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Can We Guarantee the Safety of Genetically Engineered Organisms in the Environment?

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I. INTRODUCTION

To anticipate my remarks, the answer to the title question is "No, we cannot guarantee the safety of genetically engineered organisms released into the environment." Indeed, it is a tenet of the scientific method that nothing can be proved, only disproved. Thus, we can never show that a release will be safe. We could only show that it would be unsafe, if that were the case. However, if the question is posed differently, for example, can we safely release genetically engineered organisms into the environment?, the answer is probably "yes."

My role in this review[1] is to express environmental perspectives in the deliberate release of genetically engineered organisms into the environment. With that in mind, I will do the following:

1. Describe the proposed uses for genetically engineered organisms in the environment
2. State reasons for concern about undesirable consequences of release
3. Relate some problems I believe are inherent in assessing safety
4. Indicate some of what we presently know and do not know
5. Offer some perspectives

The terminology of biotechnology is used by different people in different ways. My concern here is with genetic engineering in the sense of functional insertion of genes from one organism into another, making a mosaic organism. In deliberate release, this organism is intended to survive and reproduce in the environment for at least a few weeks. Thus, the containment policies carefully worked out in the last decade[2,3] will be intentionally bypassed. While many kinds of new technological applications are being proposed for genetically engineered organisms, this review is concerned with novel, hybrid organisms with functioning alien genes that are set outdoors with the expectation that they will grow and reproduce.

II. PROPOSED USES OF DELIBERATELY RELEASED GENETICALLY ENGINEERED ORGANISMS

Proposed environmental uses of genetically engineered organisms range from slightly modified crop plants raised under agricultural conditions to bacteria with modified substrate specificities dumped into mines and oil wells (Table 1). It is predicted that crop plants will be genetically engineered to provide more completely balanced nutrition, tolerate environmental stresses such as drought and salt, and perhaps photosynthesize more efficiently or under broader conditions (e.g. engineered wheat or peas with the C_4

Table 1
POTENTIAL ENVIRONMENTAL USES OF GENETICALLY ENGINEERED ORGANISMS[4-6]

Improve nutritional quality of food crops
Decrease dependence on chemical pesticides by construction of effective microbial pesticides
Increase plant tolerance and resistance to pathogens and pests
Decrease crop sensitivity to chemicals such as herbicides
Increase plant tolerance to environmental stresses
Increase crop yields by manipulating photosynthesis
Improve soil quality
Control weeds
Water pollution reduction
Clean up oil spills
Decomposition of organic wastes
Cloud seeding, snow making
Mining: bacterial retrieval of low-concentration metals
Increased energy production from organic biomass
Oil recovery

photosynthetic pathway). Engineered plants expressing resistance to pests and pathogens are expected to reduce the environmental damage due to herbicides and chemical pesticides. For example, by transferring herbicide tolerance to sensitive crops, lower amounts of toxic, broad-spectrum herbicides may be needed and crop injury reduced (e.g. to control grasses among wheat or com plants). Microbial applications include engineered bacteria and fungi which improve soil quality by fixing nitrogen or releasing limiting nutrients, parasitizing weed species, cleaning up water pollution by degrading the pollutants, and cleaning up oil spills by consuming the crude oil. Modified microorganisms may also be used to decompose organic wastes, such as the manure of feed lots or garbage dumps, and could certainly improve the efficiency of energy production from organic biomass by converting plants to ethanol faster or more completely. Snow is already being produced by applying the ice-forming bacterium *Pseudomonas syringae* to ski areas, and its efficiency may be improved by genetic engineering. Similarly, *P. syringae* or other bacteria may provide an improved method of cloud seeding for rain. Finally, potential mining applications include retrieving low-grade ores by injecting bacteria which concentrate valuable metals, and by introducing modified bacteria which either degrade oils into more extractable forms or produce CO_2 below the oil deposit, which will displace and raise the oil.[4-6] All of these seem to be good ideas since they address important human problems, such as hunger, energy availability, and pollution. What then is the objection?

III. REASONS FOR CONCERN

There are two chief reasons why ecologists view the release of genetically engineered organisms into the environment with suspicion in the face of the good uses to which they are to be put and the assurances of the designers that these genetic changes are minor.

