Review

Environmental protection: applying the precautionary principle and proactive regulation to biotechnology

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Biotechnology is a broad field encompassing diverse disciplines from agriculture to zoology. Advances in research are occurring at a rapid pace, and applications that have broad implications socially, economically, ecologically and politically are emerging. Along with notable benefits, environmental consequences that affect core quality-of-life issues for present and future generations are materializing. The precautionary principle should be applied to biotechnology research, activities and products, and a strengthened, enforceable and proactive regulatory framework is needed. The environmental impacts of agriculture, aquaculture, genetically modified organisms (GMOs) and even pharmaceuticals are raising public concerns and demonstrate the need for guidance from a variety of social, economic and scientific disciplines to insure the benefits of biotechnology are enjoyed without unacceptable and irreversible environmental costs.

> If science cannot lead us to wisdom, as well as power,
> it is surely no science at all.
> Aldo Leopold, *Ecology and Politics*, 1941

Introduction

Biotechnology is a diverse field that uses organisms and biological processes to produce goods and services. Four subdisciplines have recently emerged, including Blue (involving marine and aquatic species and processes), Green (agriculture and environmental applications), Red (relating to medical and pharmaceutical activities) and White or Grey (involving industrial processes). Rapid progress is being made in all of these areas of biotechnology, yielding numerous applications and products beneficial to society, yet also of environmental concern. The rate of biotechnological advances is far outstripping the ability of policy, regulatory authority and enforcement to keep up, setting the stage for serious environmental consequences that might be irreversible and hard to contain.

Biotechnology encompasses activities that both use and affect biological systems at levels from the cell to the biosphere. For example, genetically modified (GM) plants have been developed with increased resistance to insects and herbicides, yet concerns have been raised about consequences for populations of beneficial insects, the potential for allergic reactions in human consumers to novel proteins and hybridization with other plants leading to 'superweeds' [1]. A variety of pharmaceuticals that treat human health disorders are now showing up in drinking water supplies at levels considered therapeutic for children and are affecting segments of the population for which exposure was unintended. Fish cultivated in high densities from farmed stock are having genetic consequences for natural populations and have been the identified source of parasitic infections affecting wild stocks. In these three cases, the products and processes of biotechnology either have had or present the potential for widespread and persistent environmental consequences and impacts.

Increases in the volume of international exports and imports and the expansion of international trade agreements and relationships have also greatly increased the distribution of biotechnology products, the spread of GM organisms (GMOs) and opportunities for pathogen dispersal [1,2]. Additionally, the full environmental impacts of biotechnology might not be fully understood for decades (e.g. hybridization between wild and GM plants).

There are three areas in which biotechnology can have environmental consequences: (i) during research and development activities; (ii) during the application of biotechnological processes; and (iii) from the products produced by biotechnology. Pressures from industry, medicine, academia and government are acting to push biotechnology forward, and there is a need for balance to ensure outcomes do not create unacceptable risks and problems. The challenge is to develop a regulatory framework that allows innovation to occur with effective checks-and-balances to prevent serious and possibly irreversible problems. In this article, I discuss several issues relevant to biotechnology and the environment, with examples of what can and has happened when longer term concerns have been ignored for expediency or when benefits to one sector of society have overridden concerns for the costs to another.

The precautionary principle, Type I and II statistical error and uncertainty

Biotechnology is a field in which the application of the precautionary principle is critically needed. The precautionary principle states that if an activity has the potential for causing harm, appropriate steps must be taken to prevent damaging consequences, and any potential risks need to be addressed even in the absence of scientific

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certainty that problems will occur [3]. This approach requires acceptable proofs that harm will not occur prior to approval or implementation of an activity or distribution of products. Requests for concurrent review, that is, an evaluation while a project or program proceeds, assumes that if (once) a problem occurs, it is possible to undo any harm. This was Pandora's error when she peeked into her infamous box. In a more modern context, brakes only work if applied before driving over a cliff, not on the way down. The precautionary approach has too often been ignored by those with narrow vision or specific, usually short-term, financial interests that are in conflict with long-term environmental protection and sustainability. Although bureaucratic inertia can be a frustrating impediment to rapid progress, expediency can result in catastrophic consequences if appropriate concerns are not thoroughly addressed. The need to understand and weigh risks can be further explained through statistics as a framework for decision-making.

