory apparatus that links science to the consumer (Fox, 2001). In the face of an increasingly anxious and risk-averse populace, is current regulation adequate?

Current Regulation

This question evokes a fundamental difference of opinion between policymakers. In the United States, two doctrines known as *familiarity* and *substantial equivalence* prevail. Under these principles, the traits, usage, and field performance (familiarity), as well as biochemical composition (substantial equivalence), are expected to be comparable to their traditionally bred kin (antecedence). In essence, these criteria are performance based, with the characteristics of the end product determining the regulatory treatment. If the end product parallels an existing product that is generally regarded as safe (GRAS), it is deregulated and cleared for commercial planting.

Conversely, the EU policy is more prescriptive. Here it is argued that the GM methodology creates intrinsic

novelty *prima facie*, even if the end traits are identical to those generated through traditional means. In this instance, it is reasoned that the novelty inherent in the generative process justifies additional scrutiny.

Familiarity, substantial equivalence, and antecedence appear to present a relatively straightforward and convenient baseline to evaluate GM crops. In practice, such crops elicit significantly more attention than their traditional counterparts. Curiously, this is readily apparent in the United States, despite the ostensible application of an objective, trait-based assessment.

Thoughts On Reform

From its inception, GM has been the most heavily regulated crop improvement innovation in history. Given a long and successful history of cultivation, the technology appears to be at a crossroads. Many have suggested the time is appropriate for deregulation, though no consensus exists on the mechanism. Vasil (2003) recommended the relaxation and gradual elimination of oversight on GM crops that have met all regulatory requirements and been cultivated for five years. He further suggested that, barring any extraordinary risks, GM crops with previously field-deployed genes should be exempted from regulatory requirements after two years.

A 2009 white paper released by the Czech Academy of Sciences proposed a number of regulatory enhancements, including: (a) the replacement of the precautionary principle (PP) with a science-based standard; (b) an outcome rather than process based evaluative framework; and (c) risk and economic assessments based on parallel technologies, e.g., antecedence (Sehnal & Drobnik, 2009).

In addition, it has been argued that a regulatory distinction (Jacobsen & Nataraja, 2008; Schouten, Krens, & Jacobsen, 2006a, 2006b) should be made between cisgenics, the direct genetic transfer between sexually compatible donors, and transgenics, genetic transfer between taxonomically distant species.

A *De Minimus* Regulatory Framework

The regulatory encumbrances faced by GM crops are formidable. Despite this, a cursory review of statistics indicates a promising, if deceptive, yield. As of 2005, the US Department of Agriculture's Animal and Plant Health Inspection Service had received 11,600 applications for field trials. These encompassed a number of broadly grouped trait families, including insect resistance, herbicide resistance, improved product quality and agronomic quality, and virus resistance. Of those, nearly 10,700 (92%) had been approved. However, only 63 of 103 petitions for full deregulation were granted (Fernandez-Cornejo & Caswell, 2006). This represents an effective yield of 0.6% of the original field-approved cohort. As of 2010, the number of deregulated articles had marginally increased to 89 (CERA, 2010). A fraction of those have been commercialized. These numbers are dwarfed by output in the traditional breeding sphere, where varieties are cleared with little, if any, regulatory attention. In this regard, they are implicitly granted *de minimus* status. In effect, the likelihood of harm is deemed so infinitesimally small that regulation would yield no measurable benefit to society.

Bureaucracy represents a significant bottleneck to innovation and diffusion. Indeed, is it widely agreed that the current regulatory climate places an impractical onus on science to demonstrate the absolute safety of GM crops. Despite the novelty of certain traits, it is interesting to note that many of the ascribed risks are entirely reproducible with antecedent methods. This reality necessitates a workable solution to an obvious policy dilemma: the disparate regulatory treatment afforded to GM crops, despite a similar suite of ecological and human health effects.

In this manuscript we synthesize a number of the aforementioned policy reforms with our own. Firstly, regulators should adopt a method-agnostic approach, and focus on relevant ecological and biochemical characters of the end product. Moreover, any risks associated with GM should be assessed relative to their antecedent peers. This demands a performance-based framework to replace the prescriptive, one-size-fits all approach. Moreover, the precautionary principle, as invoked in the current regulatory scheme, is scientifically indefensible. It should be replaced with a flexible *de minimus* approach, which avoids the allocation of resources to address negligible risks for nominal or nonexistent gains in safety. In addition, we believe that current regulations place an acute overemphasis on hypothetical (and often unmeasurable) risks, while downplaying the advantages. In effect, this accentuates the what-if scenarios of the risk assessment calculus at the expense of demonstrable benefits. It is critical that the latter receives appropriate weight in the decision-making continuum. Indeed, Connor, Glare, and Nap (2003) suggested a regulatory reform that would juxtapose the costs of inaction with the costs of action. We believe that such an inclusion, though difficult to encapsulate in the risk evaluation equation, is a critical consideration.

