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The true meaning of 'exotic species' as a model for genetically engineered organisms

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Abstract. The exotic or non-indigenous species model for deliberately introduced genetically engineered organisms (GEOs) has often been misunderstood or misrepresented. Yet proper comparisons of ecologically competent GEOs to the patterns of adaptation of introduced species have been highly useful among scientists in attempting to determine how to apply biological theory to specific GEO risk issues, and in attempting to define the probabilities and scale of ecological risks with GEOs. In truth, the model predicts that most projects may be environmentally *safe*, but a significant minority may be very risky.

The model includes a history of institutional follies that also should remind workers of the danger of oversimplifying biological issues, and warn against repeating the sorts of professional misjudgments that have too often been made in introducing organisms to new settings.

We once expected that the non-indigenous species model would be refined by more analysis of species eruptions, ecological genetics, and the biology of select GEOs themselves, as outlined. But there has been political resistance to the effective regulation of GEOs, and a bureaucratic tendency to focus research agendas on narrow data collection. Thus there has been too little promotion by responsible agencies of studies to provide the broad conceptual base for truly science-based regulation. In its presently unrefined state, the non-indigenous species comparison would overestimate the risks of GEOs if it were (mis)applied to genetically disrupted, ecologically crippled GEOs, but in some cases of wild-type organisms with novel engineered traits, it could greatly underestimate the risks. Further analysis is urgently needed.

Key words. Ecological theory; environmental safety; exotic species; genetic engineering; introduced species; recombinant DNA; risk analysis.

Background

The use of 'exotic' (non-indigenous) species as a model for genetically engineered organisms (GEOs) should be understood in historical context.

The era of biohazard fears

Public images of the potential hazards of genetically engineered organisms (GEOs) have never been entirely liberated from polemics of the highly polarized and highly publicized debate in the 1970s[2,7,9,12,20,24]. The popular press then used elements of science fiction disasters such as the Andromeda strain or giant ants to paint amusing or sensationalistic models for the misbehavior of GEOs. Those who strongly argued for the safety of genetically engineered organisms reacted by proposing a variety of comfortably familiar and soothing models to argue that genetic engineering will always, *generically*, be safe[4,7,20,21]. These 'generic safety' models pictured organisms ranging from those that had been ecologically crippled by generations of selective breeding during the domestication process (the 'domesticated species model'), such as corn and yoghurt, to ordinary species that routinely recombine 'genes' (alleles) in every successful sexual act (the 'ordinary sexual species model').

Indeed, until the mid-1980s, most or all of the research was being done on organisms that were genetically highly specialized for laboratory conditions, therefore the 'domesticated species model' seemed suitable for the material at hand. Genetic engineers had become used to the delicate, ecologically crippled GEOs in their test-tubes, and more and more were feeling that they had overreacted to the scientific uncertainties in the 1970s. (Yet there are a variety of problems with extrapolating from the laboratory record of safety, and I have itemized them elsewhere[24,25].)

One reason for the overreaction is thought by some to have been that no ecologists were involved in the discussions of the 1970s[4,9]. I agree. My recollection is that most of my ecologist colleagues felt that the so-called 'biohazard' fear was naive, and they did not care to become involved. It seemed contrary to ecological principles that an arbitrary genetically crippled laboratory organism could accidentally escape the laboratory and become an Andromeda strain that would wipe out all human life.

The rise and fall of generic safety models

The growing feeling that there had been an overreaction led to an attitude that genetic engineering indeed would *always*, generically, be safe as some had long argued.

The one exception was found in cases where the engineered host organisms were pathogenic to begin with, or when genes critical to pathogenesis were transferred. This attitude of generic safety (for non-pathogens) evolved into a consensus among the leadership in biotechnology by the early 1980s even though there had been no systematic analysis or experimental tests of the generic safety arguments. Nevertheless, the generic safety models were rapidly gaining political importance among science policy makers. Thus the trend in the leadership in molecular biology and in some agencies in Washington such as NIH and FDA in the early 1980s was to deregulate all genetic engineering that did not involve pathogens[12].

Professional ecologists were not involved in the earlier improbable 'biohazard' debate of the 1970s, in which there were fears that an ecologically crippled GEO might somehow escape laboratory confinement and turn out to be the fiercest ecological competitor that the world had ever known. Such fears seemed strongly contrary to ecological principles. Clifford Grobstein[9] is among those who have pointed out that by focusing discussions on worst-case scenarios which nearly any biologist could agree were improbable, the leadership won the day for biotechnology, but in effect prevented serious analysis of an array of more realistic concerns. In the case of ecological risks, my own memory is that the focus of publicity on sensationalistic 'biohazard' issues of escape/global-disaster did indeed distract ecologists and evolutionary biologists from taking a serious interest in the issue.

