Erring on the side of caution: a case for increased regulatory oversight of genetically modified organisms in the United States

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Introduction

Soon after the first demonstrations of recombinant DNA technology, the potential risks to the environment and human health became evident. In 1975, a global moratorium halted research on recombinant forms until risks could be defined and confinement protocols established. Concerns were so great and an understanding of risks so limited that the decision was made to err on the side of caution (Andow & Zwahlen 2005). Leading researchers convened a meeting at Asilomar, California, to identify potential biohazards and to recommend standardized lab practices for handling GE organisms (Berg et al. 1975). The conference resulted in the U.S. National Institute of Health (NIH) guidelines for laboratory research on recombinant DNA (Andow & Zwahlen 2005). The recommended *modus operandi* was deemed the "precautionary principle" and adopted as the "precautionary approach" in the Cartagena Protocol. It maintains that when risks to human well-being are in doubt, the wise course of action is to take precautionary steps until the significance of those risks is clear (Rio 1992). Thus in 1975, independent scientists, alarmed at the hazards arising from the new technology, signed onto the moratorium; but in the decades since, there has been a radical shift in perspective, with industry-scientists now maintaining that the technology is safe and that a moratorium on its use represents a relic of unconstructive thinking.

The Cartagena guidelines were put into place early in the evolution of the biotech industry when few could have envisioned the scale on which GE organisms would be produced. There has been a striking record of growth since the first intentional releases of GE organisms in the mid 90's (Nap et al. 2003). Genetically engineered crops now grow in all ecosystems that support plant life, approximately 160Mha worldwide (FAOSTAT 2012). Despite the widespread use of GE products and their cultivation in diverse ecosystems, there has been no clear-cut environmental calamity, no loss of human life, no evident spread of plant blight. The biotech industry and its advocates have championed the safety of GE organisms, arguing that threats to human health have been exaggerated and that delays stemming from regulatory approval have harmed the industry (Fedoroff 2011). They maintain that because there has been no acute, irreversible harm, the regulatory control of biotech developments should be minimized (Borlaug 2000, Federoff et al. 2010, Giddings et al. 2012). In this brief we discuss some fallacies in this reckoning and argue that regulatory oversight of GE products should be strengthened.

In the years since Asilomar, U.S. scientific organizations have weighed in with concerns regarding the widespread adoption of genetically engineered plants and animals. Members of the Ecological Society of America (ESA) summarized the potential environmental risks of transgenic organisms in 1984, 1989 and 2005 (Brown et al. 1984, Tiedje et al. 1989, Snow et al. 2005). The most recent report summarized likely hazards to the environment and formalized recommendations for development of GE organisms. A tacit assumption of these cautionary reports was that should any of these concerns be realized, the offending GE organism would be withdrawn from commercial production. Of the six environmental concerns listed by Snow et al. (2005), four have been realized in North America: the persistence of GE organisms outside of cultivation ("escapes") (Watrud et al. 2004, Warwick et al. 2008, Zapiola et al. 2008, Schafer et al. 2011), their potential to interbreed with related taxa (Reichman et al. 2006, Zapiola et al. 2008, Wegier et al. 2011), direct and indirect effects on non-target species (Rosi-Marshall et al. 2007), and the potential for the evolution of resistance to herbicides and pests (Warwick et al. 2008, Heap 2012). Unfortunately, there has been no regulatory backlash and no government action to eradicate the escapees; nor has there been litigation concerning intellectual property rights and responsibility for clean-up. A case in point is the report of GE canola escaped from cultivation throughout North Dakota, U.S.A. Schafer et al. (2011) reported large populations, occasionally thousands of individuals, of GE canola

resistant to glyphosate or glufosinate herbicides growing outside cultivation. Among the plants sampled in the study, several expressed resistance to both herbicides (glyphosate and glufosinate resistance), a phenotype that has not been commercially released (Schafer et al. 2011). Discovery of plants with "stacked traits" indicates that new genetic forms of GE canola are evolving outside of both cultivation and regulatory oversight. The discovery brought global attention to the issue of commercial production of GE crops. Nevertheless, there has been no subsequent monitoring or clean-up by regulatory agencies or private industry. In 2012, GE canola was still cultivated on more than 90 percent of canola acres in North Dakota (FAOSTAT 2012).