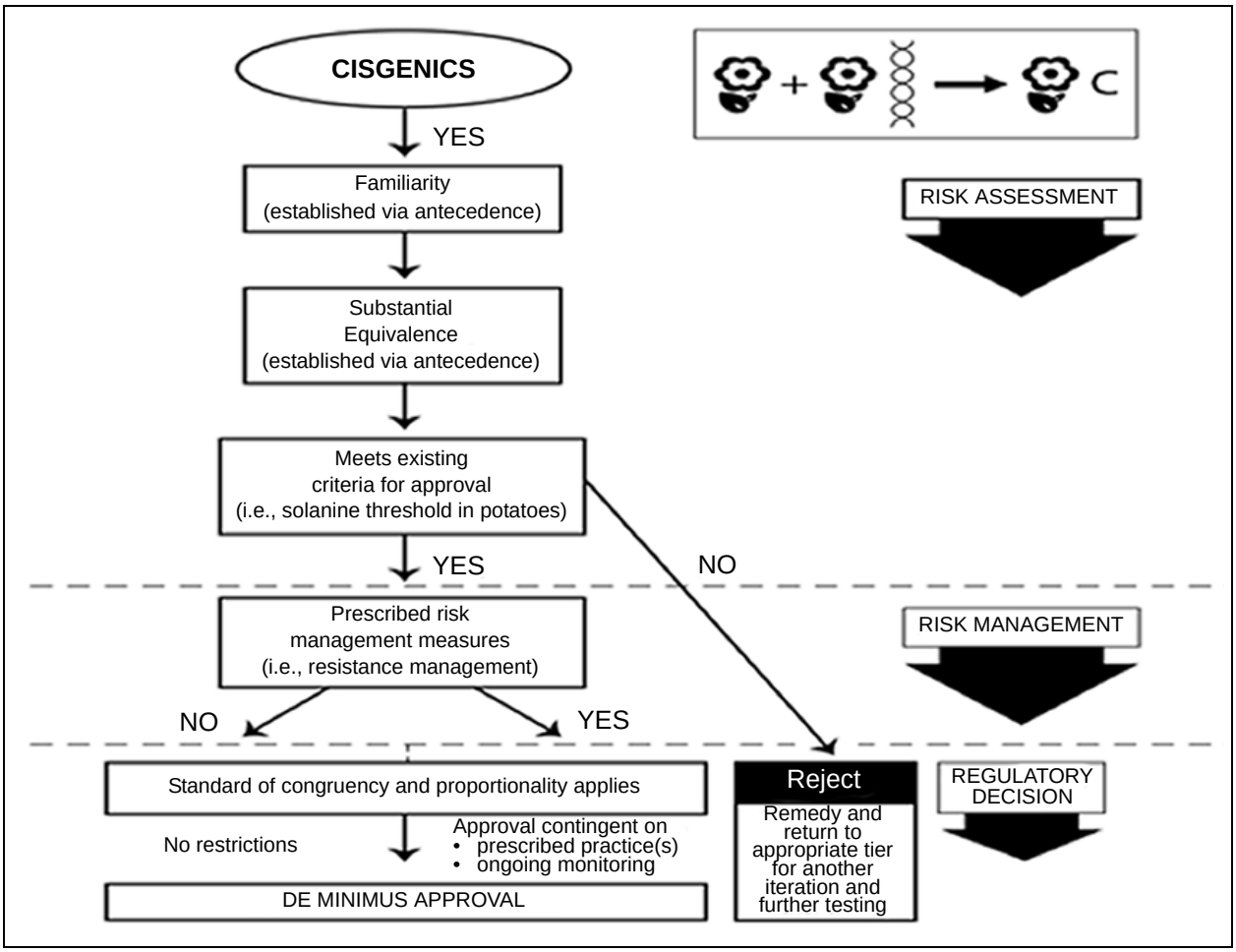

Figure 1. Proposed framework for the regulation of cisgenic articles. Cisgenics is generally conferred *de minimus* status, given the intrinsic nature of the genetic material and phenotypic reproducibility with conventional breeding. The process is partitioned into three stages: risk assessment, risk management, and regulatory decision.

Technology Assessment, The Precautionary Principle, and *De Minimus* Risk

Technology assessment (TA) is an interdisciplinary field that focuses on a concrete problem, specific technology, or perceived problem. The ultimate goal of research is to standardize a system that enables regular updating of information on diffusion and adoption of technologies and their impact on environmental outcomes (WARDA-The Africa Rice Center & Consultative Group on International Agricultural Research [CGIAR], 2003). Based on the long-term uncertainty factor, GM is often identified as a problem-induced phenomenon.

With that as a procedural guide, specific risk assessment methodologies broadly attempt to quantify the following three questions: What can go wrong? How likely is it to happen? What are the repercussions if it does happen?

In the policymaking arena, the deliberative approach has its foundations in the precautionary principle. For context, it is helpful to refer to the EU definition, which states that: "In order to protect the environment, a precautionary approach should be widely applied, meaning that where there are threats of serious or irreversible damage to the environment, lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to prevent environmental degradation" (EEA, n.d.).