From the late 1970s through early 1980s much publicity was given to the responsible development of ultra-crippled laboratory strains of experimental organisms, at the same time that much biotech research was being conducted in secrecy out of fear of journalistic sensationalism and because of an unfamiliar philosophy of industrial confidentiality that was growing as commercial ties spread among biologists. The combination of highly selective publicity, with a secrecy that most university scientists did not realize the scope of, left most academic ecologists with the erroneous impression that genetic engineers might *never* be able to make GEOs that could live in nature without human support.

That impression began to change by 1983 or 1984, as the true progress of biotechnology became more public. It became clear that it soon would be possible to engineer GEOs intended to establish self-sustaining populations in nature. It was also learned that the leadership for biotechnology was assuming that it would be safe to release ecologically competitive GEOs into the environment, on the basis of generic safety models that had been used for ecologically crippled laboratory organisms – thus raising the so-called 'deliberate release' or 'deliberate introduction' controversy. (Some argue that the conventional term 'deliberate release' implies that any GEO population may *necessarily* go out of control, and thus is inflamatory. The term 'introduction' may avoid giving this erroneous impression.)

Analysis of the generic safety models then revealed serious conceptual flaws[3,20,21]. They were based on badly outdated ecological theory, and they surely could not be applied to GEOs that were designed to be vigorous in nature, and that in some cases might gain significant ecological advantages from specific types of genetic novelty. For example, adding super-potent defensive traits against insects and viruses to an already vigorous forage grass could possibly cause it to become an especially nasty weed. This genetic modification would be completely different, in terms of enhancing ecological competitiveness, from adding ecologically irrelevant genes, such as human insulin to corn, which is basically an ecological cripple to begin with.

Why are so many domesticated organisms ecological cripples?

In the process of centuries of breeding corn for highly specialized features and growing conditions, the genetic basis for many ecologically important traits has been lost, such as resistance to various diseases. The forms of genes, alleles, that may be desired and favored by breeders, may have ecologically inferior pleiotropic and epistatic effects to those wild-types which are lost during artificial selection.

The distinction between genes and alleles is significant. An allele is a variant of a gene, and many (polymorphic) genes have a variety of alleles. The distinction is so often misunderstood even by many biologists and molecular geneticists that it is too common to refer to, for example, 'the genes for blue and brown eyes', when it would be correct to say 'the alleles'. Sexual reproduction and conventional domestic breeding typically *substitute alleles*, and do not 'add genes'. Though sometimes new genes may be introduced with 'wide hybridization', this is a relatively recent practice and is in any event restricted to fairly closely related species.

On the other hand, modern molecular techniques permit one to create quite novel combinations of genes and combinations of *major* traits, and not simply substitutions of alleles and manipulation of *minor* traits as is the case in traditional breeding over thousands and hundreds of years with its costs in terms of the frequent loss of wild-type genes and disruption of pleiotropic and epistatic balances. For example, genes from fireflies have been placed in tobacco plants artificially; ordinary sexual reproduction and domestication are clearly not appropriate models for this sort of genetic manipulation.

Sometimes artificial selection also actively breeds out certain phenotypic features. For example, humans have bred corn seed to stay on the cob, while in nature the seeds should be shed for dispersal, and should not be large, tender and vulnerable to pests.

Other reasons for genetic crippling relate to the fact that often there has been selection for the very narrow ecological conditions in the field, or culture vats (as with yogurt, beers, etc.) and thus some organisms cannot live outside of these conditions.

A third potential factor, that may be too easily overrated, is inbreeding depression.

The loss of wild-type traits in many domesticated plants is one reason that seed-banks, or germ-plasm banks have been set up around the world.

Not all domesticated forms are ecological cripples

Of course, not all agricultural organisms are so genetically crippled as are corn and some other row-crop plants, where agricultural improvement has been gained by substituting alleles that are ecologically debilitating. The term 'domesticated' simply means to bring into the house, or to bring within the sphere of human use. It does not in itself have any biological or genetic predictive power. Thus the 'domesticated species model' will not even apply to all 'domesticated' species, although surely it applies to some. Forage crops, for example, can be rather unhandicapped in their ecological functions; and many projected genetic engineering projects aim moreover to release non-crop species for forestry, fisheries, bioremediation, biocides, etc.