Despite evidence that genetically engineered crops contribute to significant environmental disruption, the industry and its advocates persist in arguing that regulatory protocols should be streamlined for approval of new biotech products (Bourlaug 2000, Fedoroff et al. 2010, Federoff 2011, Giddings et al. 2012): "Despite the excellent safety and efficacy record of GM crops, regulatory policies remain almost as restrictive as they were when GM crops were first introduced" (Federoff et al. 2010). Such appeals for limiting regulatory oversight are premature, however: evidence for the biosafety of most GE crops is scarce and regulatory oversight remains insufficient. Lack of transparency in the risk-assessment process coexists with inadequate regulatory supervision. Given this, it is not surprising that emerging problems in the regulation of GE organisms have not been fully articulated. In this brief, we present three fallacies in the argument for streamlining regulatory approval of new biotech products. These fallacies are:

- Absence of evidence is not evidence of absence
- One problem can be solved by another
- Substantial equivalence is actual equivalence

Absence of evidence is not evidence of absence. Environmental effects of GE crop cultivation, unlike acute economic results, have failed to materialize on a large scale (Federoff et al. 2010). Only a limited number of studies have linked the cultivation of GE crops to possible changes in native communities or ecosystem function. For example, several studies have documented the persistence of transgenic protein products outside the GE organism (Saxena et al. 2002, Zwahlen et al. 2003, Chambers et al. 2010), while others report effects on plant and soil (Watrud et al. 2011). Nonetheless, even under close scrutiny, large-scale effects of GE crops have not been reported (Squire et al. 2003). This absence of evidence, industry and its advocates argue, is confirmation that environmental effects are not taking place. Such an argument entails some dubious assumptions, however. Consider an alternative explanation: that the environmental effects of GE crops are undetected by current approaches or under-reported because monitoring efforts are deficient.

Community and landscape level effects will likely be cumulative and detectable only when they can be distinguished from other complex phenomena in agricultural landscapes, such as effects of herbicide overspray, declines in pollinator abundance and diversity, and climate change. Further, the effects may be taking place below detection levels because effects on soil processes, growth rates of native populations, or the structure of native communities will seldom be acute. Effects on biodiversity may be measurable only after generations of exposure and only when there is a pre-cultivation baseline available for comparison. Moreover, they are most likely to affect remote, sparsely populated areas, and only a small number of scientists are currently monitoring crop-wild boundaries. Evidence that current oversight and monitoring efforts are inadequate is underscored by the previously cited report of GE canola escape in the U.S. In the first year of a USDA-funded study, Schafer et al. (2011) documented the escape from cultivation of GE canola years after gene flow and crop migration

had been reported in the United Kingdom, Denmark, Canada, Australia, Japan and France (Crawley & Brown 1995, Mikkelsen et al. 1996, Pessel et al. 2001, Rieger et al. 2002, Simard et al. 2002, Beckie et al. 2003, Aono et al. 2006, Warwick et al. 2008). In Switzerland, where federal law mandates the eradication of GE products when discovered in the environment, a federal task force seeks out and eliminates escaped plants. Regulatory agencies in the U.S., however, eschew such aggressive action. The long lag time in discovering escapes supports the contention that regulatory and monitoring practices are inadequate for the scale at which GE crops currently are grown. To argue that the absence of evidence is evidence of absence is valid only if adequate monitoring and assessment efforts are in place to identify and track long-term effects of GE crops and their management on natural communities. In short, the lack of reports of environmental effects in the U.S. almost certainly is due to lack of investigating and reporting of such effects.

Substantial equivalence is not actual equivalence. According to current U.S. regulation, if a new food or food component is found to be "substantially equivalent" to an existing food or food component, it can be treated in the same manner with respect to safety (Isham 2006). When deemed "substantially equivalent" to its conventional counterpart, a new GE product requires fewer regulatory steps and reduced scrutiny for approval for commercial production than a novel transgene in a different crop species. Moreover, the concept of "substantial equivalence" carries with it the assumption that existing food sources can be used as a basis for comparison when assessing the safety of GE products (Mayers et al. 2002). The questions of what constitutes "substantial" - that is, what characters are to be evaluated and what represents an adequate basis for comparison - have not yet been satisfactorily challenged in the U.S. Indeed, without clearly established criteria for evaluating "substantial" or what characters must be considered "equivalent," any degree of equivalence may capriciously be labeled "substantial."