There are two general categories of statistical errors: rejecting a true hypothesis (Type I) and accepting a false hypothesis (Type II). For example, if a gun is lying on a table, and there are no data to determine if it is loaded or not, the precautionary principle dictates that all guns be considered loaded unless proven otherwise. The alternative approach (often used in environmental considerations) is that everything is safe until proven otherwise. If the gun was empty, but I accepted the false hypothesis that it was loaded, I am guilty of Type II statistical error. If the gun was indeed loaded, and someone assumed the gun was empty, they would be guilty of Type I error, by rejecting the true hypothesis and, in the course of pulling the trigger, might also be guilty of murder. Substitute the open cultivation of a transgenic plant or the release of a pathogen for biological control of a pest with the aforementioned gun, and the scenario for disaster is clear. The lack of data demonstrating something is harmful does not default to its being safe; rather, the accurate conclusion is one of insufficient data to make a determination.

Within the context of biotechnology, the genetic modification of plants and animals has great potential to affect ecosystems through hybridization and genetic leakage with associated concerns for the homogenization of genotypes and the loss of biodiversity. The development of terminator genes that make F_2 (second) generations sterile is a measure being developed to contain GMOs, yet such genes might also become an issue in the future if they enter wild populations. Restricting the rearing of transgenic plants and animals to enclosed greenhouses and other containment facilities with strict protective measures is one option for applying the precautionary principle and minimizing the chances of a serious mishap.

Uncertainty is an element of virtually all scientific research, including disciplines of biotechnology, and establishing acceptable thresholds for statistical error is another approach for addressing potential environmental impacts. The usual research standards applied to statistical significance are $p \leq 0.05$ or $p \leq 0.01$, which mean a 95% or 99% probability, respectively, that the observed outcomes were not due to chance but were the result of the specific elements of an experiment or test. Rarely are such standards used within the framework of risk or environmental impact assessments. Often, uncertainty is addressed and expressed qualitatively rather than quantitatively. An entire industry, aptly titled 'manufactured uncertainty', has evolved (e.g. surrounding the health effects of smoking) using scientific arguments to obfuscate rather than clarify and to delay decisions that could avoid undesirable consequences. A number of companies involved in agricultural biotechnology and/or transgenic research, as well as federal agencies, have applied such techniques to delay regulatory actions and the application of the precautionary principle [4]. For example, concerns about the development of 'superweeds' resulting from hybridization between wild populations of plants and transgenic crops with a gene for herbicide resistance or the effects of Bt (*Bacillus thuringiensis*) corn pollen on populations of non-target insects did not prevent the open field planting of transgenic crops in the absence of data that proved the absence of potential detrimental effects [5]. Environmental safety should be treated at least as seriously as publication in a peer-reviewed journal, and the 'wait-and-see' approach is insufficient. Establishing standards (e.g. 80% probability of no detrimental effects) based on (i) asking the right questions and (ii) an acceptable experimental design is an approach that could serve to reduce risk and provide policy makers and the public with a better understanding of the potential for future problems.