Genetic engineering is not itself necessarily crippling

A key reason why some believed that the 'safety' models should be applied generically and not simply conditionally to GEOs was the notion that one way or another the genetic engineering process would in and of itself necessarily produce ecologically crippled organisms. The conclusion of many scientists in many workshops after key meetings in 1984 and 1985 (see below) has been that *often* the engineered changes *may* cripple the organisms, but that genetic modification by molecular techniques or even radical change in body plan are *not inherently or uniformly crippling to organisms*. Genetic engineering sometimes may indeed produce bizzare and quite non-adaptive individuals, especially in the first stages of the development of new GEOs; but next the investigator selects and breeds the most viable individuals and produces more vigorous lines with undesirable traits removed as much as possible. If the added traits have adaptive value, and the organism is ecologically competent at the end of this process, then if its competitive ability has been increased, or its resource base expanded or shifted, this could lead to ecological problems. The long-used arguments that all modifications of organisms would *necessarily* reduce their fitness had been based on outdated ecological theory[3,16,20,21,23].

Scientists meet

The logical and empirical mistakes in the generic safety arguments were pointed out to the satisfaction of many scientists at key meetings of experts in both ecology and molecular biology at the Cold Spring Harbor Laboratories in late 1984 that I initiated at the suggestion of a number of university scientists, and at a multi-agency sponsored meeting in Philadelphia in 1985. The proceedings of the Philadelphia meeting, including papers and debates, have been published[10], but John Fowle of the Environmental Protection Agency (EPA) and myself, who organized the ice-breaking 1984 Cold Spring Harbor workshop, had to assure the participants a period of confidentiality, and a summary of the meeting has not been published yet.

The EPA, though, had even earlier sponsored F. Sharples to make a study of the safety question. Remarkably, she was able to avoid the unrealistic polarization that had clouded this issue. Her tentative conclusion[26–28] was that the best available model would be neither the implied 'Andromeda strain model' of the tabloids, nor models related to the 'domesticated species model' (except obviously for those GEOs made from hosts that had indeed been ecologically crippled by extensive domestic breeding), long favored by those genetic engineers whose experience had been primarily with laboratory organisms or with ecologically crippled agricultural organisms such as corn.

At the time of the 1984 meeting, Sharples' study was largely unknown in academic circles, outside of Washington, D.C. Most professional ecologists including myself also did not know about EPA-funded studies at Cornell, to focus more closely on issues raised by the Sharples study. The EPA had not informed the 1984 workshop participants of the Cornell project because they saw the independently initiated agenda for analysis of the issue as an opportunity to gain fresh views on the subject, I was later told. The Cornell studies[8] had not, in fact, examined the generic safety arguments directly, nor the question of how to decide what would be appropriate models for GEOs. They mostly outlined what could go wrong with ecosystems and communities in the event of some accident, and outlined issues concerning the containment of GEOs. Sharples also had not confronted the generic safety models directly, and so the effect of the discovery of the basic errors in them was to strengthen her analysis and model, and to make the Cornell studies more relevant to realistic concerns.

What model, though, would be appropriate to use in trying to make safety predictions about diverse projects involving this subset of GEOs? Many of the scientists and agencies who have studied this issue closely have concluded that for non-crippled GEOs with new combinations of biological traits, a much better model than the 'Andromeda strain model' or the various generic safety models would be based on experiences from the introductions of non-indigenous species – the so-called 'introduced or exotic species model'[26].

The introduced or exotic species model for GEOs

The myth

It has been feared by promoters of genetic engineering that any comparison of genetically engineered organisms to exotic species may imply to the layperson that any GEO will have an integrated set of new adaptive traits (few will), like a natural but exotic species; and that non-indigenous, introduced species easily turn into destructive pests (few have done so) such as kudzu, fire ants, zebra mussels or purple loosestrife in the United States. Much of the intense criticism of the 'exotic species model' has been misdirected by this fear of the model's potential misunderstanding by the lay public. In the minds of many in the biotechnology community the myth of the model, conjured up by their own fears, is what the exotic species model *is*, and they know no other and speak of no other.

However, the comparison of GEOs to introduced species has had very specific implications in the scientific literature, and in no way was ever intended to imply that the processes of genetic engineering might magically turn the average genetic engineering project into a disaster. Indeed, historically, the true 'exotic species model' played a critical role in the formation of the present 'relaxed but cautious' public rhetoric from U.S. government agencies and scientific circles that developed in the 1980s, especially after it was realized that the generic safety arguments were based on obsolete scientific beliefs.

The reality

Sharples[26] and Regal[20–22,25] used exotic species models to illustrate a *set* of predictions about certain types of genetically engineered organisms. For those GEOs that have not been ecologically crippled by selective breeding of the hosts or recipients, (as have been the most common agricultural plants) or by the severity of the new genetic combination, the scientific exotic species model would predict the following, based on analogy from past records of accidental and deliberate introductions.

