Serious Flaws in the Horizontal Approach to Biotechnology Risk

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Biotechnology has been widely applied for millennia for many beneficial purposes, including introductions of microorganisms and new plant varieties into the environment. The precision and power of the genetic manipulation of both macroorganisms and microorganisms have greatly increased in recent decades with the advances of molecular genetics. International organizations and professional groups that have explored assumptions about risk assessment of the new techniques have reached a wide consensus that risk is primarily a function of the characteristics of a product (whether it is inert or a living organism) rather than the use of genetic modification (*1*). This consensus is based less on empirical data than on extrapolation from general scientific principles, especially those derived from our knowledge of the biological world and evolutionary biology. These principles should serve as a guide to public policies governing the new biotechnology, including those that concern health and safety regulation.

A Consensus on Scientific Principles

These conclusions about the new biotechnology's risk have been repeatedly expressed in terms that are surprisingly congruent. Examples [see (*2*)] include the joint statement by the International Council of Scientific Unions' (ICSU) Scientific Committee on Problems of the Environment (SCOPE) and the Committee on Genetic Experimentation (COGENE) (Bellagio, Italy, 1987) (*3*), a NATO Advanced Research Workshop (Rome, 1987) (*4*), a UNIDO/WHO/UNEP Working Group on Biotechnology Safety (*5*), and various national groups. In the United States, the most definitive and comprehensive views have been expressed by the National Academy of Sciences (NAS) (*6*) and the National Research Council (NRC) (*7*). The NAS concluded that "[a]ssessment of the risks of introducing R-DNA–engineered organisms into the environment should be based on the nature of the organism and the environment into which the organism is introduced, not on the method by which it was produced."

Critics of this position have asserted that this is a consensus developed by biologists who have not given full consideration to societal and environmental concerns raised [for example, (*8*)]. These critics have embraced the myth of a "horizontal approach," which holds that there is something systematically similar and functionally important about the set of organisms whose only common characteristic is their manipulation with the techniques of the new biotechnology, and that, therefore, scanning across various organisms or experiments that use recombinant DNA (rDNA) techniques constitutes a useful category.

Flawed Approaches to Risk Assessment

That risk assessment experiments are frequently flawed and the pitfalls of a horizontal approach are illustrated by the recent elaborate attempt by Crawley *et al.* "to find out how ecological performance is affected by genetic engineering" (*9*). Conducted in three climatically distinct sites and four habitats, the experiment compared the invasiveness of an unmodified variety of oilseed rape with two variants of the plant manipulated with rDNA techniques to confer herbicide or antibiotic resistance. Some of the significant limitations of this well-executed but poorly designed experiment were described in a commentary in the same issue of *Nature* (*10*). Indeed, there is little reason to anticipate that, in the absence of the herbicide or antibiotic to which the modified plants were made resistant, selection pressure would favor the rDNA-modified forms. And one observed difference, reductions in seed survival in the modified plants, cannot be attributed unequivocally to the genetic modification, because of the presence of maternal effects and other variables.

Another example took place in the late 1970s, when one worrisome scenario involving rDNA experimentation was subjected to an experiment to test its validity. This scenario was that cloning the DNA of an animal tumor virus into a bacterium that normally resides in the human gut could produce human cancer—with the potential of an epidemic, should the bacterium escape from the laboratory. Prodigiously expensive research demonstrated that a disabled strain of recombinant *Escherichia coli* containing the entire genome of polyoma virus within its own DNA does not transmit the virus to a permissive (murine) host while growing within the animal's intestine (*11*). Although the experiment was widely cited, it was arguably not particularly well crafted: a positive result (that is, a negative effect on a mouse) required a highly improbable sequence of events.

The Fallacy of a Horizontal Approach

A horizontal approach to risk assessment, a fallacy based on scanning across experiments whose only common element is the use of the same genetic modification technique, survives in some quarters. This misconception has, in recent years, dictated the theme of major conferences and a survey of field trials of rDNA-modified organisms commissioned by the Organization for Economic Cooperation and Development (OECD). More such dubious exercises are planned. However, given the kinds of organisms that have been modified and the traits introduced, one might as well survey all experiments that were performed using plastic, as opposed to glass, pipettes; or ones that were begun on certain days of the week.

Assessing risk is not straightforward. An empirical approach, acquiring data through measurements or experimentation about the source of potential hazards, has given satisfactory answers when applied to genuine and quantifiable risks, such as those of drugs, vaccines, or pesticides that exert toxic effects. However, an empirical approach is problematical in situations where it can be deduced at the outset that risk is negligible (for example, a small-scale field trial of a ubiquitous, benign organism such as an ice-minus, nonpathogenic strain of *Pseudomonas syringae*, or of a tomato containing antisense DNA that reduces expression of a gene coding for an enzyme). In these cases, an assessment of risk must rely less on empirical data than on an extrapolation from general scientific principles that derive from our knowledge of the biological world and from our understanding of evolutionary biology.