In some respects, the precautionary principle has merit because it encourages the deconstruction of risk. Conversely, lack of full scientific certainty is frequently used as a pretext for postponing risk, effectively relegating GM to abstract conceptualizations or field trials in

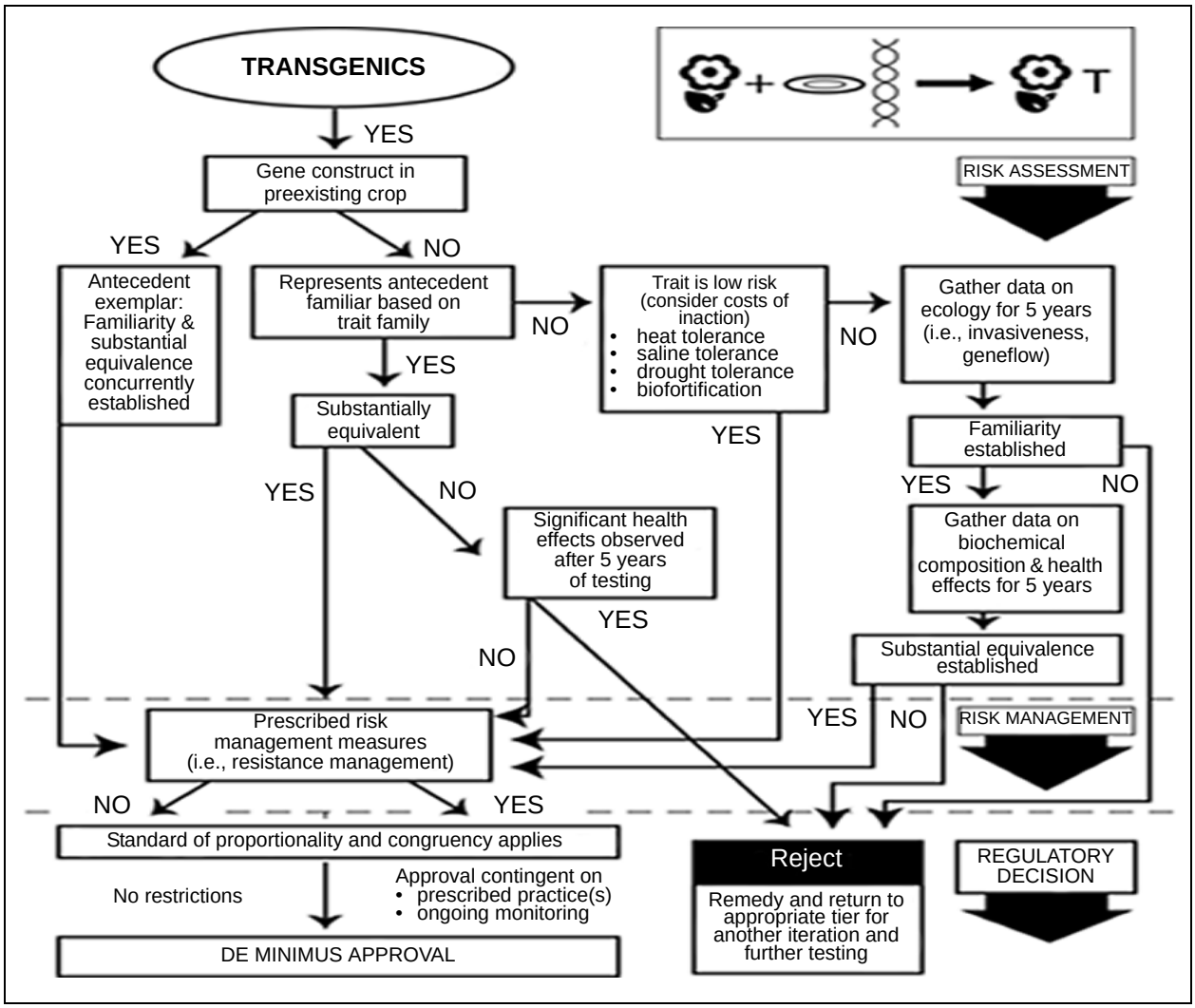

Figure 2. Proposed framework for the regulation of transgenic articles. Given the extrinsic nature of the introduced gene(s), evaluation is a composite of multiple factors, including: preexisting gene constructs, antecedence, familiarity, substantial equivalence, and the costs of inaction. When necessary, this framework accommodates a nested conventional evaluation with potential advancement to *de minimus* standing.

perpetuity. Such a doctrinaire posture is self-defeating in practice. Holm and Harris (1999) argue that the PP biases the argument towards irrational caution, even in the presence of contravening evidence.

Interestingly, a rarely invoked secondary EU definition offers explicit leverage in the policy arena, stating that: "The precautionary principle permits a lower level of proof of harm to be used in policy-making whenever the consequences of waiting for higher levels of proof may be very costly and/or irreversible" (EEA, n.d.). This language offers a proviso, explicitly acknowledging that the risk of inaction may far outweighs the risk of action. In essence, if payback exceeds adversity, then attempts to reduce small risks while leaving larger ones a countervailing approach to decision making should be adopted.