1. The vast majority of GEOs will fail to establish self-sustaining populations in nature even when they have been engineered from non-domesticated, non-ecologically crippled hosts, or have not become crippled from the transgenic manipulations. This is because the vast majority of projects will be small-scale and relatively confined tests for commercial purposes; and the odds are high that at any one time and place, local conditions of soil, weather, biotic interactions, etc. will be unfavorable for the spread of the great majority of *any* new forms. For such reasons, ordinarily introduced species have not transplanted well to new ecological conditions; and even those that have become pests were often quite difficult to introduce to begin with. Another cause of frequent failure is that large numbers may be necessary to generate sufficient genetic variability to adapt to local conditions, and to stay ahead of local mortality agents until the immigrants can adjust to the new conditions.

2. About 90% of GEOs that may actually become established may well prove to be ecologically harmless.

3. Of the remaining 10%, most forms that cause problems may cause only subtle problems.

4. A small *but significant* percentage of this residue of GEOs that may cause problems, could in principle cause enormous and expensive problems. Attempts should be made to identify such potential risks and prohibit them.

5. The issue of risk is not merely of a statistical nature. Each release will not be a 'long-shot' risk simply because most types of projects should be safe. The odds of risk and magnitude of hazard will vary with specific biological properties. Thus, proposed releases should be evaluated on a case-by-case basis with careful consideration given to the unique biological properties of each type of GEO. The extensive record of species eruptions and benign introductions should be organized, for it can provide valuable clues in making evaluations of GEOs. This 'introduced species model' only applies to ecologically non-crippled organisms – and for those GEOs that have been crippled by selective breeding, inbreeding depression, metabolic over-burdening, severe pleiotropic disruptions, etc. other, 'safety' models, may be considered, as outlined by Regal[21].

Attitudinal impact of the exotic species model

The formal exotic species analogy has in effect been used by many scientists who have studied this issue carefully to conclude that any significant risks from GEOs should be:

1) very low in frequency, so scientists must beware of overreacting and 'crying wolf.' And actual problems will probably not arise from small test populations, so scientists must beware of overconfidence and concluding that a GEO will be safe simply because 'nothing has happened' in small commercial field test plots; and

2) of a usual nature; thus, the most likely hazards to be expected, however serious, would be of sorts that ecologists are familiar with, and however expensive and destructive, of sorts that humans tend to learn to live with. Since this model predicts that the likely risks from a relatively small subset of (non-crippled) GEOs would have precedents within the experience of ecologists, scientific screening should be possible, and ecologists should be consulted during the design and evaluation stages of projects intended for release into the environment.

Policy impact of the exotic species model

All recent consensus reports, such as those of the National Academy of Sciences[16], National Research Council[17], Office of Technology Assessment[18], and Ecological Society of America[29], have in effect followed these conclusions and have rejected the earlier comparisons of GEOs on the one hand to an Andromeda strain model, and on the other hand have also rejected the more extreme forms of the earlier models that predicted the generic safety of *all* GEOs.

The consensus position since the mid-1980s has been that genetic engineering involves a low probability of risks (low but significant) but that hazards with potentially high consequences could occur. The high-consequence hazards, however, would be of a familiar nature, such as the disturbances sometimes seen after non-indigenous species have been introduced to an area.

The de facto policy has in effect been an endorsement of the exotic species model developed by Sharples[26] and Regal[21,22]. The corollary has been that ecological knowledge should be able to reduce the risks considerably; for example, the National Academy of Sciences notes, "The scientific community urgently needs to provide guidance to both investigators and regulators in evaluating planned introductions of modified organisms from an ecological perspective"[16].

The current attitude among scientists in United States government agencies such as EPA and Department of Agriculture (USDA) is that in principle proposed releases should be allowed (this is a rejection of Andromeda strain models) but that releases can and should be screened individually for possible risks to the environment (this is a rejection of generic safety models). Yet also, since most releases will probably be safe (this is an acceptance of the exotic species model in combination with *qualified* use of certain other safety models such as the domesticated species model), it should in principle be possible to establish criteria so that certain categories of introductions of GEOs will not become bogged down in unnecessarily complex regulations.

Attempts to establish acceptable criteria for excluding some GEOs from regulation are, though, still unsettled after several years of deliberations on this issue. This is because it is easy to agree *in principle* that the largest subsets of GEOs will be harmless, but it is not so easy *in fact* to develop criteria to assign many GEOs to a category of high risk, intermediate risk, or safety, especially on an a priori basis, without a specific analysis of a GEO as an ecological product.

The situation is somewhat like a medical issue, where it is known a priori that most aches will be harmless and not cancerous, but it may take an examination of each particular patient to be certain that a particular patient is healthy. And the doctor may in some cases even have to require extensive tests before a final conclusion can be made in conscience. Ideally, perhaps everyone should have routine and extensive physicals, but since this would be burdensome and in most cases unnecessary, medical science seeks criteria to try to pinpoint high risk categories.