The first reason for approaching the release of modified organisms with caution is a product of the accumulated wisdom of the discipline. Regal said it very clearly in an address to the American Society of Microbiologists meeting on deliberate release: "The lesson each generation of ecologists has taught the next is that one must be extraordinarily careful not to over simplify what one predicts of nature."[7] A central principle, learned by hard experience in 100 years of ecology, is that we often know far less than we think we do and so, as an operating principle, should never be quick to leap to conclusions or extrapolate without hard evidence.[8,9] Examples of situations in which reality has proved more complex than anticipated range from simple results of ecological research to the consequences of major human activities. Predators were not considered to control grasshopper numbers,[10,11] but studies have shown that each year 20 to 50% of the grasshoppers are eaten by birds and predatory insects.[12,13] On a grander scale, using DDT to control insect pests in Borneo led to a totally unanticipated outbreak of bubonic plague. Dead and dying insects were eaten by geckos, who in tum became ill from the DDT, making them easy targets for house cats. The house cats, receiving even higher concentrations of DDT, also died, which led to an outbreak of the rats the cats had previously controlled and the spread of plague.[14] Thus, the trained response of professional ecologists is to disbelieve predictions of what will happen in nature and the experience of the profession supports this attitude. The second reason for approaching deliberate release of genetically engineered organisms with caution comes from our previous experience with new technology. Physics promised us cheap energy and so our grandchildren will have to live with dumps of our radioactive wastes. Chemistry offered us better health and more food, and now toxic chemical wastes pollute water and soil and cause known and unknown increases in illness. Now biology promises us to solve our economic and ecological problems. Surely, there is reason to be suspicious.

One can reasonably argue that genetic engineering is nothing like nuclear power or toxic wastes: indeed, it is biodegradable! However, from a public confidence standpoint, there is no question that we have a "third cigarette effect." In the trenches of World War I, the first GI struck a match and lit his cigarette. Across no man's land, the German rifleman sat up and took notice. The second GI leaned over and lit his cigarette on the burning match. The Axis rifleman took aim. The third Allied soldier lit his cigarette and got shot![15]

Physics and chemistry "got away with" providing new technologies which may have greatly increased the quality of life, but which have been found to have substantial undesirable byproducts. Biology is "getting shot" by the consequences of previous technologies. Biology is going to have to prove itself safe in ways the previous technologies never needed to, justified or not, because of the legacy of nuclear and toxic wastes left by new technologies in physics and chemistry. Whether deserved or not, the third technology can expect to be shot at.

After studying the problem, the U.S. House of Representatives Committee on Science and Technology concluded: "The potential environmental risks associated with the deliberate release of genetically engineered organisms are best described as 'low probability of high consequence risks, that is, while there is only a small probability of occurrence, the damage that could occur is great.'"[16]

The risks that are considered are, to spell out what we might have to worry about,

1. Death or injury to people
2. Death or injury to animals and plants useful to humans (i.e. domesticated animals and crops)
3. Disruption of one or more natural communities

It is unlikely that any organism with even a remote possibility of causing human death or injury will survive the review process and be deliberately released. The possibility of a release injuring crops or domesticated animals is more likely, but most countries have well-developed animal and crop protection departments that are experts in dealing with such problems and with a wealth of experience in testing the safety of new vaccines, pesticides, and the like. Given both our good veterinary history and plant pathology and our new products' testing methods, most problems that novel organisms might raise for domesticated animals and crops would seem to fall into familiar categories. For those, testing protocols are well developed and the methodology for ensuring safety is in place.

More problematic are affronts to natural communities. In many cases the possible impacts of released organisms are many, and not enough is known about the ecosystem or the biology of the organisms to make reasonable predictions or know what sort of damage to watch for.

The central problem is really: how can the safety of something we have never done be established? Even knowing clearly what we do not want to do, what information can be brought to bear on the problem if the particular organism was just engineered in the laboratory? There are good protocols for testing the impact of new chemicals, but genetically engineered organisms, instead of staying in one area at the same or lower concentration than originally applied, may multiply. They may also actively migrate away from the test site.

We do have experience with the safety and spread of new organisms in the cases of organisms introduced to new regions, for example, from Europe to North America. However, one of the key pieces of information used to understand what an introduced organism will do in its new ecosystem is what it does in its native ecosystem. Since genetically engineered organisms do not occur in any natural ecosystem, the only way to infer what they will do is by extrapolation from the nonengineered organisms, assuming that the changes have predictable effects. Unfortunately, the possibility of unpredicted effects is precisely what the concern is about.