The principle of *de minimus* risk offers a reasonable counterweight to the overly zealous application of the PP. It conveys a simple philosophy: that the regulation of risk should exhibit a standard of congruency and proportionality. In other words, regulatory entities must demonstrate that their approaches are congruent with and proportionate to the problem they seek to address. Speaking on the issue of risk management, Comar (1979) stated that *de minimus* can "…focus attention on actions that can effectively improve health and welfare and at the same time avoid squandering resources in unattended."

Table 1. A selection of crops, transgenes, and their associated antecedent familiars.

Crop species	Trait family	Transgene	Antecedent familiar
Tomato (*Lycopersicon esculentum*)	Delayed ripening	Antisense polygalacturonase (PG) gene	Mutant, defective ripening inhibition locus (rin) gene
Various	Herbicide resistance	a) Mutant EPSPS gene (glyphosate resistance) b) *Bar* gene (Glufosinate resistance)	a) Cyclohexanedione (sethoxydim) resistance b) Imidazolinone resistance c) Sulfonyluera resistance d) Triazine resistance
Maize (*Zea mays*)	Plant incorporated pesticide	Cry1Ac gene (Bt)	None, although it potentially represents antecedence for future GM crops with pesticidal properties, e.g., Avidin
Maize (*Zea mays*)	Male sterility	Barnase expression in tapetum	Cytoplasmic male sterility (CMS) has been exploited for some time in conventionally bred corn lines
Papaya (*Carica papaya*)	Virus resistance	Genes encoding for viral coat proteins	None, although it potentially represents antecedence for future GM crops belonging to same trait family
Oilseed rape (*Brassica napus*)	Enhanced oil content	Thioesterase gene	Essentially the upregulated production of an endogenous gene, overexpressing non-transgenic mutants are conceivable

**Compiled from CERA (2010), Vrebalov et al. (2002), Laughnan and Gabay-Laughnan (1983), and Duke (2005).*

A Working Model

The validity of any technology assessment requires the development of measurement standards to allow for objective and systematic comparisons (Jannsen, 1994). In the absence of direct experience, the most appropriate guide for GM risk assessments are breeding antecedents. As previously discussed, antecedence simply refers to a preexisting modality of crop improvement. Such methods may involve cloning, induced mutagenesis and selection, chromosome doubling, protoplast fusion, grafting, embryo rescue, and microspore culture, among others. According to EU Directive 2001/18/EC (Publications Office of the European Union, 2001), many of these breeding techniques constitute GM *sensu lato*, though more ubiquitous techniques are explicitly exempted from oversight.

Using antecedence as a risk index, a *de minimus* framework can be constructed to rapidly evaluate GM crops while exercising regulatory parity with their conventional equivalents. Conceptually, this approval stream is similar to the expedited "reduced risk pesticide" framework promulgated under the US Food Quality Protection Act (FQPA) of 1996.

Candidate assessment is based on five criteria: (a) taxonomic distance (cisgenic or transgenic), (b) antecedence, (c) familiarity, (d) substantial equivalence, and (e) the costs of inaction.

Under our framework, cisgenic crops (Figure 1) are automatically conferred *de minimus* status. A number of authorities have made a compelling case for their deregulation, reasoning that the end products draw from the same genetic pool and are therefore attainable using conventional breeding methods. No further regulatory intervention is required. The exception would be where customary safety standards exist, such as solanine levels in potatoes.

Alternatively, transgenics (Figure 2) might introduce truly novel phenotypes with potentially harmful characteristics. In this instance added stringency is justified. If antecedence between a GM and conventional product based on trait family is determined (Table 1), then reciprocity is established, which implies that the end traits (including the expression profile) of the GM crop are conventionally reproducible. In our view, this product then represents an antecedent familiar (Table 1). Both are envisioned to exhibit a near identical suite of ecological effects, equivalent to familiarity. Inclusion in a trait family represents a proof of concept: that the end product has no demonstrable record of ecological harm. In this instance familiarity need not be formally established because field exemplars already exist. However, comparable human health effects are not necessarily implied. Substantial equivalence would need to be assessed separately, based on a biochemical characterization.

We also propose that GM crops with approved traits be recognized as antecedents exemplar for forthcoming GM products. *Bacillus thuringiensis* (Bt) pesticidal transgenes would be a suitable example. Independent evaluation of an identical transgenic event in a separate cultivar or species would be duplicative, resource intensive, and uninformative. Since the end product has already been vetted using the existing regulatory framework, substantial equivalence and substantial equivalence would be concurrently established.

Transgenes that introduce altogether novel traits would trigger a traditional risk assessment. The end product would be compared to a non-transgenic variety developed through antecedent methods. Such candidates would be subject to a flexible battery of tests for no more than five years to demonstrate any effects on human health and the environment. A regulatory decision will then be made based on a composite of the observed risks and the costs of inaction.