Pathogens and the environment

Pathogens are biological agents of disease and include bacteria, viruses, protozoa, fungi, parasites and certain proteins (e.g. prions). These are naturally occurring and can be cultured in the laboratory for a variety of uses. Biotechnology has been used to develop pathogens for the biological control of pests and diseases, and benefits include the reduction or elimination of the use of synthetic pesticides and antibiotics that have a history of negative environmental, human health and ecological effects. However, research on the production and application of pathogens is a double-edged sword, with both benefits and risks involved. For example, plants, unlike most animals, do not possess an active immune system but depend instead on an innate system of defense [6]. One line of biotechnology research has produced crop cultivars with pathogen- or transgenic-derived resistance that are free from susceptibility to particular viral disease strains (http://www.apsnet.org/online/feature/papaya/Top.html) [7]. The same research designed to protect plants could also be used to destroy them. In a world where terrorism (including bioterrorism) is of increasing concern, strict measures need to be in place to prevent a planned or accidental catastrophe (http://www.cissm.umd.edu/projects/pathogens.php). The US National Institutes of Health (http://www4.od.nih.gov/oba/), the US Occupational Health and Safety Administration and the US Department of Homeland Security all have active programs and guidelines that address protocols, procedures and security issues, but experience has shown that the pace of research consistently surpasses the ability of policy, regulations and enforcement to keep up [5,8].

The development and/or application of pathogens for controlling pests raises the same concerns that are associated with a variety of organochlorine and organophosphate pesticides: mobility, effects on non-target organisms and persistence [9]. The outcomes of pathogen transfer can affect human health, ecological stability and biodiversity. Agriculture, aquaculture and biomedical research are among the fields in which pathogens are a considerable concern, along with the environmental effects of chemicals used to prevent or control pathogen outbreaks.

Biotechnology applications and industries

Aquaculture

Aquaculture is a multibillion dollar industry producing commercially valuable fish, crustacean and algal species. Aquaculture has raised a number of environmental concerns, especially in association with cage culture activities. In response, the US Task Force on Marine Aquaculture recommended strict environmental guidelines and controls be put into place before permits are granted for offshore marine aquaculture in US waters [10,11]. The National Offshore Aquaculture Act of 2007 was drafted to provide the US National Oceanic and Atmospheric Administration with the authority to regulate such activities; however, the effectiveness of the proposed law is being challenged for a number of reasons, including deficiencies in the environmental review process and in the enforcement, sanction and liability provisions (http://www.foodandwaterwatch.org/fish/fish-seafood/fish-farming/problems/OOA-bill-2007).

Concerns surrounding fish cage culture include the escape of cultivated stock, the spread of diseases and impacts associated with hormones and wastes. Nutrient levels from fecal material and uneaten feed can lead to eutrophication of coastal waters [12]. Antibiotics and antibiotic-laced feeds can alter the microbiology of sediments, affecting infaunal populations of organisms responsible for xenobiotic detoxification, bioturbation and oxygenation of bottom sediments, leading to anoxia and the production of reactive sulfides that can cause oxidative stress to benthic and pelagic organisms when stirred up. Lice from cultivated, caged salmon were found to be a source of parasites to wild stocks and induced 9–95% mortality in several sympatric wild populations [13]. Fish cages were a source of pollution in the Gulf of Eilat, and the Israel Ministry of Environmental Protection recently upheld a 2005 decision requiring that the cages must be removed by June 2008 and that any further aquaculture activities must be moved into tanks on land. Land-based aquaculture facilities are easier to manage for unwanted introductions, pollution and the contamination of wild populations[*].

Pathogens (e.g. white spot syndrome) from shrimp farms have led to the requirement for quarantine measures when transporting brood stock, and a number of viruses have been found that can effect other crustaceans as well [14]. Shrimp aquaculture also has had ecosystem-level impacts. The 'reclamation' of mangrove swamps for shrimp ponds in coastal Central and South America led to the loss of critical ecological services, including the filtering out of sediments and nutrients from terrigenous runoff, which has affected the health of coastal coral reefs and associated marine ecosystems. Habitat destruction can be both a direct and indirect consequence of coastal aquaculture activities.

Figure 1. The introduced alga *Eucheuma denticulatum* overgrowing a coral patch reef in Kaneohe Bay. Reproduced courtesy of Dr Jennifer Smith.