Therefore, the key problem is one of trying to project what will happen from imprecisely analogous cases. It is also a situation in which ecologists are asked what a particular organism will do if released into a new environment, exactly the sort of question that evokes from ecologists the trained response of "no one can tell."

When the question is posed in another way, for example, as "what is the new organism likely to do?," then there are ways to approach the problem.

One set of data that can be used to understand what engineered organisms are likely to do is derived from the literature on introduced organisms. They are not genetically engineered, but they do represent organisms that were introduced into communities of organisms with which they had no previous experience. The question of the fate of genetically engineered organisms in the environment has spurred further analysis of the results of human introductions. The conclusions are not yet available. One problem is how to evaluate the chance of disasters since generally no record was kept of introductions which failed to establish, i.e. did not develop breeding populations, so, it is difficult to put the "disasters" in context. How many failures were there for each success or each disaster? Also poorly recorded were the impacts of the introduced species. If the introduced species reproduced and did whatever it was introduced for, that was usually the end of the analysis. Other information is chiefly anecdotal.

There are a number of ecologists and evolutionary biologists presently subjecting the existing information on introduced organisms to serious scrutiny and solid analyses. A consensus on what can be expected when an organism is introduced can be expected within a few years. (Getting consensus is what takes time.)

For the present, the literature suggests the following qualitative observations about introductions:[17-26]

1. The vast majority of introduced organisms perish and do not set up breeding populations.

2. A few species establish self-sustaining breeding populations, especially in or near human-disturbed areas.
3. A very few species invade intact ecosystems.
4. Even more rarely, an introduced species becomes a disaster. (By disaster, I mean that the introduced organism spreads broadly, killing or severely injuring other species.)

A very recent summary of the "effect" of introduced species is shown in Table 2.[27] Effect must be defined broadly; for example, the introduced species caused a noticeable change in

Table 2
EFFECTS OF INTRODUCED SPECIES[18,25-27]

Type of introduction	Number of introductions	Number having effect	Percent having effect
Animals and plants	184	55	30
Mammals (onto continents)	89	23	26
California (fish)	48	24	50–96[a]

[a]Insufficient information for 22 species; only two species known to be benign.

Table 3
ENVIRONMENTAL DISASTERS[17,19,24-26]

Introduced species that escaped accidentally:
- Gypsy moth in North America
- Africanized bees in Brazil

Introduced species that seemed a good idea at the time:
- Rabbits in Australia
- Mongooses in Hawaii, Jamaica, etc.
- Goats in Hawaii, the Galapagos, etc.
- Carp in the U.S.
- Opuntia cactus in Australia
- Kudzu weed in the southeastern U.S.

Introduced species that arrived on their own:
Dutch elm disease in North America
- Chestnut blight in North America
- Com leaf blight in North America
- Mediterranean fruit fly in California
- Fire ants into the southern U.S.

numbers of the other species in its environment. On that basis, most introductions that result in a breeding population have an effect. However, many introduced species, although establishing a breeding population, do not spread very much. For example, the edible frog *Rana esculenta*, whose natural range includes most of western Europe (southern Sweden to France to western Russia), was first introduced into Great Britain in 1839 as more than 300 individuals. While Lever[19] lists some nine breeding populations, they are small and isolated, despite ample time, opportunity, and presumably suitable conditions for expansion. Many other examples of successful introductions that have remained localized exist.[17,19,24-26]

In contrast are the "environmental disasters," when an introduced species is so successful that it expands its numbers and range and becomes a serious pest. A partial list of such cases is given in Table 3. It is important to note that several of such introductions producing undesirable effects, such as the gypsy moth, were recognized as potentially dangerous and they escaped only through a containment failure. The prevention of human error is beyond the scope of this paper, although problems due to human error seem inevitable.

More serious in the present context are the introductions which were intentional. In some of these cases inadequate testing occurred—the main failure of carp is that North Americans do not consider it a desirable sport fish.[28] In others, the animal did what it was intended to do and, unfortunately, more: mongooses, introduced onto islands to control rodents, also prey on ground-nesting birds, which has caused serious decreases in some native bird populations.