Three possible outcomes are possible under a *de minimus* stream: (a) fast-tracked deregulation; (b) fast-tracked deregulation with prescribed risk management measures (such as non-Bt "refuges" to minimize insect resistance); and (c) a nested conventional risk assessment with potential advancement to *de minimus* standing, with or without prescribed risk management measures.

Comparative Risk Indices

Despite pronouncements to the contrary, current regulatory systems have not effectively reconciled efficiency with the need to be informed by science. Jaffe (2006) reported that the approval window for non-regulated status has slowed considerably from the inaugural class of GM crops, from 8.6 months between 1994 and 2005 to 15.4 months between 2001 and 2005. He further outlined why stakeholders should be concerned with the unhurried pace of approvals despite a familiarity with the technology, no demonstrated evidence of risks from existing products, fewer products to review, and most notably, products with risk profiles comparable to those already reviewed.

Based on a considerable volume of data, there is no reason to believe that GM crops pose a risk any orders of magnitude greater than their antecedents. In fact, recent work by Kogel et al. (2010) suggested that traditional breeding causes more inherent genetic variability than GM. Uwe Sonnewald, a co-author of the paper, writes, "the impact of transgenes is basically limited to their immediate function." In other words, the inserted gene behaved as a good neighbor, with precise and predictable functionality.

With cisgenics, there is considerable capacity to shorten crop development time by avoiding linkage drag, the undesirable genetic baggage that invariably manifests with a traditional breeding program. Such drag can have unanticipated consequences.

Such cannot be said for conventional methods, where undesirable outcomes have been extensively documented. For example, a disease called autogenic necrosis in tomatoes is the result of an incompatible gene bred into the species, essentially causing a condition analogous to an autoimmune reaction. The Lenape potato was found to have elevated levels of toxic glycoalkaloids (Zitnak & Johnston, 1970), an artifact of traits introgressed from wild breeding stock. Batista, Saibo, Lourenco, and Oliveira (2008) found that induced mutagenesis, a standby of conventional breeding, might induce more transcriptomic changes than transgene insertion. Similarly, using various "omic" (transcriptomic, proteomic, and metabolomic) profiling techniques, Ricroch, Berge, and Kuntz (2011) expressed the need to place pair-wise differences between GM crops and their comparators in a wider context of natural variation. Further, naturally-occurring transposable elements are known to hopscotch through genomes with relative abandon.

Interestingly, some proprietary techniques such as targeting induced local lesions in genomes (TILLING) and rapid trait development system (RTDS) deliberately induce genome disruptions as a matter of course. This introduces many genotypic and phenotypic novelties while circumventing the technical definition of GM.

A frequent question raised by GM crops is field performance, particularly their potential for gene escape and invasiveness. This is typified by the incorporation of herbicide resistance (HR) traits. It has been speculated that commingling with weedy relatives would yield hybrid progeny with a distinct fitness advantage. Weeds certainly can benefit from the acquisition of new characters via increased fitness, survival and spread if they inherit HR traits (Ellstrand, 2001). Notwithstanding the limited ecological fitness conferred by resistance to a single herbicide class, it must be recognized that antecedent familiars with HR have already been developed and released into the wider environment (Conner & Field, 1995). In the case of conventionally bred ALS-resistant (HR) canola, plants have coincidentally been found to "pollute" adjacent fields with HR genes via pollen (Rieger, Lamond, Preston, Powles, & Roush, 2002). In this instance, no regulation or special precau-

tions were deemed necessary, despite a comparable risk index.

The intractability of the GM debate is exemplified in a recent US Supreme Court ruling that economic impacts such as reduced yields are tantamount to an environmental harm (Monsanto Co. et al. v. Geertson Seed Farms, 2010). Such rulings are puzzling, as yield drag trade-offs are commonly found in antecedent varieties bred for disease resistance (Brown, 2002). To date, no such principle has been retroactively applied. It is also questionable how the mere threat of gene flow can be used as a pretext for continued regulation, especially when the phenomenon has already been demonstrated in antecedent HR varieties.

Although not necessarily evident, the cost of inaction represents another potential risk for GM crops. For example, the insecticidal properties of Bt have been employed for decades as a formulated spray. GM varieties have been developed with the ability to produce the insecticidal protein *in planta*, which targets administration to pest herbivory. In addition to eliminating non-target effects, the use of transgenic soybean, canola, cotton, maize, and sugarbeet has been estimated to reduce pesticide use by 352 million kilograms of active ingredient (Brookes & Barfoot, 2010).

Rationale for *De Minimus*

Most fundamentally, current regulations impede the most routine exchange of genetic material, even when the source gene is from an identical species or of minimal genetic distance. For instance, after analyzing the genome of a wild species, researchers at the University of Wisconsin characterized a gene that confers resistance to potato late blight, *Phytophthora infestans* (Song et al., 2003). Though the trait could conceivably be bred into the standard variety, other desirable characteristics would be lost. Precision is thus a major consideration for fast-tracking.