Research on the cultivation of commercially valuable algae has also had ecosystem-level impacts in Hawaii and other parts of the world [2]. Species of algae were imported and cultivated because of their content of carageenan, a compound widely used as an emulsifying, thickening or stabilizing agent for food products (e.g. ice cream) and some pharmaceuticals. The fleshy algae *Kappaphycus alvarezii* and *Eucheuma denticulatum* have become major causes of coral reef habitat loss after their release into the wild. These invasive algae out-compete indigenous species and have been responsible for ecosystem-level phase shifts by overgrowing corals and inhibiting benthic invertebrate larval recruitment (Figure 1) [15].

Agriculture

Agricultural applications are among the most rapidly expanding and advancing uses of biotechnology research, with both benefits and concerns at the forefront of policy discussions. GM plants can cut down on the use of chemical pesticides that have had well-documented environmental impacts. However, the environmental consequences of the open field cultivation of GM plants has not been fully evaluated, and the potential for hybridization between non-GM plants and pest- and herbicide-resistant strains already under cultivation are simply not known. The effects of genetic homogenization are also a concern for biodiversity because of the potential loss of both wild and cultivated genotypes. Although efforts are underway to bank seeds as a hedge against these potential losses, it will be impossible to effectively protect existing biodiversity by this means. The effects of pesticides on a variety of ecologically important non-target organisms were found only years after the approval of their widespread use, and I expect history will repeat itself with some of the GMO applications.

[*] Israel Ministry of Environmental Protection, http://www.sviva.gov.il/bin/en.jsp?enPage=e_BlankPage&enDisplay=view&enDispWhat=Object&enDispWho=News^l3762&enZone=e_news.

The use of organisms as agricultural biological control agents was also developed as an alternative to chemicals and has had mixed results. Numerous examples exist where a plant or animal was introduced for food or agricultural purposes, was subsequently found to be a pest and then efforts at biological control made things worse. The African snail, *Achatina fulica*, was introduced into Hawaii and other Pacific Islands as a potential food item, and it subsequently became a pest on vegetables. Later, a predatory snail (*Euglandina rosea*) and a flatworm were introduced as control agents because no natural predators for *A. fulica* occurred on these islands, but since these secondary introductions were made, several species of indigenous tree snails have been pushed to the verge of extinction partly because of predation by the 'controlling' carnivores released to undo the damage from the initial African snail introduction [16].

Hormones used in agriculture and aquaculture to boost growth rates in cattle and fish have become a concern for the ecosystem and human health. Many ecological interactions in marine, freshwater and terrestrial ecosystems are chemically and hormonally mediated, and key cycles, such as those involved in the reproduction and recruitment of organisms, can be affected by compounds used in agriculture and aquaculture (Box 1). Chemicals and biological agents such as hormones can interfere with key biological functions and environmental cues. Some of these endocrine-disrupting compounds can have widespread and long-term impacts [17,18]. Although many effects might be sublethal to adult organisms, that is, not causing outright mortality, associated decreases in fecundity, growth and fitness can lead to ecological losses at the population, community and ecosystem levels. Hormones used in beef production have been found in streams and ponds receiving runoff from feedlots and pastures. Metabolic wastes from treated animals and leachate from treated feeds can contain hormone residues that enter the environment, and environmental studies are demonstrating broader impacts than originally expected [17].

Endocrine disruptors might enter the environment as a result of a number of biotechnology applications and industries (pharmaceuticals are addressed below). One of the more interesting and concerning effects of endocrine disruptors (compounds also found in plastics, compounds used in biotechnology research and in antifouling biocidal paints) is termed imposex, in which female organisms (e.g. gastropods) take on male characteristics, including the growth of a penis [18]. The expression of female attributes in male organisms has also been observed in response to exposure to endocrine-disrupting compounds, and effects include reductions in fecundity and outright sterility.