There is little opposition to 'regulation' if that means a convenient rubber-stamp system that leads the public to believe that the technology is being monitored. But there are abundant opponents of serious regulation that could become inconvenient, and who do not want to send each 'patient' (project) to a 'doctor' for an examination[1,15]. The reasons include[7]:

1) the time and expense of hiring ecologists as staff or consultants, or, the time and expense of having to become educated in modern ecology, especially since the statistically most common projects should hold no risks;
2) the perception that one could ask endless questions about the potential ecology of a questionable GEO and come to no conclusion anyway;
3) the industry's fear of giving up rights connected with industrial confidentiality;
4) the widespread fear that 'environmental activists' would use environmental unknowns as excuses to attack companies legally;
5) the fear that treating potential risks seriously would hurt the image of biotechnology among investors. This is a fear that one sees even in biotech companies that do not plan on ever releasing a GEO; and
6) some may truly believe that the technology as a whole holds no risks or only trivial risks.

One member of the National Institutes of Health Recombinant DNA Advisory Committee (RAC) who wanted to *deregulate*, depicted this motivation to maintain regulation in order to maintain appearances as follows;

"Scientific and lay members [of the RAC] alike ignored the question of 'Will this make the world a safer place to live? in favor of 'How will this play in Peoria?' The most influential opposition to our motion came not from traditional advocates of genetic regulation but from industrial and academic sources [who were concerned that] if RAC withdrew regulatory supervision of most recombinant DNA research, political pressures at other levels would mount. From that time onward RAC became, in may opinion, a dummy committee with a sham function. Ostensibly it protects the public from danger, but in fact it serves more to protect Harvard from the Cambridge City Council and Genentech from the California State Assembly[2]."

In any event, several hundred so-called 'deliberate releases' into the environment of GEOs with minor modifications have to date been approved on a case-by-case basis, although these have been mostly of domesticated forms, mostly with transgenic features that would add no adaptive advantage, and mostly into contained test-plots only.

Some scientists argue that because 'nothing bad has happened' as a result of hundreds of small field tests, genetic engineering is indeed generically safe. The policy should be to (effectively) deregulate, by not requiring serious review of applications.

But proponents of regulation reply that the technology is still in its infancy and that these releases have been of the safest sorts imaginable, and were thus not even opposed by informed 'critics'. Moreover, even *if* there had been any suspected risks, the sample sizes have been too small and the experimental designs inappropriate to allow conclusions about safety or risk, since the tests were generally designed to answer commercial questions and not ecological questions[30]. Thus, the proponents have argued, since appropriate empirical data relative to safety are lacking, policy and evaluations must continue to be based on scientific theory.

Given such controversy and uncertainty over regulatory philosophy, there continue to be good reasons to seek the most secure scientific basis possible for evaluating GEOs as the technology becomes more powerful, and as projects advance from the contained-test-plot stage to commercial, uncontrolled release into various ecological zones of the country and world.

Technical points needing to be resolved

Both Sharples[26] and Regal[20,21] stated that while the exotic species model was a major scientific improvement on comparisons of non-crippled GEOs to Andromeda strains and corn/yogurt-safety, use of the model should be tentative – it was merely the *best* one available at that stage of analysis, a starting point.

The model has allowed a certain amount of stability in U.S. governmental policies, and a certain degree of basic consensus in the scientific community, despite a great deal of feuding on the surface. Yet it is possible to criticize the scientific version of the introduced species model as it has stood either for overestimating the risks from GEOs, or for underestimating the risks from GEOs.

1. *The overestimation arguments*

(GEOs are much safer than any formal or informal comparison to exotic species suggests.)

Statement of arguments. A) Any given exotic species brings thousands of new genes into a new environment, while a transgenic *native* form may have only 1–10 or so new genes. Therefore GEOs could not cause environmental problems. B) Exotic species have coadapted genomes, while transgenic forms have new and unintegrated combinations of genes. Therefore GEOs could not be competitive in nature.

The rebuttals. A) What matters in terms of ecological adaptation is *not* the *number* of genes, but the ability of any novel traits, or properties, of physiology, behavior, or anatomy to alter the relationship of an organism to its limiting factors or to its utilization of resources. In principle, even one new gene that removes the effect of a limiting factor or broadens the resource base could allow a population to go out of control, all else being equal. Some available data may support this expectation (see ref. 17, pp. 40–42). B) Population genetics theory predicts that *if* a new gene brings with it a sufficiently large positive contribution to fitness, it will be selected for even if it tends to destabilize the genome somewhat, (or is not fully integrated in terms of pleiotropic and epistatic effects); and selection over subsequent generations can be expected to improve the balance of positive and negative contributions to fitness, and thus increase the overall fitness of the organisms with the new genes over time.

Comments. The arguments that the exotic species model overestimates risks and hazards of engineering adaptive traits into wild-type hosts seem unconvincing.