Finally, a series of introduced species have spread across new habitats without conscious help from humans. At present, such movement of genetically engineered organisms is improbable because nowhere are they common and abundant. However, when a sizeable number have been released, problems with unintentional dispersal to susceptible regions will have to be considered serious.

Alexander[29] analyzed the risk of disadvantageous results of introduction as the multiplicative probabilities of survival, multiplication, dissemination, transfer, and harm ($p_s \cdot p_m \cdot p_d \cdot p_t \cdot p_h$). The crucial probability is harm. How likely is the recombinant organism to cause harm? If it will not cause harm, then introduction should pose no problem. Two substantive issues that will have to be dealt with are (1) the measurement of harm, especially in light of the fact that most introductions have a detectable impact on existing species (Table 2), and (2) the cost-benefit aspects of the release. If the release causes some harm, but alleviates greater harm (a microbial pesticide that is less toxic than the chemical it replaces, but still toxic to some), is it "safe" for release?

Considering the case of a genetically engineered organism, there are four ways for its release to cause harm. These are

1. Careless release
2. Inadequate testing
3. Invading-species effect
4. Evolutionary change in the organism after release

The first two situations involve human error or a breakdown of the regulatory system and I will not deal with them further. They constitute a real risk to the environment, but represent situations we are attempting to prevent. On the other hand, some introduced species have attacked nontarget hosts or spread well beyond their intended environments[17,19,24-26] (Table 3). In addition, organisms may change their host species or broaden their tolerance; such shifts are well known in plant pathogens.[21,30,31] Both of these represent very important potential disasters that are difficult to anticipate and to prevent.

IV. PROBLEMS WITH THE PROBLEM ITSELF

There are some problems associated with determining the hazard posed by an introduction that cloud the crucial issues and make a difficult problem even worse.

A. "Safe" Cannot be Proven, Only Disproven

This was my introductory point, but bears repeating. It is an axiom of science that no hypothesis can be proven; it can only be disproven.[32] However, people want to be assured of safety of products. Speaking in the language of science, no one will ever say anything is safe, only "apparently safe." Teaching nonscientists to understand the nature of evidence is desirable, but not very imminent. What is needed is a method of expressing relative safety that responds appropriately to the need of the public to have technologies that do not pose a significant health or safety hazard and do not compromise the scientific method.

B. It is Very Difficult to Get Consensus on "Safe Enough"

The preceding paragraph would imply that if informed individuals conferred seriously over the problem, they could determine a standard of safety (e.g. one personal injury in 1 million, one death in 100 million), which is so much safer than automobiles, extension cords, and neighborhood dogs that it will be universally acceptable. Then all that would be required is the research to establish the safety of each product. However, I do not think this is the case. People's tolerance for hazard varies as widely as, for example, their driving styles. Furthermore, people profiting from or working with a technology are generally more tolerant of its risks than those who do not perceive that they can gain from the technology and who perceive that they might receive injury. It is probable that there are people who will in all honesty desire assurances of complete safety for genetically engineered organisms, the kind of complete safety that simply cannot be provided, and for whom this technology is then entirely too risky to ever be worthwhile.

C. Process and Product Get Entangled

Genetic engineering is a technology that can produce diverse products. Some of the products could be quite novel, some are identical to those produced in nature as mutants, and some differ little from the products of traditional human manipulation of plants and animals. What will be released into the environment is actually the product of the techniques, not the techniques themselves. Thus, the same processes can produce a plant expressing bacterial genes and a bacterium lacking an enzyme due to a single amino acid deletion in a structural gene. Our ability to predict the behavior of these two is widely different, because the bacterium can be related to dozens of other mutants in that pathway, while the plant is truly novel. As a result, the call to monitor the safety of the product, not the novelty of the production method employed,[33] seems to be a sound and simplifying suggestion. Even this approach is difficult to support, however, where the genes were engineered using poorly characterized DNA from pathogenic organisms and crude methods of checking which genes were actually transferred. Consequently, process and product get tangled up in the discussion of releasing safe organisms. This could be disentangled to everyone's benefit if the organisms for release into the environment were engineered with precise methods free of any pathogenic sequences. This approach would alleviate several concerns about safety until such time as we have a database on released organisms that demonstrates that what they are, not how they were made, is the factor relevant to safety in the environment.