Even biotechnology advances in medicine and personal hygiene have recently come under scrutiny. Due to the rapid evolutionary rates of bacteria and other pathogens, new antibiotics are constantly needed to keep up with the challenges of human and animal health. The overuse of antibiotics is believed to have accelerated the evolution of resistant bacterial strains, which are now a major concern for hospital patients[†]. The mass production and distribution of antibiotic hand and bath soaps might also be responsible for increasing episodes of antibiotic-resistant infections [19] and might have impacts extending into nature. The effects of antibiotics on natural microbial communities is poorly studied, despite their potential to alter ecological interactions at the community and ecosystem levels owing to the increasing amounts of compounds released from sources including cattle and swine production and aquaculture. Antibiotic resistance and shifts in microbial community structure, which have resulted in the loss of sensitive species or clades and rapid increases in resistant populations, demonstrate how unexpected outcomes can have broad and widespread effects and highlight the importance of developing guidelines for the use of the products of biotechnology. The environmental fate of ubiquitous antibiotics requires further study.

Pharmaceuticals

The fate of partially metabolized or disposed medications that have been released into the environment has only recently come under scrutiny. Many pharmaceuticals are developed to be persistent in the human body to overcome 'detoxification' by multidrug resistance (MDR) proteins, and they remain active once excreted or released into the environment. Levels of pharmaceuticals in the range of parts per million to parts per billion have been found in municipal drinking water in parts of Europe [20,21] and might be approaching therapeutic levels for children. Pharmaceuticals in streams, rivers and coastal areas, often associated with sewage outfalls, include antidepressants, analgesics and estrogenic compounds from birth control pills [22,23]. Some of these endocrine disruptors have been observed to have effects on organisms, including the pro-

Box 1. Xenobiotics and their effects on invertebrate reproduction

Cycles of reproduction and recruitment in many marine invertebrates and some fish contain a number of chemically mediated steps that are sensitive to the presence of a variety of toxicants and compounds associated with biotechnology, including biocides, antibiotics, hormones, plasticizers, enzyme substrates, heavy metals and pesticides. Many reef-building corals, for example, release their eggs and sperm into the water column during limited yearly spawning events. There are six links in their reproduction chain, and if any of these are broken, it could result in the failure of population replenishment. The links are:

(i) Reproductive synchronization among conspecific colonies during spawning events
(ii) Egg–sperm attraction and interactions leading to fertilization
(iii) Embryological development
(iv) Selection of appropriate settling substrata via chemical cues
(v) Metamorphic induction, often tied to chemical inducers associated with the substratum, preferred prey or conspecifics
(vi) Acquisition of the correct type of symbiotic dinoflagellate algae (zooxanthellae)

Steps (i), (ii), (iii) and (vi) are particularly sensitive to water soluble compounds, and steps (iv) and (v) are sensitive to lipophilic substances. Endocrine disruptors from pharmaceuticals and hormones used in livestock production might also interfere with critical chemical cues and lead to reproductive failure.

[†] US Food and Drug Administration, http://www.fda.gov/oc/opacom/hottopics/anti_resist.html; Centers for Disease Control and Prevention, http://www.cdc.gov/drugresistance/community/.

duction of the protein vitellogenin (an egg protein naturally found only in females) in male fish. Many organisms have hormonal cycles that affect reproduction, and pharmaceuticals discharged into rivers, streams and coastal areas can impact populations of aquatic vertebrates and invertebrates. There is presently no formal regulatory process involved in tracking, controlling or monitoring medications being released into the environment, and only recently have techniques been developed to assay for the presence of these bioactive substances [24]. As more medications are being prescribed to more individuals, the environmental impacts are sure to be of increasing concern in the future.

Biotechnology tools and their applications to environmental protection

Although I have focused on environmental concerns associated with biotechnology, it should be recognized that biotechnology is providing valuable tools supporting environmental protection, notably in the areas of environmental forensics. Research on the application of molecular biomarkers of exposure to physical and chemical stressors has demonstrated that specific proteins are upregulated (or in some cases downregulated) by organisms exposed to toxicants and other stressors, and this research is allowing the determination of cause-and-effect relationships and an understanding of the synergistic effects of multiple stressors. Traditionally, environmental monitoring programs have focused on mortality as the metric of change, tracking the loss of individuals, populations or species. In order for environmental assessment and monitoring programs to be effective, they must be able to detect changes at the sublethal level, prior to mortality, when intervention can yield positive results [25].