2. *The underestimation arguments*

(A) The probability of risks from engineered *native* species has commonly been underestimated due to misapplication of the exotic species model. B) Some GEOs have the potential to cause considerably more damage than any exotic species yet observed have caused.)

Statement of arguments. A) Non-crippled transgenic forms engineered from *native* hosts would already be adapted to local soils, weather, diseases, predators, etc. and thus would have a great advantage over the average exotic introduction in terms of ability to establish self-sustaining populations in nature. Thus, the effect of making ecologically potent new combinations of traits in native hosts, such as removing the effects of limiting factors or expanding the resource base could pose a higher probability of risk than would be involved in adding ecologically potent new traits to a similar exotic form and then attempting to introduce it. This issue is directed to the probability of risk more than to the magnitude of hazards.

B) (This next issue is independent of the last and concerns the magnitude and novelty of hazards.) The technology is only in its infancy. As it advances, will it be possible to make transgenic forms with truly unusual and potentially dangerous modes of ecological adaptations, or extremely competitive forms with unusual ecological properties?

For example, unusually competitive bacterial GEOs which are methane-producing could in principle become abundant and pollute the atmosphere and contribute to the greenhouse effect at levels for which we have no precedent from present-day exotic species. (New organisms that changed the atmosphere drastically are, however, known from the fossil record[11].) An adaptive novelty that opened a new 'adaptive zone' for a GEO could in principle lead to unprecedented ecological consequences. Cell-fusion, recombinant DNA, and related advanced techniques for genetic modification could, in principle, be used to produce oganisms with such radical new adaptive and competitive capacities. Evolutionary and ecological leaps did take place in the distant past when the ancestors of mitochondria began to live in more complex cells, or when the photosynthetic apparatus was transferred to more complex cells. And this suggests that *some* organisms with bizzare complexes of *adaptive* traits may be viable and could have profound ecological impacts if the benefits of their new competitive features outweigh the costs of other features, no matter how clumsily improbable they might appear at first glance to human eyes.

Rebuttals. A) Ecological relationships are complex and populations may seldom be limited by single factors. (I do not agree with this rebuttal.) B) The technology will never improve to the point where uniquely competitive organisms can be made. Many of the spectacular claims that have long been made for the technology have been merely promotional and should not be taken seriously. (I do not agree completely with this.)

Comments. There do seem to be reasons to be concerned that the erroneous impression has been left that it would be relatively safe to engineer native species with new adaptive capacities and then reintroduce them to nature.

It is difficult to rule out the possibility that for some truly novel GEOs the exotic species model may greatly underestimate the magnitude of possible hazards.

In terms of our present experience with the technology and its progress, one judges that a truly novel and highly competitive organism of this sort could only be built with considerable ingenuity and expense even in the future. Thus, such an unprecedented disaster could happen from a *misjudgment*, but probably not from an *accident* of the sort pictured in the biohazard brouhaha of the 1970s. Biohazard referred to the idea that an ecologically crippled laboratory organism that no one suspected could cause problems, might surprise everyone and turn out to be a fierce competitor in nature. Misjudgment refers to cases when good advice is available but it is not sought or is ignored in favor of bad, due to self-interest, *hubris*, institutional inertia and so on.

Microorganisms

It is clear that transported pathogenic microorganisms *do*, disturbingly, often behave very much like problematic exotic species. Chestnut blight, syphilis, plague, and other diseases are familiar examples. Because of host specificity and because the modes of transmission are limited, living host species may function much like geographic islands.

Non-pathogenic microorganisms have tended not to cause problems when moved from one continent to another. Thus it has been argued that an exotic species model based on macroorganisms should not apply to non-pathogenic microorganisms.

One hypothesis to explain the lack of disasters caused by introductions of non-pathogenic bacteria has been that microbial communities are so tightly integrated that they are completely resistant to disturbance. Another hypothesis has been that microbial communities have so many ecologically redundant species already that adding one more cannot upset them. There is no proof of either speculation, but if either were correct, it would be reassuring in terms of concerns over the introduction of novel GEMs into microbial communities in soils and waters.

On the other hand, let me suggest that the exotic species model *may* be completely appropriate for microorganisms and it is simply the case that since microbial spores have been carried by winds to all parts of the earth, the earth has acted so far as a single island or continent. In essence, there have been no truly exotic non-pathogenic microbial species from which to observe adverse effects, since the earth has been one large collection of non-isolated microbial communities. If this hypothesis is correct, a genuinely novel and ecologically competent engineered organism could indeed become a rogue species in nature.

Obviously this is a serious and difficult question and studies are very much needed to resolve the different theories before science will have a clear idea of what experiences from the importation of non-indigenous macrospecies mean for the possible release of novel, ecologically viable, non-pathogenic microorganisms.