The absence of unexpected persistence, invasiveness, or gene transfer in field trials with rDNA-modified plants that have been protected against interpollination with related crop or wild plants does not indicate that an incorporated trait may not under specific circumstances be hazardous. A rigorous demonstration that an rDNA-modified plant presents a level of hazard different from a non-rDNA new variety of that

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species or plants of that species in regular use must entail experiments that provide reasonable opportunities for the manifestation of identified hazards. Despite the virtual absence of untoward effects in the more than 1300 field trials of recombinant organisms performed to date, the scientific community knows barely more about their risk than before the trials were performed. Moreover, increasing exponentially the number of similar negligible-risk trials would not substantially enhance our understanding about risk.

Two Correct Approaches

Such understanding may be acquired in two ways. The first is by performing genuine risk-assessment experiments analogous to those of Israel *et al.* (*11*) or Crawley *et al.* (*9*), but better designed. The experiments might include, for example, attempts to convert a benign, nontoxic, noninvasive plant into one with undesirable traits, or to induce any plant with a newly acquired trait to transfer it by outcrossing. An example of the latter would be herbicide resistance under the positive selective pressure of the herbicide in the test environment. These experiments should be carefully designed to measure the relevant effects of introduced traits that are known to be related to risk, for example, those traits that affect persistence and invasiveness, weediness, or gene transfer. Investigators need not persist in testing and retesting the hypothesis that the use of rDNA techniques, per se, enhances such risk-related characteristics.

The other way to improved understanding is to exploit the consensus view expressed in the National Research Council report that "no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes" (*7*). This approach leads directly to the conclusions—based on the enormous experience with traditional techniques—that risk is a function of the characteristics of the organism and its environment, and that the variety of an organism's potential characteristics and environments is vast. Thus, the most rational approach to risk assessment when risk is not readily demonstrable is to use established scientific principles and to identify significant gaps in our understanding that can be bridged by properly designed experiments. Such a "vertical" approach to risk assessment should, for example, be applied to the recombinant *P. syringae* or antisense tomato alluded to earlier, and to most other applications. Thus, a tomato breeder or regulator of polio vaccines who wishes to assess the potential risks of a new rDNA-derived tomato or vaccine, respectively, would rely more on information about tomatoes and poliovirus manipulated by traditional techniques, than on information about rDNA-manipulated pigs or bacteria.

The assessment of safety and risk should be approached in a way that is logical. It is one thing to conclude, as many others and we do, that trials of recombinant plants and microorganisms have been safe. It is quite another to attempt to generalize from negligible-risk field trials or to ascribe to them a predictive value. Our concern about the propensity to focus on rDNA modification and to draw broad conclusions from inadequate experimentation is not simply that they elicit a profusion of articles, conferences, or surveys. Even when such activities are superfluous, when they add little to our fund of knowledge and when they contribute to the myth of the basic uniqueness of rDNA modifications, they hardly constitute a significant societal burden.

The Danger of a "Horizontal Approach"

The danger is that the false assumptions about risk that underlie the horizontal approach will become an accepted basis for assessing and managing risk. This is what is happening in the United States and the European Community, where regulations are being formulated or modified according to the results of field trials of recombinant organisms. For example, the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture (USDA) recently finalized regulations that make certain plants eligible for field trials upon a notification instead of submission of an application and prior approval by the government (*12*). One criterion for this simplified procedure is that the test plant be a member of the so-called "group of six": corn, cotton, potato, soybean, tobacco, and tomato. And why is USDA sanguine about new variants of these plants? In the words of the regulation, because "we have had the most experience with evaluation of field tests" for the rDNA-modified variants of the six listed crops. Field trials with all other recombinant crops, therefore, continue to be subject to regulatory red tape, delays, and a governmental risk assessment. Moreover, the USDA proposal nowhere clarifies the scientific rationale why, even within the group of six, a trait never before introduced or field tested in that plant should be presumed to be without risk. Thus, we have a prime example of flawed assumptions about risk assessment applied to regulatory policy.

We conclude that there is no demonstrated, scientifically based need for additional experiments of the kind performed in the 1970s and more recently to assess the risks of rDNA-modified organisms as a category. Moreover, there is no evidence that rDNA-modified plants pose significant hazards not discernible from information about the host crop, the newly introduced traits, and the site of the introduction. Thus, no constructive purpose is served by continuing assessments, surveys, and discussions based solely on field trials of rDNA-manipulated organisms. This horizontal focus, this preoccupation with the genetic engineering techniques themselves, can engender a variety of mistakes ranging from the wrong conferences to flawed risk assessment rationales for regulatory policy. Inadequate corrections of regulatory regimes based on such dubious experience—often touted as enlightened deregulation—are not a saving grace for regulatory problems created unnecessarily in the first place.

Important scientific questions relevant to the behavior and performance of organisms in field trials can and should be addressed. These questions should be approached systematically, with an understanding of the sequence of events that is necessary before a potential hazard becomes manifest, and in ways that are consistent with recognized scientific principles and procedures. In this way, we can avoid myriad risk assessment experiments that are unnecessary and costly in terms of research funds squandered and innovation lost.

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