Selection of a conventional crop variety as a standard of comparison for GE products unduly limits the scope of risk assessment to the effects of the transgene itself. This procedure has already created an unfortunate reputation for U.S. regulatory agencies. A case in point is LL601, an experimental rice cultivar that carries a transgene for glyphosate herbicide resistance. LL601 was grown in field trials in several U.S. states from 1998 to 2001 until the owner of the product, Bayer CropScience, decided against further commercial development (Vogel 2006). In 2006, however, evidence of LL601 contamination was discovered in rice stores in Missouri and Arkansas. Soon after this was made public, LL601 contamination was reported in Sweden, France and Germany. In response, the European Union, Japan and South Korea banned imports of U.S. rice. On the very day that the contamination came to public notice, Bayer CropScience applied to the U.S. Department of Agriculture for retroactive approval of LL601 for commercial distribution. The USDA responded with a risk assessment from which it concluded that the appropriate decision was to approve the variety based on "substantial equivalence" to a non-GM rice cultivar and a transgene already approved for use in the human food supply (APHIS/USDA 2006). Thus a new transgenic product was approved by the USDA after it had contaminated rice stores intended for humans because it was deemed "substantially equivalent" to approved products. The criterion of "substantial equivalence," especially when a judgment is made after release, cuts short regulatory review and provokes mistrust and suspicion of the regulatory process. The case of LL601 suggests that the USDA acted less as a regulatory agency than as an institution poised to approve whatever a corporation placed before it.

In addition to its conceptual inadequacy, the notion of "substantial equivalence" fails to acknowledge that management of new GE varieties may differ fundamentally from conventional

crops. The clearest example is the management of GE herbicide resistant varieties for which the costs of transformation for herbicide resistance are recouped only when crop fields are sprayed with herbicide. From 1996 to 2011, the cultivation of herbicide resistant crops increased from 12 million to 160 million hectares worldwide (FAOSTAT 2012). Increased herbicide use is now linked to the rapid evolution of herbicide-resistant weeds (Powles 2008, Heap 2012). In addition, the mounting use of herbicide poses threats to native vegetation, neighboring crops, and open water sources, especially when recalcitrant herbicides such as 2,4-D (2,4-Dichlorophenoxyacetic acid) are part of the package. The vertical integration of seed source with herbicide use carries additional risks linked to herbicide application for conventional crops. Application of herbicide should therefore be incorporated into the risk assessment of herbicide-resistant GE products. Operating under the rubric of "substantial equivalence", then, fails to acknowledge the full risks of the GE product and creates vulnerability in risk assessment protocol.

One problem cannot be solved by another. GE organisms increasingly involve individual plants expressing multiple transgenic traits. For example, in response to the evolution of herbicide-resistant weeds, multiple herbicide-resistances are now "stacked" in single plants. Stacking allows farmers to treat crop fields with a cocktail of herbicides that can effectively eliminate those weedy plants that have evolved resistance. Similarly, stacking pest resistances with a family of Bt cry transgenes makes a single variety resistant to a suite of harmful insects. Multiple pesticides will only delay the evolution of Bt resistance; resistance to herbicides and pesticides evolves quickly in organisms with short generation times. Stacking multiple resistances therefore will merely delay the evolution of more resistant plants and insects. Under strong selection and with gene flow, novel combinations of resistances evolve rapidly. The spontaneous evolution of multiple resistances has already been demonstrated in feral canola populations (Knispel et al. 2008, Schafer et al. 2011). Release of commercial varieties with multiple beneficial transgenes will create even greater problems for weed and pest control. Products like SmartStax corn, which carries eight transgenes for resistance to herbicides and insects, has been released in the U.S. The risks of releasing multiple, effective resistance to all families of pesticides poses a serious threat to agricultural productivity when nearly every major crop can hybridize with a native species in its geographic distribution (Ellstrand et al. 1999). Plants bearing stacked traits demand more careful scrutiny that any single transgene inasmuch as risks of escape pose problematic issues whose resolution will be costly to the individual farmer as well as to society as a whole.