Research needs to refine the exotic species model

As stated, the *informal* comparison of GEOs to exotic species is often criticized as a threat to the public relations image of biotechnology. The fear is that the lay public may misunderstand it and assume that the ordinary GEO has the potential to become a dramatic pest simply because of the process by which it was made.

The true *scientific* use of an exotic species model, though, is legitimate and raises significant scientific questions that can only be answered by more directed study both of a variety of GEOs and of a variety of exotic species. Progress on the following issues would greatly help scientists to better focus on degrees and magnitudes of legitimate concerns for different classes of GEOs, and to better focus on developing a base of concepts and data for estimating the adaptive potential of particular GEOs.

How ecologically important can simple genetic features be?

One example of an important scientific issue where leadership and support would be helpful in advancing knowledge has to do with the common questions about what possible ecological effects one or a few new genes could have. Have there been cases where ecological eruptions of native or introduced forms resulted from modifications in the relationship of a form to a single limiting factor? (Addresses overestimation argument, point A.) How common have any such eruptions been, and could scientific criteria for classification and prediction be developed from studying them? What have been the detailed mechanisms of these eruptions and can knowledge of the mechanisms allow us to say if and when altering a GEO with regard to one factor could set the stage for species eruptions?

On the one hand, a 1988 OTA report[18], for example, implied (p. 87) that GEOs will not be comparable to exotic species because the former introduce only 1 to 10 new genes to a habitat, while an exotic species brings 4000 to over 20,000 new genes. Taken out of context, these numbers might seem to favor an often-voiced speculation among non-specialists that when introduced species erupt it is because they have a large number of novel traits that give them an advantage. Examples can easily be found in support of this view, such as the paperbark tree in Florida that has a complex of features that allow it to resist both flood and fire better than its competitors in Florida.

Yet ecologists have often estimated that it has in fact sometimes been only one or a few of the properties of other introduced species that have been *critical* in allowing them to escape potential control by physical or biological features in the new habitat. And in principle a single potent disease-resistance factor, drought resistance factor, herbivore or disease protection mechanism, or ability to utilize new resources, could, under the right circumstances produce a population eruption. It is widely believed that the common European carp has become an ecological problem in the United States because it has an unusual tolerance for low oxygen concentations. African *Tilapia* fish may be a problem in parts of Florida and in New Guinea largely because they can tolerate exceptionally well the high temperatures and low oxygen concentrations in warm Florida waters. In principle, simply by engineering native fish to tolerate low oxygen concentrations and/or temperature extremes, the same ecological destruction could have been produced. For other examples see NRC report[17].

Yet there can be differences of opinion, and other experts believe that the African *Tilapia* have erupted in Florida because they can breed throughout the year, while native species were derived from temperate species and breed seasonally. (If this second theory is true, then engineering a simple genetic change could inactivate the trigger that terminates the breeding season of a native species and this could in principle turn the native species into a pest.)

These differences of opinion on the origins and nature of species eruptions have remained unresolved in large part because generally it has not been the aim of funded research to answer such questions, and experts take up such questions as side issues, often out of personal curiosity. But as the answers to such questions become significant in policy debates in biotechnology, and in attempts to make regulatory evaluations of GEOs, it becomes much more important to have a better scientific base for understanding the dynamics of species eruptions.

In contrast to the 1988 OTA report, a 1989 report of the National Research Council[17], while it noted that most eruptions of exotic species have seemed to involve multiple traits, also identified several examples of plants where one or a few traits indeed seemed to make the difference between an introduction that was a problem and one that was not. Statements such as the following highlight a legitimate need for more research on this issue.

"These examples illustrate that small genetic differences between closely related plants can produce phenotypes with different ecological properties that can increase or alter a plant's geographic range or enhance its aggressiveness in its normal range. [But . . .] We do not know to what extent successful naturalization of exotic organisms hinges on their possession of one or a few traits rather than a group of characters. Multiple genes inducing multiple traits should [in principle] increase the probability of assembling an organism that can cause ecological changes if grown on a large scale[17]."

Making use of the fossil record. Does the paleontological record allow scientific generalizations about cases where novel combinations of traits resulted in unusual or drastic alterations of the environment? (Addresses underestimation argument, point B.) Could genetic engineering allow the production of organisms with novel competitive properties and/or with especially potent ecological effects in a drastically collapsed time frame compared to rates of evolution estimated from the fossil record? Superficially, at least, the fossil record does appear to support concerns, so this deserves critical analysis.

The applicability of genetic theory: fitness and cost benefit of new genetic traits. Population genetics predicts that a new gene with a sufficiently strong contribution to fitness may spread in a population if its benefits outweigh its costs in terms of adverse effects to the organism. Is this applicable to GEOs? If not, why not? (Addresses underestimation argument, point B.)