Molecular biomarkers of stress can be used to determine causation and the effectiveness of mitigation measures. For example, classes of cytochromes P450 are produced in response to xenobiotic exposure. Other proteins are indicative of oxidative stress (superoxide dismutases), protein metabolic condition (ubiquitin) and genomic integrity (mutY) [26,27]. When used in the context of environmental health assessments, molecular biomarkers allow quantification of responses, both positive and negative. The upregulation of specific protein biomarkers of exposure indicates an organism is undergoing and responding to stress, whereas downregulation can indicate a reduction of stressor impacts and the effectiveness of mitigation activities. As such, biotechnology can be used to guide and evaluate responses to a variety of environmental problems, including pollution and climate change.

Research in the field of population genetics is also providing valuable tools applicable to environmental protection. Studies of species biodiversity have already been used to evaluate the effects of anthropogenic disturbance on ecosystems, but assessing genetic variation within populations is also important. Genetic diversity is the basis of the evolution and survival of species in a changing environment. Tracking the loss or the differential survival of specific genotypes in response to anthropogenic disturbances provides an unprecedented tool for understanding the role of genes and their products in adaptation and homeostatic regulation. For example, regional coral-bleaching events caused by global climate change and the subsequent mass mortality of affected colonies might set the stage for the 'Irish Potato Famine' of these diverse ecosystems because both species and population diversity are lost and few resistant genotypes remain. As genotypic diversity decreases, the chance of local extinction events increases (Box 2). Maintaining genetic diversity within a population is a central problem in the emerging field of restoration biology, because replacing lost plants and animals with cultivated or transplanted individuals representing a single genotype sets the stage for a single pathogen or physical stressor to be able to eradicate the 'restored' populations [28]. Reductions in biodiversity are also a central concern with GMOs, which might hybridize with wild stock and eliminate novel genotypes. Advances in molecular genetics are allowing for a better understanding of gene flow among populations, data that are critical to the establishment of networks of marine protected areas (MPAs) and for identifying corridors for wildlife migration.

Bioremediation is a third area that holds promise for environmental protection. This technology uses bacteria, fungi or plants to convert some organic, inorganic and metal compounds and waste into a less environmentally harmful state [29]. The advantages over traditional remediation techniques include *in situ* treatment versus moving contaminants from one site to another and costs, which might be lower than with more labor-intensive measures. Concerns remain regarding large-scale applications of bioremediation, the longer time periods needed and the potential toxicity problems, because 'breakdown' products might be more toxic or bioactive than the original compounds (e.g. the methylation of mercury by bacteria rendering it bioavailable) [30,31]. To date, several applications of 'designer bacteria' have yielded positive results, for example for cleaning up oil spills, and the potential for future uses in environmental mitigation is under investigation [32,33].

Box 2. Genetic diversity and the Irish Potato Famine

The Irish Potato Famine of the 1840s was attributed to an outbreak of the plant pathogen *Phytophthora infestans*, which destroyed the potato crop, the staple of the Irish economy. The underlying biological lesson is the need for ecological and intraspecific genetic diversity. The selection for one crop and one genotype (monoculture) that did well under the local climatic conditions set the stage for a local extinction when the pathogen outbreak occurred. Genetic diversity is the biological insurance policy for organisms, allowing some genotypes to survive and thrive when others fall prey to physical, biological or chemical stressors in their environment. Genetic bottlenecks caused by anthropogenic stressors superimposed over natural cycles of stress and the loss of novel genotypes by hybridization and genetic homogenization with GMOs set the stage for population loss and species extinction.