D. Existing Methods Are Not Necessarily Safe

Discussions of the safety and regulation of genetically engineered products are often complicated by the concerns of the experts about the safety of existing methods. Much that is currently being done is environmentally undesirable. However, pulling safety considerations about existing practices into discussions of release of new organisms brings in considerations that are not germane to the issue. For example, proposed engineered organisms may express *Bacillus thuringensis* (Bt) toxin. Legitimate concerns may be raised about the desirability of widespread application of Bt toxin (Is it allergenic? Does it attack many high-gut-pH nontarget lepidopteran larvae?), but the safety of current practices is not relevant to the safety of engineered Bt. Current practices meet existing safety standards, and those are not the question for deliberate release.

E. It May Not Be Possible to Get Data on the Safety of Released Organisms without Releasing the Organisms

Ecologists generally do not work much in terraria or growth chambers. These microcosms, however carefully designed, have not been shown to be very effective models of nature. Thus, although preliminary testing in various microcosms is essential to screen out obvious dangers, the ultimate tests will have to be done in natural ecosystems. However, one of the reasons that there is so much concern about the deliberate release of genetically engineered organisms is that once some organisms are placed out in the natural field situation, it may not be possible to ever recapture all of them. Crucial tests cannot be done without going outdoors, and yet, once outdoors, it may be impossible to reestablish complete control. There does not seem any way around this paradox: some risks are going to have to be taken.

These points represent some aspects of deliberate release that can be relied upon to reduce the orderly process of assessment by reasoning people into a morass of cross-purposes and misunderstandings.

Table 4
POSSIBLE CLASSES OF MODIFICATIONS THAT ARE INHERENTLY SAFE

Deletion of gene(s)
Change of a single amino acid or nucleic acid
Transfer of genes within a species
Movement of genes between organisms within the same genus
Enhancement of preexisting genes in the same species
Changing regulatory not structural genes

V. ARE THERE MODIFICATIONS THAT ARE INHERENTLY SAFE?

One appealing approach to cautious release is to designate a series of categories of relative risk and treat them differently. In this context, it has been proposed that some types of genetic engineering are quite safe and should be exempt from special scrutiny. Unfortunately, serious objections can be raised to every possible “exempt” category.

A list of manipulations that have been proposed for exemption from risk evaluation because of inherent safety is given in Table 4. Briefly, deletion of a single gene was proposed as being inherently safe[34] because genetic material is removed and because such changes often occur in nature. However, viruses and bacteria can broaden their host ranges through deletion of a nuclear gene or a plasmid.[29,30,35] Thus, the simplicity of deletions does not guarantee safety.

A second type of change that has been suggested as inherently safe is a single nucleotide pair or amino acid change. Unfortunately, this flies in the face of some of the best-studied Mendelian mutants in which a single allele, whose difference is due to a single amino acid, has a profound effect; for example, sickle cell hemoglobin in humans. Furthermore, plant pathology is replete with cases of gene-for-gene interactions in which a single substitution in the host makes it resistant instead of susceptible and a single substitution in the virus allows it to utilize a new host strain.[29-31] The majority of single nucleic acid changes may be benign, but one cannot categorically state that all will be harmless.

Transfer of genes within a species by genetic engineering seems to be a safe modification; very little may be novel about the traits expressed. However, many species contain pathogenic or weedy races. Some strains of *P. syringae* are plant pathogens, some are not; some strains of *Escherichia coli* are pathogenic, most are not.[31,36] Thus, if some genes were moved, pathogenicity could be transferred, depending on the particular nature of the genes transferred. One cannot simply call within-species transfer safe: you have to know what genes were moved and their activity in the new genetic context. The same objection applies to the movement of genes between individuals of the same genus.

Enhancement of preexisting genes, i.e. the amplification of the DNA for some desirable trait, could also seem an innocuous activity. However, many substances which are essential in small amounts are toxins in large amounts. An example here is vitamin A in human physiology: a little is essential, a lot is toxic. Other substances act in complex regulatory functions that depend on competition for substrate-binding sites or other dose-dependent action. For example, multiple copies of the tetracycline resistance operon in *E. coli* produce complex changes in the overall level of tetracycline resistance of the organism.[37] Duplication of an existing gene can have unexpected effects on phenotype and fitness.