Genetic theory: selection will harmonize the genome. Theory predicts that natural selection over time will tend to balance the genome to new ecological conditions, and hence increase the fitness of a population. Are there examples from introduced species where a sub-optimal arrangement of genes (in the context of the new environment) was optimized by selection over time? Can species eruptions be related sometimes to selection and increases in fitness and competitiveness following an introduction? This possibility should be kept in mind for GEOs of special concern, since any early measurements of fitness may be unrealistically low if there has not been time for natural selection to balance the genome to natural conditions.

Genetic novelty and species eruptions. It has been suspected that some ecological eruptions have been associated with genetic rearrangements or novelty (through hybridization) in the introduced populations, but the issue has not been studied in detail or resolved. This genetic issue has been raised for fire ants in the southern United States, and for Africanized bees in the new world, for example. Studies on the genetics of species eruptions, when possible, would in any event help to shed light on the role of genetic adjustments in the early adaptation of populations to new conditions, or on the other hand to understand the process of co-adaptation of new genetic elements and host genomes.

Yet good opportunities to make such studies are seldom taken advantage of. For example, as 'African' genes move through populations of honeybees in the Western hemisphere, there is now, for a short number of years, an opportunity to learn how the new genes enter new genomes, co-adapt with them, and seemingly produce a new sort of bee that can be a significant pest. (Another, controversial, view is that the so-called 'killer-bee' problem simply involves African bees displacing the resident bees. But in fact, the bees interbreed freely and much evidence suggests that it is 'Africanized' hybrids that are causing the problems. There have been studies on small numbers of individuals that showed that these had mitochondrial DNA all from African mother bees. But this is by no means proof that the pesty bees have simply African genomes[19].)

The need for synthesis and a general elevation of the baseline of knowledge. The highly important 'underestimation propositions' may have to be evaluated mostly from refinements in theory, from direct experimental studies with appropriate GEOs, and by careful analysis of the factors responsible for eruptions of native populations of organisms.

There are some specific research areas that have particular significance for evaluating non-crippled GEOs[21,22], and research issues strongly implied by discussions in the NRS study (see ref. 17, e.g. pp. 39–42). Yet an improvement in our general knowledge about species eruptions can contribute to basic ecological knowledge and in this way help to strengthen the capacity of ecologists to screen for safe introductions of GEOs. Research on the eruption of species – both on the usually *temporary* eruptions of native species such as grasshoppers or red-tides, that sometimes occur, and on the more *permanent* eruptions that sometimes have happened with introduced species – will be very important to improving the knowledge-base of concepts and details of nature's diverse taxa and communities that must be used in making evaluations of introductions of *any* organisms, including GEOs.

Analysis of the history of institutional errors and successes

Sharples and Regal have also compared GEOs and introduced species in terms of the institutional process of evaluating or predicting the potential biology of a new combination of phenotypic traits in an ecological community. According to Regal, "The lesson that each generation of ecologists has taught the next is that one must be extraordinarily careful not to oversimplify what one predicts of nature. History shows that avoidable mistakes were made over and over when species were deliberately released in new settings, because responsible people had oversimplified expectations repeatedly"[20].

Elsewhere he notes, "The lesson of introduced species is a lesson in the dangers of oversimplification, of idealistic expectations, and of institutional dynamics and momentum. From such tragic experiences society had been starting to learn that science and government must be more careful. But now with genetic engineering, society has a new cast of players who do not know this history very well"[25].

Many of the most destructive introduced forms were indeed deliberately introduced. There clearly were professional misjudgments made[13]. Why? In many cases it is evident that the officials and scientists who made the misjudgments idealized and oversimplified the task of making predictions, sometimes yielding to economic pressures and/or bureaucratic momentum. They ignored good advice for bad and failed to anticipate that forms may have a latent potential to adapt to local conditions in ways that were not obvious when they were studied under too limited conditions before introduction. In some cases decision makers may have been using outdated, superficial ecological theory to make predictions.

In this sense, the accumulated history of deliberate introductions of exotic species is a model of institutional dynamics that illustrates how dangerous it can be to assume that one is sufficiently familiar with an organism to make predictions when the familiarity is not based on a detailed understanding of the mechanisms of adaptation and range of latent adaptive potentials of the organism. This model's most obvious implication for research needs is that there should be analysis of barriers to information transfer of basic scientific concepts and knowledge to the decision-making process. In past cases where successful introductions were made, was good and effective information transfer a factor and how was this accomplished? In cases where mistakes were made, was poor and ineffective information transfer a problem; and why did the best available information fail to reach decision makers, or why was it rejected by them? What could be done to improve the decision-making process in the future?

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