Brevity represents a parallel rationale. Kershen (2004) recalled a dialogue with a scientist from Southeast Asia, who inquired whether he was permitted to transfer a disease resistance gene from a landrace of one species to a domesticated version of the same under the Cartagena Protocol on Biosafety (CPB). Such transfers were not permitted under current agreements. As a consequence, the scientist estimated that it would take 15 years to develop, as opposed to 6-7 years with recombinant DNA (rDNA) techniques. He commented that hundreds of thousands of the poorest societies would suffer needlessly.

Ironically, regulatory indecision can instigate the very problems risk managers seek to avoid. Weary of continual approval delays, indignant Indian cotton farmers founded a veritable cottage industry in 2001, and hybridized contraband GM seed with their own locally adapted varieties (Jayaraman, 2004). Although the Indian Genetic Engineering Approval Committee (GEAC) greenlighted Bt cotton in 2002, emboldened farmers continue to defy local authorities.

Current regulations also represent a curious paradox for the most ardent critics of GM. In many instances the costs of biosafety research and development are concentrated in the hands of those with the combined capacity for product development and costly regulatory compliance: private, multinational corporations. Crop improvement efforts are overwhelmingly proprietary and skewed toward agronomic commodities. Crops grown by the poor are effectively ignored. Predictably, it is difficult to justify investments in products with limited returns, particularly when facing indefinite delays for regulatory decisions. As a result, public-good initiatives for orphaned, underutilized, and specialty crops languish under the current framework.

Toward Regulatory Harmonization

The current regulation of GM crops requires a candid renegotiation of acceptable risk, given the broad reproducibility of similar phenotypes in conventionally-bred kin. We believe that the current approach to GM crops is fundamentally flawed, because it relies on inferential and unsubstantiated risk judgments. The current level of regulation is unprecedented: Never before has such excessive regulation been crafted to respond to (as of yet) hypothetical risks.

In particular, the precautionary principle places an impractical onus on science to demonstrate the absolute safety of GM crops. It is likely that no quantity of voluminous data, however unequivocal, will placate critics. Kasanmoentalib (1996) estimated that it would take 10 to 100 generations of data collection and analysis to thoroughly absolve a GM crop of risk. In policymaking, ten generations is a relative eternity. Appropriately, drawing from the TA questions already in practice, Connor et al. (2003) formulated a new risk assessment parameter to consider in policymaking: the costs of inaction.

GM crops are often assumed to have a higher risk index relative to their antecedent peers. Procedurally, the potential certainly exists to create end products with deleterious (and thus regulatory actionable) characteris-

tics. However, such risk is ultimately embodied in the end product and not the generative process, per se. Reasoning that generative novelty alone justifies added oversight unfairly typecasts GM. More importantly, it is a type of *a priori* judgment, which lacks an empirical basis.

It is important that the regulation of risk not turn into the risk of regulation (Nap, Metz, Escaler, & Connor, 2003). Accordingly, regulatory stringency should be indexed to actual and not hypothetical risk. The *de minimus* approach represents an appropriate level of protection, while normalizing their regulatory treatment. If risks associated with an antecedent technology are functionally congruent and have been exempt from regulation, then a parallel technology should enjoy a comparable regime.

To date, no conceptual distinction can be made between genetic modifications of plants by classical methods or molecular techniques that introduce a modifying gene product (Anonymous, 1992). Indeed, it is arguable that the term "GM" is merely semantics, that is, a procedural descriptor with little predictive power in characterizing the end product itself. The convergence of traditional and molecular breeding has rendered the term obsolete and made strict procedural-based distinctions and disparate, two-tiered regulations increasingly irrelevant.

De minimus is interrogative, transparent, and operational. It provides a pragmatic, science-based rubric for assessment, decoupling politics and science. Most importantly, it does not impose unnecessary burdens on crop development based on unrealistic assessments of risk.

It is explicitly designed to streamline approval of crops with a nominal risk profile commensurate with antecedence. Underutilized and specialty crops could benefit substantially from such a regime. To date, it has been difficult to ascertain lack of demand or outright market rejection of these crops when regulatory uncertainty renders development uneconomical or unfeasible (Miller & Bradford, 2010).

However, we also recognize that certain transgenic crops may pose unique regulatory challenges. For those crops with an evidently higher risk index, the amenities of precaution would be preserved.

Admittedly, a risk assessment cannot claim to comprehensively identify all contingencies of a given problem. Despite the downstream uncertainties, evidentiary facts point to the safety of GM crops. Therefore, they should not have to undergo a more thorough credentialing based on generative pedigree alone.

Appropriately, it is questionable whether conventionally bred crops should be granted a brand of special policy dispensation based on perceived safety. If anything, policymakers may be remiss in underestimating the dangers of traditional breeding (Gewin, 2002). Certainly very little is known about the potential long-term health effects of any traditional food (WHO & FAO, 2000). According to the US National Research Council, we are in a more enviable position to predict the phenotypic expression of organisms modified by molecular methods (National Research Council, 1989). If the ability to predict phenotypic expression is the *de facto* vanguard of risk assessment, then GM crops generally represent a significant improvement in that sphere.