Also suggested was that changing regulatory rather than structural genes might be considered inherently safe because this is just "tuning" the organism, not making it basically different. Unfortunately, there are examples of regulatory mutants that have distinctly different properties from their parental types. The entire range of possible changes in fitness have occurred.[38]

Table 5
CHARACTERISTICS AFFECTING POTENTIAL FOR EVOLUTIONARY CHANGE BY RELEASED ORGANISMS

- Genetic system of released organisms
  - Principle: the more recombination that is possible, the more opportunity for subsequent evolutionary change
  - Information needed includes
    - Can the introduced organisms cross with other organisms?
    - Are genes transferred via plasmids or viruses?
    - Do they undergo meiosis?
    - Are two sexes required for breeding or can single individuals start a population?
- Number of organisms released
  - Principle: the more released, the greater chance of evolutionary change
- Selection pressure on the released organisms
  - Principle: the greater the selection pressure for a change in organismal characteristics, the more likely that the organisms will show evolutionary change

The net result of all of this is not that any of these categories are particularly likely to produce a problem, but that there does not seem to be anyone type of change that is inherently safe. Examples of potential problems can be found with every type of alteration. Blanket exemptions from scrutiny, comparable to, for example, the drugs that are generally regarded as safe (GRAS), do not seem feasible at this time.

VI. GENETIC CHANGE IN RELEASED ENGINEERED ORGANISMS

Among the most basic concerns about the chances of an introduction resulting in a serious problem is the worry that a genetically engineered organism that was apparently safe in testing may evolve into something that is detrimental. For example, a pathogen released for weed control might by mutation and selection broaden its host range to include crop plants. While there is probably no way to prevent evolutionary change in a reproducing population, some groups are more evolutionarily responsive than others. Some factors that correlate with evolutionary response are outlined in Table 5. Safety is, of course, only relative. However, adaptation to new conditions requires an adequate pool of differing alleles upon which selection can act. The more genetic recombination that occurs, the more combinations of genes can be tried in different arrangements, and the more combinations tried, the greater the chance of an effective but undesirable combination occurring. In addition to recombination within the released organisms, this problem is exacerbated if the released organisms can exchange genes with any organisms in the environment, whether of the same or different species. Mutation is a random process with a low probability of occurrence in any particular genetic locus. Thus, the larger the number of organisms released, the more chance there is for mutation taking place among the population of released organisms and affecting important loci.

Finally, although there must be some evolutionary change in every population over time, serious harmful effects are least likely where there are no environmental conditions which cause selection on the released organisms for adaptation to adverse conditions. Contrast genetically engineered bacteria released to concentrate copper in ore dumps and engineered bacteria released to consume oil in oil spills. The former will be maintained at steady population and will be provided the copper ore they need to sustain their populations. The latter will be dumped in great numbers onto a large but finite amount of spilled oil. When the oil is consumed, a huge population of bacteria will suddenly come under severe selective pressure to find an alternative food source. No strictly comparable situation of "adapt or die" exists in the copper mine. Thus, the oil-consuming bacteria are more likely to evolve to utilize a novel food source than are the copper-reducers.

Table 6
SOME RELEASES SEEM SAFER THAN OTHERS

Well-characterized genetic sequence> poorly characterized sequence
Nonpathogenic organism > pathogenic organisms
Disarmed pathogen > pathogen
No pathogenic relatives> pathogenic relatives
Few organisms released > many organisms released
Well-known niche> poorly known niche
Well-known ecosystem> poorly known ecosystem
Easily detected organism> difficult to detect
Release can be "terminated" > cannot be recalled

Note: > = safer than.

The overall outcome of considering harm, invasion, and evolutionary potential is that, while it is impossible to dub any release absolutely safe, it is possible to determine categories of organisms for release that pose fewer hazards than other potential releases. A series of such comparisons is given in Table 6. Most of these depend on two factors: (1) availability of information on the organisms and ecosystem and (2) a relatively low potential for causing harm. The ability to effectively monitor the released organism is also important. Thus, crop plants are probably safer than most other organisms because they are well known, grow in well-characterized ecosystems, and are of low mobility. Organisms released into soil ecosystems become problematic because of the difficulties in detecting their presence.[35,39] Finally, where "recalling" the release is more feasible, experiments can be conducted in greater confidence. For example, a genetically engineered com plant can be harvested, and if necessary even the root zone can be excavated and autoclaved, whereas similar recapture of a release into a stream would require biociding a river system and might still not be effective in eradicating all of the released organisms. Releases into agroecosystems appear generally safer than releases into native ecosystems, and releases into relatively closed ecosystems (ponds) appear safer than releases into relatively open ecosystems (streams). Releases where the organisms are on the safe end of several spectra constitute releases that pose the least risk of a problem.