Legislative and regulatory issues

A patchwork of laws and authorities regulate biotechnology, leaving sizable gaps in effectiveness. The US presently has three agencies – the Environmental Protection Agency (EPA), the US Department of Agriculture (USDA) and the FDA – that jointly oversee biotechnology under the

Coordinated Framework for Regulation of Biotechnology (http://usbiotechreg.nbii.gov/). An examination of the regulatory framework reveals a strange array of laws that do not directly address many of the aspects of biotechnology that are of greatest environmental concern. For example, the EPAs regulatory role is based on the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetics Act as amended by the Food Quality Protection Act of 1996 (http://www.epa.gov/opp00001/biopesticides/reg_of_biotech/eparegofbiotech.htm). Biotechnology is a dynamic field, and existing legislation, much of which is over a decade old, simply does not address or provide adequate protection for environmental and human health in the context of the rapid advances that are taking place.

A key piece of legislation, the US National Environmental Policy Act, was passed into law by the US Congress in 1970[‡]. The law includes a process for assessing potential environmental consequences of activities through the development of an Environmental Impact Assessment (EIA) and, if deemed necessary, a more detailed Environmental Impact Statement (EIS). Unfortunately, the assessment and review process is flawed by allowing conflicts-of-interest between consultants performing the studies and the companies or industries paying for the work, often compromising objectivity and accuracy. Consultants often use an 'absence of proof' argument regarding possible environmental impacts and neglect to address potential environmental consequences rather than admit that sufficient and relevant data simply do not exist. The responsibility for reviewing EIAs and EISs often falls to government agencies that might lack the appropriate human resources to provide an adequate and accurate review, and there is often political pressure on government administrators from industry and the private sector to push for quick approval of permits for expediency, ignoring future consequences.

Funds would need to be provided up-front by industry to help support regulatory review and oversight of their proposals and for monitoring their activities once underway. Federal agencies should be required to engage independent, qualified, third-party reviewers without conflicts-of-interest in the review process (similar to peer-review for the scientific literature) through neutral parties such as the National Academies of Science. Although each of the three collaborating regulatory agencies has highly qualified scientists on staff, their guidance can be (and has been) overridden by politically appointed administrators lacking appropriate expertise, with little recourse. Approval of activities and associated permits should never be the default action taken when there are insufficient data to draw definitive conclusions. The burden of proof needs to be reversed in the environmental review process to ensure those wishing to pursue an activity with potential environmental consequences provide adequate and accurate data demonstrating that their activities will do no harm, with both enforceable financial and civil penalties applied should any damage occur. History has shown a lack of adherence to the precautionary principle by the federal regulatory agencies, with numerous instances of pesticides (DDT), drugs (thalidomide, Vioxx) and food items being recalled or removed from the marketplace after problems surfaced, environmental damages occurred and/or individuals died [34,35]. Many of these agencies' regulations are directed towards permitting activities rather than preventing environmental damage, and there is substantial influence by industry in their permit review and approval processes and protocols. A broader, updated and unified biotechnology law is needed that would include the application of the precautionary principle for specific types of activities and, as an additional means of encouraging a precautionary approach, a requirement for posting bonds of an appropriate value for mitigation and response should problems occur.

Recent attempts at overhauling biotechnology legislation have largely been focused on agriculture and specifically on GM crops. Two issues are mainly addressed: (i) potential human health effects of GM crops and (ii) the ecological effects of gene flow between GM plants and natural populations (http://www.pewagbiotech.org). The Pew Initiative on Food and Biotechnology reports that 134 bills were introduced by US state legislators during the 2005–2006 sessions (http://www.pewagbiotech.org). Nearly a third of these bills were pre-emptive, that is, they proposed to prevent localities from regulating agricultural biotechnology, arguing that such local laws might pre-empt statewide legislation for the cultivation or control of GM crops. This confirms that while research and applications, including open field cultivation of GM crops, are fully underway, policy and legislation remain in the developmental stages.