The alternative to a *de minimus* approach is a potentially stymieing policy framework that stresses a system of upregulatory harmonization. Canada has implemented such a system, where novel traits generated by traditional breeding methods such as wide hybridization are regulated alongside transgenic plants (Canadian Plant Biosafety Office, 2002). However, it is doubtful that other countries would exercise the political wherewithal to emulate this model.

To synergize a *de minimus* framework, we believe that cross-border reciprocity agreements (i.e., clearinghouses) would effectively partition risk assessments among nations. This is a viable mechanism to avoid regulatory duplication. It would also represent a prudent use of scarce regulatory resources, which would allow countries to focus on specific domestic issues that a GM crop might pose. To ensure consistency, it would also be prudent for individual countries to vest oversight in a single body, modeled in principle on New Zealand's Environmental Risk Management Authority (ERMA).

Application of the *de minimus* principle need not be plant exclusive. We also envision utility in other domains, including transgenic arthropods. An example would be the development of pesticide resistant biocontrol agents. In this case, antecedence represents the selection of pesticide resistant strains. Similarly, phenotypic expression profiles that confer a fitness disadvantage, such as engineered sterility, could also receive a low-risk regulatory treatment.

Although select GM crops may pose unique regulatory challenges, it is important that the regulation of risk not turn into the risk of regulation. Thus, the most appropriate regulatory approach for all GM crops is to evaluate the end product, irrespective of the generative methodology, and assess under a *de minimus* framework, while futuring the costs of action versus inaction.

References

Anonymous. (1992). US BioTechnology Policy: Products pose no special risks just because of the processes used to make them. *Nature*, 356, 1-2.

Batista, R., Saibo, N., Lourenco, T., & Oliveira, M.M. (2008). Microarray analyses reveal that plant mutagenesis may induce more transcriptomic changes than transgene insertion. *Proceedings of the National Academy of Sciences*, *105*, 3640-3645.

Brookes, G., & Barfoot, P. (2010). Global impact of biotech crops: Environmental effects, 1996-2008. *AgBioForum*, *13*(1), 76-94. Available on the World Wide Web: http://www.agbioforum.org.

Brown, J.K.M. (2002). Yield penalties of disease resistance in crops. *Current Opinion in Plant Biology*, *5*, 339-344.

Canadian Plant Biosafety Office. (2002). *Decision documents: Determination of environmental and livestock feed safety.* Available on the World Wide Web: http://www.inspection.gc.ca/english/plaveg/bio/dde.shtml.

Center for Environmental Risk Assessment (CERA). (2010). *GM crop database* [online]. Washington, DC: CERA, International Life Sciences Institute (ILSI) Research Foundation. Available on the World Wide Web: http://cera-gmc.org/index.php?action=gm_crop_database.

Comar, C.L. (1979). Risk: A pragmatic de minimus approach. *Science*, *203*, 319.

Conner, A.J., & Field, R.J. (1995). Herbicide-resistant crops: A new approach to an old problem or a radical new tool? In G.D. McLean & G. Evans (Eds.), *Herbicide resistant crops and pastures in Australian farming systems* (pp. 53-71). Canberra, Australia: Bureau of Resource Sciences.

Connor, A.J., Glare, T.R., & Nap, J.P. (2003). The release of genetically modified crops into the environment: Part II. Overview of ecological risk assessment. *Plant Journal*, *33*, 19-46.

Duke, S.O. (2005). Taking stock of herbicide-resistant crops ten years after introduction. *Pest Management Science*, *61*, 211-218.

Ellstrand, N.C. (2001).When transgenes wander, should we worry? *Plant Physiology*, *125*, 1543-1545.

European Environment Agency (EEA). (n.d.). *Precautionary principle* [online database]. Copenhagen, Denmark: EEA, European Union. Available on the World Wide Web: http://glossary.eea.eu.int.

Fernandez-Cornejo, J., & Caswell, M. (2006, April). *The first decade of genetically engineered crops in the United States* (Economic Information Bulletin No. 11). Washington, DC: US Department of Agriculture (USDA), Economic Research Service (ERS).

Fox, J. (2001). EPA re-evaluates StarLink license. *Nature Biotechnology*, *19*, 11.

Gewin, V. (2002). Academy proposes tighter crop monitoring. *Nature*, *415*, 948.

Holm, S., & Harris, J. (1999). Editorial. *Nature*, *400*, 398.

Jacobsen, E., & Nataraja, K.N. (2008). Cisgenics—Facilitating the second green revolution in India by improved traditional plant breeding. *Current Science*, *94*, 1365-1366.

Jaffe, G. (2006). Regulatory slowdown on GM crop decisions. *Nature Biotechnology*, *24*, 748-749.

James, C. (2010). *Global status of commercialized biotech/GM crops: 2010* (ISAAA Brief No. 42). Ithaca, NY: International Service for the Acquisition of Agri-Biotech Applications (ISAAA). Available on the World Wide Web: http://www.isaaa.org/resources/publications/briefs/42/executivesummary/default.asp.