The three fallacies detailed above reveal their pernicious consequences when placed in the nexus between commercial enterprise and public policy. It is a truism of both economics and cognitive science that perceived advantage, such as commercial profit or self-aggrandizement, almost always trumps objectivity. Profit is one of the most potent incentives known to man; but the profit motive does not inevitably align incentives in a socially desirable way. Ever since the Progressive Era (1890s to 1920s), the federal government has created regulatory agencies to oversee finance, medicine, schooling, and industry as a consequence of the recognition that the public must be protected by private or corporate interests seeking profit. The case of GE commodities should be treated in the same, well-tried fashion.

Corporations argue that making public the details of the GE organism, that is, the transgene sequence, its promoter, and its protein product, would expose them to exploitation. They argue that the GE organism represents confidential information, a source of deserved revenue.

To protect commercial interests, regulatory agencies allow the corporation to complete a suite of toxicology studies and report their findings in confidence to the regulating agency. In the previously mentioned case of widespread contamination by LL601 rice, 40 percent of the industry-generated risk assessment data were judged “confidential business information” and not available to the public--even after it had contaminated the food-supply chain (Clapp 2008). In the U.S., independent risk assessment by academic researchers or even federal regulatory agencies such as the U.S. Environmental Protection Agency (US EPA) is prohibited without a Memorandum of Understanding (MOU) that must be negotiated with the corporation. The MOU is developed after corporate review of the research plan of the submitting agency and is signed by both parties. As a result, the corporation regulates who has freedom to operate with the GM organism in question. In short, pre-release risk assessment is done by profit-seeking corporations; review by outside scientists or by federal regulatory agencies is fatally restricted. Clearly, there is a conflict of interest when a corporation assesses the risks of a GE organism from which it will profit. Bringing GE products to the approval stage typically costs tens of millions of dollars (Isham 2006). With so much at stake, it is surely not advisable to expect a corporation responsibly to evaluate potential risks. Independent investigation by the public sector is the only guarantee that the effects of a transgene product will be effectively assessed within the context of public policy (NAS 2002).

Conclusion

The concerns spelled out in reports by the Ecological Society of America (2005) and the National Academy of Science (2005) are clear: prudence is warranted and existing regulatory policies are inadequate to prevent harmful release of genetically engineered organisms. Crops already recognized as problematic have been approved for engineering and release. Alfalfa (*Medicago sativa*) is known to grow outside of cultivation (Bagavathiannan et al. 2010), yet a cultivar engineered for herbicide resistance recently was cleared for release in the U.S. SmartStax corn, which is widely distributed, contains eight unique transgenes that confer resistance to multiple herbicides and herbivores. Similarly, corn with multiple resistances to herbicides, glyphosate and 2,4-D has been approved for production despite the long half-life of 2,4-D and its toxicity to pollinators (Zepp et al. 1975).

In a larger perspective, agronomists, ecologists and conservationists recognize that herbicide-resistant weeds are evolving rapidly following the release of glyphosate and glufosinate resistant GE crop cultivation. Yet GE cultivars with resistance to multiple environmental challenges have been approved for release in the U.S. In contrast, countries from Sweden to South Korea have taken action based on the precautionary principle; but the latter is rarely cited in U.S. courts (Foster et al. 2000) and regulatory oversight accordingly has slackened across the board.

The stakes at issue can hardly be exaggerated. Sustainable agriculture, land management, crop production, indigenous cultures, food security, dietary regimes, and public health are all potentially at risk as GE crops gradually expand around the world. GE organisms now flourish in all arable ecosystems, In the near future, without appropriate restriction, they will surely prosper in the cultivated fields of all nations. They have gained a secure global foothold in 160 million hectares—an area the size of the subcontinent of India—and can look forward to overrunning the remaining 13.4 billion hectares of the planet in the future. Furthermore, when the balance tips in that remote prospect, and GE crops come to dominate, a return to the *status quo ante* will be impossible. We will all live under a radically altered botanical regime.

To be sure, some of these GE products may confer immense benefits on humanity; but others, as research already confirms, decidedly will not. This is an argument to err on the side of

caution. “First do no harm”—the equivalent in medicine to the precautionary principle in scientific research, is a standard that researchers, corporations, regulatory agencies, and governments would do well to adopt in considering the future of GE products. The Cartagena Protocol should guide future action: “Where there is uncertainty as to the existence or extent of risks to human health, the institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent” (Rio 1992).

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