VI. PERSPECTIVES

Genetic engineering can be expected to be the source of revolutionary changes in the useful plants and animals that we depend upon for food and other products, with the probable result being great strides forward in the quality of life. In order to reap the benefits without undue associated costs, the impact of modified organisms on humans, on other animals and plants, and on the natural ecosystems supporting all life should be, and certainly will be, critically examined.

Perfect safety cannot be guaranteed, even if we exclude human error. Organisms which are released in self-maintaining form are, despite our best analysis, at least potentially capable of affecting the ecosystem in an unexpected way and may evolve novel characteristics after release.[21,23,24] However, serious scientific scrutiny of the organisms, their genetics and ecology, and of the ecosystems into which they are to be released suggests that the chances of a problem can be made insignificant. Coupling the existing literature of relevant disciplines with well-designed experimental tests should render unexpected results rare.

It is critically important for scientists to find ways to express the realistic chances of problems when discussing deliberate release with regulators and nonscientists. Specifically it is important to avoid arousing public anxiety simply because nothing in science can be proven. After all, as scientists somehow we manage to define laws and principles and move forward in our understanding of nature even though we never prove anything!

In particular worst-case scenarios seem generally counterproductive, since we can imagine all manner of disasters that are highly improbable. Worst-case scenarios should certainly not be allowed to paralyze action. One can generate a gruesome worst-case scenario about the commute home tonight, but none of us will stay at the office as a result.

The problem of deliberate release is a problem of managing uncertainty. Successful evaluation of the risks is difficult in any event, but some unnecessary problems can be avoided if we don't get tangled up trying to prove absolute safety.

Despite the many viewpoints and needs that go into a problem of this complexity, it seems likely that there are releases that are less risky than others and that broad agreement can be obtained on classes and categories of relative hazard. This would allow graded levels of testing, and grades of testing rigor would facilitate releases of relatively safe organisms while giving more problematic releases thorough study. Under these conditions, it seems possible that release of genetically engineered organisms into the environment can proceed in a logical order. Doing so will allow the information gathered from the early release of relatively safe organisms to be applied to preventing problems with subsequent releases.

Separating process and product is desirable in our concerns about safety in relation to the regulatory structure implemented to ensure it. It is the product that is released into the environment. The testing procedures can be made much clearer and more precise if the question stays focused on "what will the organisms (product) do?" and avoid becoming complicated by considerations of the method of production. However, while this is a highly desirable situation to facilitate safe release, it will only work if there is no suspicion that a genetically engineered organism to be released contains sequences of uncharacterized DNA from a pathogen. Thus, it seems incumbent on the genetic engineers to be fastidious about producing organisms for release via methods that insert only well-defined sequences and that utilize nonpathogenic intermediates. This careful approach is extremely important until far more data exist to demonstrate that the process of genetic engineering does not, of itself, increase the potential for harm. While it seems obvious to me that the process is not the problem, it is clear from public reaction that it is not obvious to all.

Finally, I would recommend accelerating research relevant to the safety of engineered organisms in the environment. Some research is already under way as industries seek support for their releases and as research branches of regulatory agencies analyze safety aspects. However, many huge areas of ignorance exist and will retard informed analysis of the risks of proposed releases or, worse, will allow a major problem to develop. Some of these areas are ones in which important basic research can be done while contributing to understanding deliberate release. The ecology of microorganisms, soil, and marine ecosystem processes, as well as the principles underlying the success of invading species, represent a few such areas. Additionally, the field of ecology will benefit from testing established principles in microorganism communities or soil ecosystems. For example, perhaps the rules that we have for bird interactions do not apply well to bacteria because of some principle relating to size or reproductive rate.[40] Thus, well-documented investigations could allow researchers both to improve our understanding of the working of natural systems and to facilitate deliberate release that does not lead to undesirable consequences.

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