Jannsen, W. (1994). *Biotechnology priority setting in the context of national objectives. State of the art*. Paper presented at Asia Regional Seminar on Planning, Priorities, and Policies for Agricultural Biotechnology, Singapore.

Jayaraman, K.S. (2004). Illegal seeds overtake India's cotton fields. *Nature Biotechnology*, *22*, 1333-1334.

Kasanmoentalib, S. (1996). Deliberate release of genetically modified organisms: applying the precautionary principle. In A. van Dommelen (Ed.), *Coping with deliberate release: The limits of risk assessment* (pp. 137-146). Tilburg, the Netherlands: International Centre for Human and Public Affairs.

Kershen, D. (2004, March 6). LMOs and modern biotechnology definitions in the Cartagena Biosafety Protocol. Auburn, AL: AgBioWorld. Available on the World Wide Web: http://www.agbioworld.org/newsletter_wm/index.php?caseid=archive&newsid=2037.

Kogel, K.H., Voll, L.M., Schäfer, P., Jansen, C., Wu, Y., Langen, G., et al. (2010). Transcriptome and metabolome profiling of field-grown transgenic barley lack induced differences but show cultivar-specific variances. *Proceedings of the National Academy of Sciences*, *107*, 6198-6203.

Laughnan, J.R., & Gabay-Laughnan, S. (1983). Cytoplasmic male sterility in maize. *Annual Review of Genetics*, *17*, 27-48.

Miller, J.K., & Bradford, K.J. (2010). The regulatory bottleneck for biotech specialty crops. *Nature Biotechnology*, *28*, 1012-1014.

Monsanto Co. et al. v. Geertson Seed Farms, 09-475. (2010).

Nap, J.P., Metz, P.L., Escaler, M., & Connor, A.J. (2003). The release of genetically modified crops into the environment. Part I. Overview of current status and regulations. *Plant Journal*, *33*, 1-18.

National Research Council. (1989). *Field testing genetically modified organisms: Framework for decisions*. Washington, DC: National Academies Press.

Powell, D. (2000). Food safety and the consumer: Perils of poor risk communication. *Canadian Journal of Animal Science*, *80*, 393-404.

Publications Office of the European Union. (2001). Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. *Official Journal of the European Community*, *106*, 1-38.

Ricroch, A.E., Berge, J.B., & Kuntz, M. (2011). Evaluation of genetically engineered crops using transcriptomic, proteomic, and metabolomic profiling techniques. *Plant Physiology*, *155*, 1752-1761.

Rieger, M.A., Lamond, M., Preston, C., Powles, S.B., & Roush, R.T. (2002). Pollen-mediated movement of herbicide resistance between commercial canola fields. *Science*, *296*, 2386-2388.

Schouten, H.J., Krens, F.A., & Jacobsen, E. (2006a). Do cisgenic plants warrant less stringent oversight? *Nature Biotechnology*, *24*, 753.

Schouten, H.J., Krens, F.A., & Jacobsen, E. (2006b). Cisgenic plants are similar to traditionally bred plants. *The EMBO Journal*, *7*, 750-753.

Sehnal, F., & Drobnik, J. (Eds.). (2009). *White book, genetically modified crops: Scientific opinion of Czech researchers working with GMO*. České Budějovice: Biology Center of the Academy of the Sciences of the Czech Republic.

Sinclair, C. (1971-1972). The incorporation of health and welfare risks into technological forecasting. *Research Policy*, *1*, 40-58.

Song, J., Bradeen, J.M., Naess, S.K., Raasch, J.A., Wielgus, S.M., Haberlach, G.T., et al. (2003). Gene RB cloned from Solanum bulbocastanum confers broad spectrum resistance to potato late blight. *Proceedings of the National Academy of Sciences*, *100*, 9128-9133.

Vasil, I.K. (2003).The science and politics of plant biotechnology—A personal perspective. *Nature Biotechnology*, *21*, 849-851.

Vrebalov, J., Ruezinsky, D., Padmanabhan, V., White, R., Medrano, D., Drake, R., et al. (2002). A MADS-box gene necessary for fruit ripening at the tomato ripening-inhibitor (rin) locus. *Science*, *296*, 343-346.

WARDA-The Africa Rice Center & Consultative Group on International Agricultural Research (CGIAR). (2003). WARDA strategic plan 2003-2012. Bouaké, Côte d'Ivoire: Author. Available on the World Wide Web: http://www.africarice.org/publications/Strategic%20Plan/fullversion.pdf.

World Health Organization (WHO), Food and Agriculture Organization (FAO). (2000). *Safety aspects of genetically modified foods of plant origin* (Report of a Joint WHO/FAO Expert Consultation on Foods Derived from Biotechnology). Geneva, Switzerland: Author.

Zitnak, A., & Johnston, G. (1970). Glycoalkaloid content of B5141-6 potatoes. *American Potato Journal*, *47*, 256-260.

Acknowledgements

The authors would like to thank Dr. Indra Vasil for reviewing a draft of this manuscript. We would also like to thank Trisha Dubina for her graphical expertise.