A blast from the past – putting risk into perspective

There have been no documented major disasters resulting from biotechnology research and applications to date, although the topic is a common theme in science fiction books and movies (note: history has shown that science fiction writers have demonstrated a high degree of prescience in the past). However, there are lessons to be learned from other branches of technology, which I believe are relevant to disciplines of biotechnology, especially in instances involving the use of pathogens and GMOs. The impacts of disregarding the precautionary principle and not adequately planning for unforeseen outcomes can be seen in the nuclear research and testing programs carried out by the US during the 1940s and 1950s [36]. Radiation biology research and nuclear testing are good proxies for biotechnology involving pathogens and genetic modifications that are not visible to the naked eye and that can be widely dispersed unknowingly. The byproducts of the nuclear weapons tests were not restricted to the atolls on which they were carried out and were later found to have reached around the world as particles from the larger tests entered into the stratosphere [37]. Subsequent studies in areas as remote as the artic tundra found that bioaccumulation of radionuclides occurred in a variety of flora and fauna. The nuclear experience provides lessons for open space agriculture using transgenic crops, because

[‡] 'The purposes of this Act include: To declare a national policy which will encourage productive and enjoyable harmony between man and his environment; to promote efforts which will prevent or eliminate damage to the environment and biosphere and stimulate the health and welfare of man' (www.nepa.gov/nepa/regs/nepa/nepaeqia.htm).

dispersion, persistence and impacts on biodiversity are of serious concern. Biotechnology has not yet had an incident resulting in such dramatic and far-reaching environmental impacts, which is a strong argument in support of stringent precautionary protections.

Recommendations for interdisciplinary guidance and communications

There are environmental, economic, social and ethical concerns surrounding biotechnology research and applications that often lead to strong public reactions and resistance because inadequate information is available on long-term consequences. A series of articles and communications in the journal *Nature* provide a striking example of the financial stakes, competing interests, fears, professional conflicts and level of passionate discourse surrounding biotechnology research and applications, specifically involving transgenic crops. A paper published in *Nature* in November 2001 [38] reporting that transgenic DNA had introgressed into corn being cultivated in Mexico resulted in 16 additional *Nature* articles and communications over the following four years (i) refuting this finding, (ii) supporting the key result, (iii) challenging the integrity of the researchers on both sides of the controversy, (iv) following the denial, appeal and granting of tenure for one of the authors of the original paper, (v) tracking some of the media attacks to a public relations firm's computer and (vi) challenging ties between industry and academia [39–43]. The series of articles provides an exemplary case history worthy of inclusion in university courses on the issues of science, ethics and biotechnology and is suggested reading for a broad audience. The presentations and exchanges provide insight into the overlapping and competing interests involved in biotechnology and highlight the need for an effective framework for guiding and regulating the field. In order for policy makers to be meaningfully involved, there are some underlying issues that also need to be addressed.

Scientific disciplines are jargon rich, and although the use of specialized vocabularies might be helpful in communicating with colleagues, it forms a barrier in communicating important ideas to managers, policy makers and stakeholders. People have an inherent fear of the unknown, and efforts to provide adequate and accurate information in clear terms supports a framework for sound decision making. Science has the greatest value to society when it is understood, appreciated and appropriately applied. In order for this to occur, scientists need to do a better job of explaining research and outcomes, concerns, costs and benefits and the degree of certainty based on the best available science.

Cost–benefit analyses that address long-term concerns are needed for the guidance of biotechnology and policy decisions, and costs to all segments of society and the environment need to be clearly stated and understood. History's lessons prove that prevention of environmental problems, from pollution (e.g. attempts to clean up Superfund sites: see http://www.epa.gov/superfund/) to control of invasive species, is far more practical and cost-effective than mitigation after any damage. Whereas biotechnology has been expanding at an ever accelerating pace, advances in human foresight, wisdom and resulting policies have not kept up. In mythology, the last 'bug' to be set free from Pandora's Box, after a thoughtful delay, was hope. As a researcher, spouse, parent and beneficiary of biotechnology, I (and I believe most people) hope that biotechnology will be able to advance without an overly constraining regulatory system, but one guided by adequate checks and balances. The state of the environment is a legacy we leave for future generations, and a focus on long-term environmental impacts and costs of activities is critically important. This remains a great challenge under political leadership systems based on short-term electoral cycles that often overlook the longer term future consequences of our present activities [44].

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